Diabetes Mellitus Interagency Coordinating Committee
Workshop on Research Supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*

May 30-31, 2019
Bethesda, MD

Summary

INTRODUCTION

A panel of scientific and lay experts from across the United States, with expertise relevant to type 1 diabetes and its complications, convened in Bethesda, Maryland on May 30-31, 2019. The goal of the 2-day workshop was to obtain input from panel members on draft concepts for research initiatives that could be pursued with funds from the *Special Statutory Funding Program for Type 1 Diabetes Research ("Special Diabetes Program" or "the Program")* in Fiscal Years (FY) 2020 and 2021. Furthermore, the panel was invited to propose other ideas for new and emerging opportunities for type 1 diabetes research that could be pursued with funds from the *Special Diabetes Program*. Thus, the workshop served as one of many key sources of input to the government for informing future research directions. A summary of initiatives is presented here, including descriptions of these proposals and summaries of the relevant panel discussion.

Background on Workshop: To inform decisions about how best to use a possible extension of the *Special Diabetes Program* funds, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) prospectively convened a panel of 21 scientific and lay experts to solicit input on future research directions. The 20 scientists had expertise in a variety of areas, including type 1 diabetes, type 2 diabetes, diabetes complications, genetics, immunology, beta cell biology, behavioral research, clinical trial design, epidemiology, translational research, and islet transplantation. One lay panel member with broad expertise in type 1 diabetes was also invited to provide important input from the patient perspective.

Because the *Special Diabetes Program* is a trans-Department program of the U.S. Department of Health and Human Services (HHS), the NIDDK initiated a call for proposals/initiatives to other Diabetes Mellitus Interagency Coordinating Committee (DMICC) member organizations for research that could be pursued in FY 2020 and/or FY 2021, if the funds were extended. Specifically, the NIDDK requested proposals for:

1) New concepts for basic, pre-clinical, or clinical research that could advance understanding of type 1 diabetes or its complications; and
2) Continuations or expansions of ongoing programs supported by the *Special Diabetes Program.*

Thirty-three proposals, submitted by three National Institutes of Health (NIH) Institutes and the Centers for Disease Control and Prevention (CDC), were presented to the panel. The proposals comprised 24 new initiatives and 9 continuations or expansions of ongoing programs. Written summaries including proposed cost and duration, background and justification, and goals and

objectives for each of the 33 proposals were provided to the panel members prior to the workshop.

Workshop Agenda: The workshop began with an overview of the *Special Diabetes Program* given by Dr. Philip Smith, Acting Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK and included welcoming remarks from Dr. Griffin Rodgers, Director, NIDDK.

The workshop was organized around six broad topics related to type 1 diabetes research:

- Artificial Pancreas
- Clinical Management
- Pancreatic Pathobiology
- Beta Cells: Assessment and Therapies
- Diabetes Complications
- Autoimmune Etiology, Clinical Trials, and Epidemiology

The submitted proposals were grouped under the relevant topic area. For each proposal, an NIH or CDC staff member gave a presentation to describe the concept and goals. The presentation was followed by a question and answer period and a panel discussion period. Two or three panel members were assigned to serve as primary discussants for each proposal and were asked to make initial comments and moderate the discussion. Panel members involved in an ongoing program were asked to leave the room during the relevant panel discussion. After all proposals had been discussed in a topic area, the panel members participated in an overarching discussion of the proposals, which gave them an opportunity to suggest other ideas for future research directions that could propel progress in that topic area.

At the beginning of the workshop, the lay panel member gave a short presentation of her perspective, and there was a closing discussion during which panel members were asked to comment on any gaps and emerging opportunities in the overall *Special Diabetes Program* research portfolio and suggest other new and emerging areas of research that could be pursued to advance type 1 diabetes research.

NIDDK REMARKS

Welcome

Dr. Griffin Rodgers welcomed the panelists and thanked them for taking time to attend and participate in the workshop. He also thanked staff from the NIH and CDC for their extensive efforts to prepare materials for the workshop and to present the initiatives and welcomed attendees from other Federal agencies and patient advocacy communities. Dr. Rodgers reiterated the importance of the *Special Diabetes Program*, noting that the Program has supported many scientific advances that have improved the lives of people living with type 1 diabetes, including the tremendous progress in developing artificial pancreas and other glucose management technologies that are helping people today. NIDDK has used the *Special Diabetes Program* funds to undertake challenges that would have been impossible to address with NIDDK's regularly appropriated funding alone. This included conducting certain types of trials, like comparative effectiveness trials and trials of generic drugs, that were unlikely to have been conducted by the private sector.

Responsibly administering the *Special Diabetes Program* funds and maximizing their value are among NIDDK's highest priorities, which was why the workshop was convened to solicit input from the panel of scientific and lay experts. The *Special Diabetes Program* is slated to end at the end of FY 2019. Because of the timing required to effectively plan for and develop new initiatives, it was the right time to discuss how best to use possible future funds in FY 2020 and FY 2021 to support cutting-edge research on prevention, management, and ultimately a cure for type 1 diabetes. Dr. Rodgers concluded by noting that input from previous panels has been critical for use of the funds and that NIDDK expected that this panel will provide similarly important input.

Overview of the Special Diabetes Program

Dr. Smith thanked the panel members for participating in the workshop and provided them with an overview of the *Special Diabetes Program*.

The *Special Diabetes Program* is a trans-HHS program administered by NIDDK. The Program augments regularly appropriated funds that the NIH receives for diabetes research, and the funds have been distributed to multiple NIH Institutes and Centers and the CDC. The *Special Diabetes Program* funds have been used differently from regular NIH appropriations to take on broad challenges in type 1 diabetes research that could not have been addressed otherwise. The Program has been used to support large-scale, collaborative, high-risk, high-reward research consortia and clinical trials networks that supplement, but do not supplant, research supported with the regular appropriation. Unlike regular appropriations, the funds from the *Special Diabetes Program* are limited in time and require renewal in law.

Dr. Smith noted that Program planning is a collaborative effort with other Institutes and Centers at NIH, the CDC, and other federal agencies and has included the participation of various non-federal stakeholders, including the JDRF, the American Diabetes Association (ADA), and the Leona M. and Harry B. Helmsley Charitable Trust. The Program is coordinated by the statutory DMICC. By fostering coordination and collaboration across federal agencies, the DMICC has played an important role in guiding the *Special Diabetes Program*.

Additionally, planning and evaluation meetings such as this workshop have been pivotal to the effective use of Program funds. These meetings are one way that the NIDDK obtains external input on research supported by the *Special Diabetes Program*. The feedback generated by these planning meetings has been critically important for identifying gaps and emerging opportunities for type 1 diabetes research funding. A Diabetes Research Strategic Plan (2011) also serves as an important guidepost for type 1 diabetes research. This Plan was developed under the auspices of the DMICC with broad input from the scientific community, patient advocacy groups, and the public.

Dr. Smith discussed examples of previous achievements supported in whole or in part by the Program, including new treatments for diabetic macular edema and diabetic retinopathy, early development or testing of FDA-approved devices for glucose management, the progress of artificial pancreas technologies that are excelling in trials in real-world settings, the development of glucose-responsive Smart Insulin, the first national surveillance data on rates of childhood diabetes, trials to preserve beta cell function in people with new-onset type 1 diabetes,

completion of an islet transplantation trial aimed at validating a process for islet cell manufacturing for submission to the FDA as a biologic product, identification of distinct beta cell subtypes, and refining the stages of type 1 diabetes disease. Additional information on Program achievements is available in the Special Statutory Funding Program for Type 1 Diabetes Research: Progress Report. In addition, ongoing research holds great promise and may yield important new insights.

Dr. Smith also noted that the same set-aside requirements regarding research conducted by small businesses that apply to the NIH regular appropriation also apply to the *Special Diabetes Program* (for more information, see the NIH SBIR/STTR website). Dr. Smith asked the panel members to consider opportunities to utilize those funds.

PATIENT PERSPECTIVE

Ms. Lorraine Stiehl provided comments from the patient perspective. She noted that even with recent advances, most people with type 1 diabetes are not meeting their blood glucose targets. Complications from the disease have been reduced, but not eliminated despite progress in glucose management technologies. The patient community is frustrated by glycemic variability and wants predictability in their diabetes. She commented that most people with type 1 diabetes do not understand the heterogeneity of the disease and that every person with type 1 diabetes is different. She encouraged the scientific and medical communities to share this information—as well as how complicated the pathology of type 1 diabetes is—with the patient population to help them understand why, with so many resources and so much time, type 1 diabetes has not yet been cured.

Ms. Stiehl shared that the patient community is enthusiastic about ongoing research. For example, she mentioned excitement that the Human Islet Research Network (HIRN) is working to identify new biomarkers that could non-invasively measure the health of beta cells and could reduce the costs of clinical testing of novel therapies. She cited the advance from Type 1 Diabetes TrialNet and other *Special Diabetes Program*-supported efforts defining the stages of type 1 diabetes as a "game changer" for patients and clinical research. Ms. Stiehl commended NIDDK for investing in technology advances and addressing barriers to adoption of these technologies, pointing out that many patients start using technologies and then stop due, in part, to the burden of wearing these technologies on their bodies. The patient community also appreciates that NIDDK is driving research and development in novel next-generation insulin therapies, such as glucose-responsive, liver-targeted, and ultra-rapid insulins. Ms. Stiehl noted that the community is anxiously awaiting the first approved immune therapy for type 1 diabetes and is excited about research involving the intersection of beta cells and immunotherapy as well as the progress being made in repurposing drugs and in creating combination therapies.

Ms. Stiehl also encouraged research collaborations among type 1 diabetes researchers and scientists working in other autoimmune diseases, particularly in the area of the microbiome. She noted the importance of behavioral and psychosocial support for patients and their caregivers and asked the scientific community to address the significant barriers to technology use and treatment, especially for at-risk and underserved populations. She also suggested utilizing novel designs for clinical trials to innovate, shorten, and make them nimbler, and encouraged clinical research to include patient-reported outcomes and to involve patients in risk-benefit decisions.

She noted the great need for biomarkers to prove clinical trial efficacy, especially in disease intervention, and the need for more endocrinologists and trained diabetes specialists. Finally, with all the vast data emerging from *Special Diabetes Program*-supported consortia, she encouraged sharing and partnerships to enhance data analysis.

DISCUSSION OF PROPOSALS

Panel members provided input on the proposals and, in some cases, suggested enhancements. This summary includes proposals which may not be supported for a variety of reasons, may be partially supported, may be supported if contingencies are met, may be supported through mechanisms other than the proposed Funding Opportunity Announcement (FOA), or may be supported as described.

TOPIC 1: ARTIFICIAL PANCREAS

Current Efforts in Artificial Pancreas

Dr. Smith noted that in this area, ongoing investigator-initiated grants supported by the Program include one award made under "Diabetes Impact Award—Closed-Loop Technologies: Clinical, Physiological, and Behavioral Approaches to Improve Type 1 Diabetes Outcomes" (RFA-DK-14-014); one award made under "Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes" (RFA-DK-14-024); one award under "Type 1 Diabetes Pathfinder Award" (RFA-DK-15-030); three awards under "Clinical, Behavioral and Physiological Research Testing Current and Novel Closed Loop Systems" (RFA-DK-16-009, RFA-DK-17-023); and one award under "Development and Integration of Novel Components for Open and Closed Loop Hormone Replacement Platforms for Type 1 Diabetes Therapy" (RFA-DK-17-025). In addition, new awards are expected to be made under the following: "Small Business Innovation Research (SBIR) to Develop New and Closed-Loop Automated Technologies for Diabetes Therapy and Monitoring" (RFA-DK-18-022), "Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes" (RFA-DK-18-025), and "Data Coordinating Center for the Advanced Clinical Trials Consortium to Test Artificial Pancreas Device Systems" (RFA-DK-18-026).

Development and Integration of Novel Components for Open- and Closed-loop Hormone Delivery for Type 1 Diabetes Therapy

Primary discussants: Dr. John Buse, Dr. Pratik Choudhary

While recent advances in technology such as continuous glucose monitors (CGMs) and "smart" insulin pumps that can help calculate insulin doses have helped many people with type 1 diabetes, recapitulating the dynamic control of blood glucose levels imposed by the beta cells of the pancreas is still impossible with current methods. These limitations determine a high risk of acute complications when current glucose control regimens and associated technologies are used. Therefore, it is important to promote research on the development and optimization of novel self-management systems components, including personalized digital insulin dosing decision support systems, linked or not to remote monitoring and telemedicine resources, in parallel to the optimization of closed-loop systems and their components. Also, a new generation of more physiological (*i.e.*, intraperitoneal, liver-targeted insulin delivery), less burdensome, and user-

friendly components (*i.e.*, implantable) are needed to increase efficacy, usability, and acceptability of these devices.

The goal of this proposal is to address barriers that limit progress toward safe and effective open- and closed-loop glucose control systems, tackling the most important obstacles at the level of sensing, hormone formulations and delivery, automated controllers, self-management decision support systems, and the design of proper controllers/algorithms able to manage an integrated platform adaptable to remote monitoring and telemedicine when needed. This initiative would give preference to innovative research leading to the development of a new generation of devices and systems engineered to maintain euglycemia and avoid hypoglycemia while increasing quality of life.

The panel commented that previous research supported under similar FOAs had yielded benefits to patients, as technologies were coming close to clinical application. One panelist noted that this initiative is integral to seed the development of next-generation technologies. The panel remarked on several barriers to these technologies that could be addressed in the initiative, including the need for improved power supplies/batteries and the need to improve the on-body experience for patients by miniaturizing components and improving adhesion. Panelists also suggested that, because most people with type 1 diabetes are not using closed-loop systems, promoting research to improve open-loop systems needs to be encouraged.

Support for Small Business Innovation Research to Develop New Technologies for Open- and Closed-loop Systems to Improve Type 1 Diabetes Monitoring and Treatment
Primary discussants: Dr. Michael German, Dr. Bruce Verchere

Despite the availability of increasingly effective treatment modalities, including insulin analogues, CGMs, and continuous subcutaneous insulin infusion devices, a substantial proportion of people with type 1 diabetes cannot achieve adequate glycemic control and avoid acute complications such as hypoglycemia. Therefore, it is important to stimulate collaborative research that may generate new technologies or optimize the operability of current systems and/or their components to achieve the goal of clinically viable, functionally integrated open- and closed-loop systems with commercial potential and high usability and acceptability by people with type 1 diabetes.

The goal of this proposal is to stimulate small business innovative research to generate new technologies or optimize the operability of current systems and/or their components to achieve the goal of clinically viable, functionally integrated diabetes control systems with commercial potential. Examples of topics that could be emphasized in a new FOA are: 1) technologies to support interoperability of devices and plug-and-play platforms/hubs; 2) more effective fault-tolerant control systems algorithms; 3) novel smart hormone infusion systems with longer durability and that are less prone to failure; 4) new generation of sensors, including non-invasive and long-term implantable devices; 5) better integration and synchronization of closed-loop components; 6) novel hormone replacement formulations with improved kinetics and stability; 7) novel glucose-responsive smart biomaterials for a physiological delivery of insulin and glucagon; and 8) development of remote monitoring systems to optimize performance and safety of the integrated platforms.

The panel commented that small businesses are big drivers of technology development and an important bridge between academic laboratories and patient application. One panelist noted how important research in this area is to the design of insulin analogs and that many research opportunities exist to address some of the barriers of currently available insulin formulations. Several panelists suggested making the FOA broad enough so that applicants have the flexibility to propose development of other new technologies.

Clinical, Behavioral, and Physiological Studies of Open- and Closed-loop Systems
Primary discussants: Dr. Pratik Choudhary, Dr. Vicki Helgeson

Emerging and next-generation technologies for managing blood glucose levels require further translational research to evaluate and improve their safety, accuracy, and efficacy as research progresses from animal and simulated models to human trials. It is therefore important to continue supporting collaborative research to clinically test current and new technologies to optimize their operability, taking into consideration patient preferences and behavioral and physiological factors, to achieve the goal of viable, functionally integrated open- and closed-loop systems for routine use. It is also critical to conduct studies to test these technologies in people usually not included in clinical trials and considered high-risk (for instance, those with: high HbA1c, frequent severe hypoglycemia, hypoglycemia unawareness, high glycemic variability/lability, recently diagnosed, tendency to develop diabetic ketoacidosis, autonomic neuropathy) who may be the ones with the greatest need for these advanced interventions.

The goal of this proposal is to build on current technologies and ongoing clinical research to address barriers that limit progress toward developing physiological pancreatic hormone replacement open- and closed-loop systems. Specifically, the initiative would support research to: 1) test and improve the safety, reliability, and clinical efficacy of these technologies in humans; 2) address behavioral/psychosocial factors that play a role in the usability and acceptance of these systems and validation of measures that may be used as outcomes for the demonstration of efficacy and benefit; 3) test these technologies in subpopulations of patients not usually included in clinical trials of these technologies who may benefit the most from their use; and 4) use the technologies as tools to advance understanding of glucose regulation pathophysiology in people with type 1 diabetes. Research goals include improved metabolic control with decreased glycemic excursions, prevention of acute and chronic complications, and improved quality of life in people with diabetes.

The panel commented that previous FOAs in this area led to important clinical research. Panelists felt that research in this area is especially needed in understudied patient populations such as individuals with renal impairment, recurrent diabetic ketoacidosis, gastroparesis, and groups that are generally underrepresented in clinical research. One panelist commented that research to identify the people most likely to use and benefit from these technologies would be helpful, noting that the behavioral aspects to use of these technologies are very important to understand. Another panel member encouraged studies incorporating family members, friends, and/or schools to look at their roles in use of these technologies and suggested that studies use existing quality-of-life measures to enable comparisons to other patient populations.

Consortium and Data Coordinating Center for Advanced Clinical Trials to Test Artificial Pancreas Device Systems for Type 1 Diabetes
Primary discussants: Dr. Pratik Choudhary, Dr. Michael Rickels

NIDDK and other organizations support an active portfolio of research to develop next-generation devices that may be implantable or have other features reducing patient burden and enhancing acceptability. Given the fast rate of progress of these technologies, the expectation is that the testing of new platforms in more definitive outpatient real-life studies will expand during the next decade. Thus, it is considered important to continue supporting clinical trials of emerging technologies including algorithms to generate safety and efficacy data toward commercially viable, user-friendly, and accessible systems.

The goal of this proposal is to encourage investigative teams that have developed and initially tested an artificial pancreas device system with robust, promising results to expand the testing in clinical and outpatient settings with trials designed to generate data able to address safety and efficacy requirements by regulatory agencies for the approval of a user-friendly and accessible multicomponent product. Research goals include improved metabolic control with decreased glycemic excursions, prevention of acute and chronic complications, and improved quality of life in people with diabetes. To achieve these goals, a consortium with an individually funded data coordinating center would be established.

The panel commented that testing interventions in underserved populations will likely require a network of coordinated and integrated centers. Panel members remarked that participants currently in artificial pancreas trials are early adopters of new technologies and may differ from the general population. Panelists also commented that a data coordinating center that collects data from a wider spread of studies could enable mining of data to answer a variety of questions like who does well on these technologies and how do outcomes from artificial pancreas studies relate to outcomes in complications.

TOPIC 2: CLINICAL MANAGEMENT

Current Efforts in Clinical Management
Dr. Smith noted that ongoing investigator-initiated grants supported by the Program include three awards under "Career Development Programs in Diabetes Research for Pediatric Endocrinologists" (RFA-DK-15-006); two awards under "Impact and Use of Glucose Monitoring and Control Technologies on Health Outcomes and Quality of Life in Older Adults with Type 1 Diabetes" (RFA-DK-15-028); four awards under "Improving Diabetes Management in Pre-Teens, Adolescents, and/or Young Adults with Type 1 Diabetes" (RFA-DK-16-001); and one award under "Improving Diabetes Management in Children with Type 1 Diabetes" (RFA-DK-16-003). In addition, new awards are expected to be made under the following: "Impact of the Use of Glucose Monitoring and Control Technologies on Health Outcomes and Quality of Life in Older Adults with Type 1 Diabetes" (RFA-DK-17-024); "Career Development Programs in Diabetes Research for Endocrinologists" (RFA-DK-17-026); "Incorporating Patient-Reported Outcomes into Clinical Care for Type 1 Diabetes" (RFA-DK-17-027); "Treating Diabetes Distress to Improve Glycemic Outcomes in Type 1 Diabetes" (RFA-DK-17-028); and

"Elucidating the Effect of Glycemic Excursions on Patient Well-being and Cognitive Status in People with Type 1 Diabetes" (RFA-DK-18-003).

Impact of the Use of Glucose Monitoring and Control Technologies on Health Outcomes and Quality of Life in Older Adults with Type 1 Diabetes
Primary discussants: Dr. Pratik Choudhary, Dr. Vicki Helgeson

Clinical and observational studies indicate that real-time self-monitoring of blood glucose in people with diabetes treated with insulin helps to improve self-management of the disease. Recent studies suggest that older adults, particularly those with longstanding diabetes, are more prone to hypoglycemia and hypoglycemia unawareness and may have increased vulnerability to cognitive impairment and/or multiple co-morbidities which may affect the use and effectiveness of these technologies. Hypoglycemia and lack of awareness of it is especially risky in this older population. Thus, this population might greatly benefit from the use of glycemic control technologies that could also help to avoid hypoglycemia and its potentially lethal consequences. Research is needed in this population to inform clinical decision making, coverage/reimbursement decisions, and public health policies.

This proposal would seek to support clinical studies of the use of current and emerging technologies for monitoring blood glucose and insulin administration in older adults with type 1 diabetes. These studies would seek to determine whether glucose control technology interventions—including adaptable, usable self-monitoring and decision support systems; CGMs and/or combinations of sensing and pancreatic hormones delivery devices in an open- or closed-loop system; or other adjuvant technologies—might contribute to better clinical and psychosocial outcomes in this population. The goal of this research would be to inform better strategies to improve health, glucose control, and quality of life for older people with type 1 diabetes.

The panel commented that this is an important area. The panel pointed out that some older adults with type 1 diabetes are technologically savvy and able to use and manage current commercial glucose management technology, but that others have multiple comorbidities that affect their use of these technologies. Technologies using a CGM without a pump, for instance, or other standard glucose monitoring methods are underrepresented in research, and the panel suggested that the proposal could help encourage study of those types of approaches. Cognitive dysfunction and visual impairment were mentioned as particular areas where more research needs to be done to find whether these technologies can be used in this population. It was also mentioned that research in this area could target caregivers and families, who may also contribute to barriers and successful use of these technologies. Behavioral factors could also be studied, as resistance to new technologies may be high if previous glucose management strategies are successful. Finally, another suggestion was to target the study population by frailty, rather than chronological age, as the two do not always co-occur.

Technology Adoption and Health Disparities in New-onset Type 1 Diabetes
Primary discussants: Dr. John Buse, Dr. Vicki Helgeson

Major advances in diabetes treatment, including insulin analogues, insulin pumps, continuous glucose monitoring, and closed-loop systems, have the potential to dramatically improve

outcomes in individuals with type 1 diabetes. However, glycemic control remains suboptimal for many individuals with type 1 diabetes in the United States, particularly youth, and especially those from racial/ethnic minority populations. In addition, minority youth are less likely to be treated with insulin pumps or to use continuous glucose monitoring. Many studies suggest that socioeconomic status does not fully account for existing disparities, and the reasons for these disparities and the barriers to technology use are not well-understood. It is also critical to understand the current treatment landscape for type 1 diabetes, especially outside the elite academic diabetes centers.

This initiative would support a clinical network to recruit youth with type 1 diabetes across diverse healthcare settings. Research supported by the initiative would: 1) describe treatment practices, 2) understand barriers to and facilitators of technology uptake in both health care providers/practices and patients/families, and 3) understand barriers and facilitators of diabetes self-management and treatment regimen adherence. Research would include a focus on social determinants of health, including factors that affect health care access and utilization, as well as patient-reported outcomes. The overarching goal would be to describe the "state of care" of type 1 diabetes, as well as factors that influence care decisions by both health care practitioners and people with type 1 diabetes, to inform future interventional studies to improve clinical outcomes and reduce disparities.

The panel commented that this proposal was interesting. One suggestion was for the study to also include family members and others in the participants' support system to identify barriers and facilitators. Another suggestion was for the study to examine the interactions between the participants and their health care practitioners through some sort of observational component, to determine whether provider assumptions change patterns of care. The panel also noted that this type of study might also be valuable if performed at all stages of diabetes duration, not just in new-onset type 1 diabetes. One concern raised was that recruitment might be an issue and that the focus on recruiting in diverse healthcare settings might make it difficult to achieve the desired number of participants. Thus, it was noted that investigators with experience in recruitment and retention of underserved populations could be beneficial.

Decreasing Diabetes Distress in Individuals with Type 1 Diabetes
Primary discussants: Dr. Vicki Helgeson, Dr. Michael Rickels

The constant self-management demands of type 1 diabetes, as well as fear of complications, are associated with diabetes distress, a negative emotional response to the chronic burden of living with the disease. Diabetes distress may significantly impact adherence to medication and other self-care behaviors and has been linked to higher hemoglobin A1c levels. However, it is not known whether ameliorating diabetes distress will lead to improved self-care and better glycemic management. Furthermore, the most efficacious and cost-effective approaches for ameliorating diabetes distress have not been determined.

This proposal would seek to support clinical trials testing interventions targeting diabetes distress in individuals with type 1 diabetes and/or their caregivers, with the goal of understanding whether lowering diabetes distress will improve glycemic control and quality of life. These trials

would be encouraged to reflect a practical, team-based approach to screening for and treatment of diabetes distress that could realistically occur in an average clinical setting.

The panel commented that reducing diabetes distress is an important goal, regardless of whether it results in better clinical outcomes. The panel noted that there is a larger pool of scientific publications on diabetes distress in people with type 2 diabetes than type 1 diabetes and encouraged drawing from that pool when crafting the proposed Request for Applications (RFA). It was also noted that the health care system and health care practitioners can be a source of diabetes distress, so researchers could consider involving the health care system in this research. The panel also acknowledged that it may be difficult to tease apart the effects of diabetes distress from other factors such as glycemic control and the burden of self-management, as these factors tend to influence each other, and thus suggested encouraging researchers to have a longitudinal component to their application.

Hypoglycemia Unawareness and Hypoglycemic-associated Autonomic Failure in Patients with Type 1 Diabetes: Obstacles to Prevention
Primary discussants: Dr. John Buse, Dr. Elizabeth Seaquist

Severe hypoglycemia is the second most common cause of event-related admission to the emergency room and is associated with significant hospital care costs. Repeated episodes of hypoglycemia induce a vicious feed-forward cycle resulting in hypoglycemia unawareness and hypoglycemia-associated autonomic failure (HAAF), in which recognition of the need for external glucose is diminished, as are the internal metabolic responses necessary to increase circulating levels of glucose. People with type 1 diabetes with HAAF have a 25-fold increased risk of severe hypoglycemia, as well as increased morbidity and mortality. However, though some risk factors have been identified, there has been little progress towards preventing hypoglycemia unawareness and HAAF. Treatment of HAAF also remains elusive, partly because the biological and molecular mechanisms mediating the formation of these impairments in humans have not been identified. Many of the clinical studies investigating hypoglycemia, hypoglycemia unawareness, and HAAF are not actually conducted in people with HAAF or do not identify which people have hypoglycemic unawareness and HAAF. Therefore, there is inadequate data overall in the population suffering from this condition.

The goal of this proposal is to support new research in this area. The first step would be to hold a multidisciplinary workshop focusing on hypoglycemia unawareness and HAAF in people with type 1 diabetes to identify key scientific gaps. Topics to be addressed at the workshop would include: 1) primary care issues such as reporting of hypoglycemic events, identification of HAAF in individual patients, and identification of at-risk populations; 2) the use of new technologies and algorithms for detecting hypoglycemia and declines in blood glucose; 3) mechanisms contributing to hypoglycemia unawareness and HAAF; and 4) prevention and treatment of hypoglycemia unawareness and HAAF. Based on this input, an RFA focused on hypoglycemia unawareness and HAAF in people with type 1 diabetes could be developed.

The panel commented that this is an under-investigated area. They supported having a workshop prior to the release of an RFA, to help define the most important questions. The panel also discussed the large behavioral component required for adoption of technology. Also noted was

that definition of hypoglycemia unawareness needs to be refined, as does the ability to identify people who experience HAAF.

TOPIC 3: PANCREATIC PATHOBIOLOGY

Current Efforts in Pancreatic Pathobiology
Dr. Smith provided an overview of the current research portfolio, including discussion of an ongoing program in which funding decisions have already been made—the Human Islet Research Network-Human Pancreas Analysis Consortium (HIRN-HPAC).

Type 1 Diabetes and Exocrine Function
Primary discussants: Dr. Michael Rickels, Dr. Bruce Verchere

Recent studies confirm that pancreatic volume is decreased after the initial diagnosis of type 1 diabetes, and that a ~30 percent loss of pancreatic mass is observable within 3 months after disease onset. This loss of pancreatic mass is in excess of the effects of the loss of islet mass alone, which has been calculated to be 2 percent of total pancreas volume. In addition, studies of non-diabetic, anti-islet antibody-positive first-degree relatives of people with type 1 diabetes also reveal decreased pancreatic volume. These findings suggest that the loss of exocrine tissue mass is related to the autoimmune process, although the mechanism(s) of this loss of exocrine tissue, and the type of exocrine tissue lost, is unknown. Additionally, the loss of pancreatic exocrine function has multiple secondary effects which may adversely affect the health status of people with type 1 diabetes. Thus, identifying strategies to prevent and treat exocrine tissue loss in people with type 1 diabetes could improve health outcomes.

The goals of this proposal are: 1) to characterize the incidence, timecourse, and mechanism(s) of pancreatic exocrine dysfunction and tissue loss in type 1 diabetes; 2) to assess the interrelationship between endocrine and exocrine pancreas in the setting of autoimmune (type 1) diabetes compared to non-autoimmune (type 2) diabetes; and 3) to develop possible therapeutic strategies for the prevention and treatment of exocrine loss in type 1 diabetes.

The panel commented that this proposal addresses an interesting and novel area of research. They noted that type 1 diabetes is usually thought of as a disease in which the immune system specifically attacks the beta cells, but it may be necessary to think about the disease in the context of a much broader immune inflammatory process occurring in the pancreas. The panel thought that pursuing research in this area was high-risk but also high-reward, and could shed new light on type 1 diabetes pathogenesis. Suggestions from the panel included partnering with HIRN-HPAC; supporting research to improve biomarkers for exocrine pancreas function, potentially by partnering with other pancreatic experts (*e.g.*, in cystic fibrosis or pancreatitis); and studying the underlying biology that is contributing to the loss of exocrine tissue in type 1 diabetes, such as by using mouse models.

Type 1 Diabetes and Acute Pancreatitis
Primary discussants: Dr. John Buse, Dr. Michael Rickels, Dr. Maria Grazia Roncarolo

Acute pancreatitis results from acute inflammatory injury of the pancreas, due to duct obstruction, trauma, or the toxic effects of drugs, infectious agents, or metabolites; it accounts for over 300,000 hospital discharges per year in the United States. Recently, studies have revealed that 30-40 percent of patients developed diabetes or impaired glucose tolerance within 3-4 years of a single episode of acute pancreatitis. More surprisingly, the development of diabetes did not correlate with the severity of the index episode of acute pancreatitis. Additionally, the prevalence of diabetes occurring as a result of acute pancreatitis was assumed to be quite low until a recent study reported that cases of diabetes occurring after acute pancreatitis were almost twice as common as diabetes occurring after the development of chronic pancreatitis, and that the diabetes which occurred after acute pancreatitis required insulin therapy in more than 20 percent of cases, which was more than twice as frequent as in people with type 2 diabetes. These observations suggest that the occurrence of diabetes after acute pancreatitis is far more common than previously thought, and that the diabetes was significantly more insulin-dependent than type 2 diabetes.

The goal of this initiative is to examine acute pancreatitis as a cause of type 1 diabetes, including the frequency, classification, and evidence of autoimmunity in new cases of diabetes that occur after one or more episodes of acute pancreatitis.

The panel commented that conducting a longitudinal study would be the most informative approach toward answering key questions. They also suggested that this research be supported through a cooperative agreement grant mechanism so that the NIDDK could partner in the research. Suggestions from the panel included incorporating a broad genetic component and mechanistic studies; studying people who develop type 1 diabetes after treatment with checkpoint-inhibitor drugs, recognizing that there are additional factors to consider when studying those patients (*e.g.*, other therapies they are taking); and including international sites to study larger numbers of people. The panel also cautioned that the effort not be focused on a single hypothesis about how acute pancreatitis is causing type 1 diabetes, but rather should collect data that is broad enough to test several hypotheses.

Continuation of the Integrated Islet Distribution Program
Primary discussants: Dr. Mark Huising, Dr. Bruce Verchere

The Integrated Islet Distribution Program (IIDP) is an ongoing effort organized by NIDDK to enhance the availability and quality of human islets provided in support of type 1 diabetes research. The IIDP has facilitated many important scientific advances and accelerated the pace of human islet research. Given this success, demand for these valuable tissues continues. The IIDP now receives islets from five expert isolation laboratories and serves over 120 investigators pursuing peer-reviewed research programs focused on molecular and cellular features of human islet cell function.

The goal of this initiative is to renew support for a Coordinating Center that would be responsible for soliciting, implementing, and overseeing a national network designed to procure and distribute live human islets for basic research to an expanding research base of type 1 diabetes investigators.

The panel commented that this valuable program has been transformative for the human islet biology research community. They were pleased that IIDP has been supporting investigators new to the human islet biology field, as well as phenotyping islet preparations using standardized protocols—areas that they thought should continue in the next project period. The panel members also felt that IIDP should continue to coordinate efforts with the Network for Pancreatic Organ Donors with Diabetes (nPOD) and HIRN-HPAC and consider how to leverage assays that are being developed by the broader scientific community.

Immunology of Xenotransplantation Cooperative Research Program
Primary discussants: Dr. Michael Rickels, Dr. Bruce Verchere

Transplantation has emerged as an effective therapy for individuals whose type 1 diabetes is not adequately managed with exogenous insulin, as evidenced by the NIDDK- and National Institute of Allergy and Infectious Diseases (NIAID)-supported phase 2 and phase 3 trials of purified human pancreatic islets in people with type 1 diabetes and intractable severe hypoglycemic events. However, human pancreata for the manufacture of islets are severely limited. Xenotransplantation offers a promising alternative approach to treat refractory type 1 diabetes and end-stage organ disease. However, despite the many advances in xenotransplantation, immunological and physiological impediments to reliable engraftment, survival, and function of xenografts remain. NIAID's Immunobiology of Xenotransplantation Cooperative Research Program (IXCRP) conducts research using swine-to-non-human primate preclinical models of pancreatic islet, kidney, heart, lung, and liver xenotransplantation with the overall objective to understand and address immunological and physiological issues essential to xenograft engraftment, survival, and function.

The goal of this proposal is to support islet-focused projects of the IXCRP. Islet-specific opportunities and areas for further study include, but are not limited to: 1) the use of islet-specific promoters in pig genome editing to enhance islet engraftment, survival, and function; 2) strategies for pig islet isolation, encapsulation, viability, and implantation; 3) optimizing insulin production and maturation of neonatal islets; 4) evaluating clinically acceptable immunosuppression and tolerance strategies; and/or 5) identifying and addressing pathways of islet xenograft rejection and/or loss of function. Continued support for this multi-disciplinary, collaborative research program is critical to overcoming the remaining barriers to clinical translation of xenotransplantation.

The panel commented that this is an important and interesting program, especially with opportunities emerging from CRISPR/Cas9 technologies. Panelists noted that use of both the porcine beta cell and the non-human primate model are strengths of the program, and one suggested that these studies could also be used to gather mechanistic insights into grafting sites and methods of grafting.

TOPIC 4: BETA CELLS: ASSESSMENT AND THERAPIES

Current Efforts in Beta Cells: Assessment and Therapies
Dr. Smith provided an overview of the current research portfolio, including discussion of an ongoing program in which funding decisions have already been made—the Collaborative Islet

Transplant Registry. He also noted that ongoing investigator-initiated grants supported by the Program include two awards under "Consortium on Beta-cell Death and Survival (HIRN-CBDS)" (RFA-DK-14-021); one award under the "Type 1 Diabetes Pathfinder Award" (RFA-DK-15-030); three awards under "Therapeutic Targeting of the Human Islet Environment" (RFA-DK-17-003); six awards under "Competitive Collaborative Projects for Human Islet Biology" (RFA-DK-17-004); one award under "Discovery of Early Type 1 Diabetes Disease Biomarkers in the Human Pancreas [HIRN Consortium on Beta Cell Death and Survival (CBDS)]" (RFA-DK-17-021); eight awards under "Development of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for Type 1 Diabetes" (RFA-DK-17-030, RFA-DK-18-004); and one award under "Direct Phase II SBIR Grants to Support Biomedical Technology Development" (PAR-14-088).

In addition, awards are expected to be made under "Human Islet Research Network - Consortium on Human Islet Biomimetics (HIRN-CHIB)" (RFA-DK-18-011); "Human Islet Research Enhancement Center for the Human Islet Research Network" (RFA-DK-18-012); "Human Islet Research Network - Consortium on Modeling Autoimmune Interactions (HIRN-CMAI)" (RFA-DK-18-013); "Human Islet Research Network - Consortium on Targeting and Regeneration (HIRN-CTAR)" (RFA-DK-18-014); and "Development of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for Type 1 Diabetes" (RFA-DK-18-023).

Characterization of Islet-derived Extracellular Vesicles for Improved Detection, Monitoring, Classification, and Treatment of Type 1 Diabetes
Primary discussants: Dr. Mark Huising, Dr. Bruce Verchere

While the appearance of early-onset type 1 diabetes can be predicted in at-risk individuals through the detection of multiple autoantibodies in the blood, there are currently no molecular biomarkers to help diagnose and monitor the earliest signs of beta cell dysfunction. One possible approach to address this gap is by studying extracellular vesicles (EVs). EVs are nanoparticles released by most tissue types into the blood and other bodily fluids. The "cargo" carried by EVs changes in a dynamic fashion, reflecting environmental changes imposed on the cells of origin, and can serve as "liquid biopsies" for detecting the appearance of cellular dysfunctions or disease environments. Additionally, research suggests that islet-derived EVs may contribute to disease initiation or progression in human type 1 diabetes. Therefore, a greater understanding of the biology of islet-derived EVs and the development of tools to isolate and study them and their cargo, could open new avenues for assessing islet health, diagnosing early disease, improving classification of disease subtypes, monitoring treatment, and identifying new therapeutic targets.

One goal of this initiative is to support the development of efficient protocols for the isolation and molecular characterization from blood of populations of EVs produced within the human islet environment. Another goal is to understand their biological function and/or their possible involvement in type 1 diabetes initiation and progression.

The panel commented that identifying biomarkers of beta cell function and death is critically important. They stated that it is not yet clear whether islet-specific EV-based biomarkers hold more promise than DNA-based biomarkers. Therefore, they suggested focusing this initiative on

studying the biology of islet-derived EVs, with their potential as biomarkers being a small subset of the broader research area. Because this research as it relates to type 1 diabetes is at an early stage, the NIDDK might also consider making small pilot awards to jumpstart this field.

Engineering Immune Cells for the Monitoring and Therapeutic Targeting of the Pancreatic Environment in Type 1 Diabetes
Primary discussants: Dr. Alexander Marson, Dr. Maria Grazia Roncarolo, Dr. Jane Salmon

Means to detect initiation of type 1 diabetes prior to the development of widespread beta cell autoimmunity could facilitate the use of early therapeutic approaches to prevent the progression to early-stage type 1 diabetes. An outstanding challenge for early detection of type 1 diabetes is to develop non-invasive strategies to report on a disease environment developing in a small tissue compartment (the pancreatic islet) nested within the deeper layers of the body. One possible approach to accomplish this goal is to build on progress achieved in the cancer immunotherapy field by engineering immune cells to home to the pancreatic tissue, detect the appearance of cellular stress or damage during the earliest stages of the disease process, report on these events by producing a unique and easily detectable synthetic signal, and, ultimately, deliver therapeutic interventions.

The goal of this initiative is to support the engineering of immune cells to target the human pancreatic environment, to report on previously inaccessible information about diabetes initiation and progression, and to deliver therapeutic responses to restore islet health and prevent the progression to type 1 diabetes.

The panel commented that this proposal had potential to build on progress in the cancer field and benefit people with type 1 diabetes and other autoimmune diseases. They acknowledged that parts of the research are high-risk but are also high-reward. The panel suggested that NIDDK make the RFA broad enough so that researchers have flexibility to develop novel ideas. The panel also discussed an appropriate budget. Some panel members thought that the budget should be limited because the research is at such an early stage, while others thought that a larger budget would be needed to attract top researchers to study type 1 diabetes-related projects in this area.

Development and Testing of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for Type 1 Diabetes
Primary discussants: Dr. Michael German, Dr. Bruce Verchere

Even with significant recent progress in the field of islet transplantation, there is still limited viability of engrafted islets and even the most innovative immunosuppressive regimens required for transplant survival still have significant side effects. Therefore, there is a need to support new and emerging research for the development of novel technologies for bioartificial long-term cell replacement therapy without systemic immunosuppression.

The goal of this initiative is to stimulate and support innovative basic, translational, and clinical research in academic centers and small businesses for the development of novel and supportive technologies to improve cell replacement therapies. For example, research could be supported to: improve delivery technologies and implantation strategies, including the development of

novel and safe immune-protective strategies, devices, bio-hybrid platforms, and encapsulation technologies; expand cell sources and functional testing; and optimize generation, differentiation, maturation of novel cell sources plus islet/islet cells isolation, preservation, transportation, *ex vivo* expansion, and long-term storage methods to improve access to replacement/transplantation interventions.

The panel commented that this proposal is critically important. They stated that the proposed budget was too modest to address all the suggested research areas and felt that a larger investment of funds could help to propel progress in this field. They suggested that NIDDK make the RFA broad enough so that researchers can develop creative and novel ideas. The panel also suggested that a way to promote success in this area would be to encourage collaborations among experts in immunology, gene therapy, and bioengineering.

Triggers and Biomarkers of Early Type 1 Diabetes (Human Islet Research Network Consortium on Beta Cell Death and Survival)
Primary discussants: Dr. Michael German, Dr. Mark Huising

Starting in 2014, NIDDK established a new team science program, the Human Islet Research Network (HIRN), with an overall mission to better understand how human beta cells are lost in type 1 diabetes, and to find innovative strategies to protect or replace functional beta cell mass in people with diabetes. The HIRN program is configured as a modular network of small research consortia, each defined by a specific set of research priorities. The HIRN-Consortium on Beta Cell Death and Survival (HIRN-CBDS) is one of the four founding HIRN consortia. Since its inception, HIRN-CBDS investigators have used human pancreatic tissues and islets to discover biomarkers of asymptomatic type 1 diabetes, explore cellular dysfunctions that may contribute to disease pathogenesis, and develop strategies to stop beta cell destruction early in the disease process.

The goal of this initiative is to expand HIRN-CBDS to include research to explore human pancreatic tissues to discover early biomarkers of type 1 diabetes pathogenesis, identify cellular and molecular events that may contribute to the asymptomatic phase of type 1 diabetes, develop clinical diagnostic tools for the detection and staging of early type 1 diabetes in at-risk or recently-diagnosed individuals, and identify therapeutic targets for the development of preventative or early treatment strategies.

The panel commented that this was an important area to pursue, particularly in light of the fact that research is now finding approaches to intervene in the type 1 diabetes disease process, so it is important to identify people who could benefit from those approaches. The panel was supportive of the proposal to increase focus on understanding the underlying biology of beta cell dysfunction, which could lead to the discovery of novel biomarkers or therapeutic targets. A panel member noted that it is possible that an ideal biomarker for beta cell death may not exist or at least not be detectable. Even if that turns out to be the case, they were still supportive of pursuing this research because information on how beta cells are damaged is critical for informing new therapeutic approaches.

HIRN Early Stage Investigator Pilot Award

Primary discussants: Dr. Mark Huising, Dr. Rama Natarajan

HIRN's overall mission is to better understand how human beta cells are lost in type 1 diabetes, and to find innovative strategies to protect or replace functional beta cell mass in people with diabetes. Two important aspects of this mission are to help build a highly interactive and diverse community of investigators focused on problems in human type 1 diabetes, and to foster the development of the next generation of diabetes researchers. One approach to fostering the development of junior investigators in diabetes research is to facilitate their career maturation to fully independent research positions. As such, in 2018, HIRN organized the first HIRN New Investigator Pilot Award competition that was open to any interested junior investigator from a U.S. research institution with postdoctoral experience, current early stage investigator status as defined by NIH (https://grants.nih.gov/policy/early-investigators/index.htm), and an interest in HIRN scientific priorities.

The goal of this initiative is to build on the success of the 2018 HIRN New Investigator Pilot Award and support a small number of new investigators of exceptional creativity who propose to apply bold and highly innovative new research approaches to biological problems under current investigation in HIRN.

The panel commented on the importance of mentoring junior investigators and encouraging their career development. However, they suggested that future initiatives be spearheaded by NIDDK, rather than by the HIRN Coordinating Center, to expand the program's reach. As such, panel members also thought that this program could be a model for supporting the career development of clinical researchers being mentored by *Special Diabetes Program*-supported clinical consortia.

TOPIC 5: DIABETES COMPLICATIONS

Current Efforts in Diabetes Complications

Dr. Smith noted that ongoing investigator-initiated grants supported by the Program include one award under "Neurocognitive Effects of Glycemic Dysregulation in Type 1 Diabetes" (RFA-DK-16-007). In addition, new awards are expected to be made under the following: "Understanding Skeletal Effects of Type 1 Diabetes" (RFA-DK-18-002) and "Establishing a Cohort to Clarify Risk and Protective Factors for Neurocognitive Complications of Pediatric Type 1 Diabetes - Planning Cooperative Agreements" (RFA-DK-18-007).

Preventing Early Renal Loss in Diabetes

Primary discussants: Dr. Thomas Gardner, Dr. Rama Natarajan, Dr. Ann Marie Schmidt

Diabetic kidney disease (DKD) imposes an extremely high social and economic burden on the country and on people with type 1 diabetes, and progress in treating DKD has advanced little over the last 20 years. Better understanding of the pathophysiologic processes leading to progressive DKD is urgently needed so that new targets for treatment can be discovered. NIDDK's *Special Diabetes Program*-supported Preventing Early Renal Loss in diabetes (PERL) is an ongoing double-blind, placebo-controlled, randomized clinical trial testing the hypothesis that serum uric acid reduction with allopurinol can prevent or slow DKD progression in

individuals with type 1 diabetes and mild-to-moderate glomerular filtration rate impairment. PERL represents a unique cohort of participants, including the largest, best-characterized cohort of those with both type 1 diabetes and mild-to-moderate glomerular filtration rate loss available for further longitudinal studies. PERL will be completed in June 2019, and results are expected to be reported later in 2019.

The purpose of this proposal is to support PERLage, a proposed observational long-term follow-up of PERL, that would extend the 3-year follow-up of PERL participants for an additional 5 years. The overarching goal would be to provide the platform and resources to discover novel determinants of progressive DKD and related outcomes via a large, standardized, observational cohort of individuals with type 1 diabetes-associated kidney disease. A primary focus would be the identification of underlying molecular pathophysiologic processes that explain and identify varied DKD sub-phenotypes and varied outcomes, which can lead to individualized therapies. The support of PERLage would allow researchers to advance understanding of DKD in those with type 1 diabetes through: (a) detailed delineation of the natural history of early DKD and associated non-renal outcomes, (b) investigation of clinical and molecular determinants of DKD progression and varied related outcomes, and (c) identification of potential novel therapeutic targets for treatment.

The panel commented that PERL/PERLage is a precious cohort of participants that could provide critically important information about a costly and debilitating complication of type 1 diabetes. They emphasized that gaining the maximum amount of information from the study samples should be a high priority, and that these samples will be extremely valuable to the scientific community as a whole. Other areas that the panel supported PERLage investigating were spatial transcriptomics of the kidney biopsies, genetic studies to identify protective genes or mutations, longitudinal sampling, comparisons with a control group of people with type 1 diabetes who have stable kidney function and using skin biopsies as stand-ins for longitudinal kidney biopsies. The panel agreed that the study needs to be funded adequately to perform its proposed work and that it could provide useful contrasting data to the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study, as the study populations have different characteristics. Panelists reiterated that there is a need for studies into kidney disease that do not exclude people with type 1 diabetes, as many industry studies do.

Continuation of the Diabetic Retinopathy Clinical Research Network
Primary discussants: Dr. Thomas Gardner, Dr. Katherine Tuttle

Diabetic retinopathy remains the leading cause of vision loss in the U.S. working age population and in other developed countries. Although therapies with anti-vascular endothelial growth factor (anti-VEGF) agents and laser are generally effective in improving visual outcomes, approximately 50 percent of patients with diabetic macular edema (DME) do not respond fully to these treatments. Thus, there is a critical and unmet need for safer and more effective novel therapies for diabetic retinopathy (DR) and DME. These approaches need to be affordable and scalable to reach the rapidly growing population of patients at risk for vision loss from diabetic eye complications. The National Eye Institute (NEI)'s DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network [DRCR.net]) provides the infrastructure to

conduct multiple concurrent and consecutive studies in DR and other retinal disease, with the ability to rapidly develop and initiate new protocols, incorporating standardization of multiple study procedures, utilization of novel technology, and extensive integration of information technology. Since its inception in 2002, the Network has successfully made numerous and substantial contributions to the improvement of visual outcomes in patients with DR.

The goal of this proposal is to provide support for the implementation of trials that meet the Network's objectives and advance the development of numerous interventions for DR. The Network's major goals over the next 5-year period include: 1) completing their 9 ongoing studies; 2) continuing to develop and implement protocols in a rapid and efficient manner while maintaining absolute scientific rigor and integrity; 3) maintaining a transparent and open collaborative Network; and 4) continuing to effectively disseminate trials results, treatment algorithms, and datasets to clinicians and other researchers.

The panel commented that the Network was of tremendous value and noted that its broad scope allows scientific achievement and translation at the point of clinical care to be effective. Panelists encouraged the Network to move towards learning how to treat earlier stage disease and prevention. Panelists felt that there was an opportunity to enhance the yield of studies with more systemic involvement of endocrinologists and other scientists to learn about the whole patient and the interrelationships between complications, such as through collaborations with other groups studying complications. The panel also encouraged the Network to consider new ideas for trial designs. A panelist also encouraged the Network to incorporate plans related to dissemination and implementation of positive results in the initial trial design to help encourage adaptation of those results to populations who could benefit from them, including those who live in remote or low-access areas.

Establishing a Cohort to Clarify Risk and Protective Factors for Neurocognitive Complications of Pediatric Type 1 Diabetes
Primary discussants: Dr. Vicki Helgeson, Dr. Elizabeth Seaquist, Dr. Katherine Tuttle

There is growing evidence that there are neurocognitive complications of type 1 diabetes, with approximately 28 percent of middle-aged adults and 48 percent of older adults meeting criteria for clinically significant cognitive impairment. However, age-related changes and vascular complications associated with type 1 diabetes in adults and older adults make isolating mechanisms complex, and clinical targets may be less modifiable as individuals age and disease burden increases. Therefore, research earlier in the developmental spectrum may help increase understanding of the mechanisms for neuropsychological complications of type 1 diabetes, critical periods for prevention and intervention, and strategies to mitigate the risk of these complications later in life. If specific risk or protective factors for adverse or optimal neurocognitive outcomes could be defined, treatment protocols could be developed to limit these neurocognitive complications.

This proposal would support a planning phase to determine whether a rigorous, adequately powered, national, multisite, observational cohort study to prospectively examine the risk and protective factors for neurocognitive complications of pediatric (onset approximately ages 5-10 years) type 1 diabetes could be designed and what resources would be required. Contingent on

the outcome of the planning phase and the availability of funds, this proposal would seek to support a consortium to complete the proposed study. The study would be expected to inform future research to decrease adverse neurodevelopmental outcomes and long-term neuropsychological sequelae of type 1 diabetes.

The panel commented that the neurocognitive effects of type 1 diabetes are an important problem that requires more study. The panel felt that it was important to study these neurocognitive effects in a pediatric population, to try to avoid other cognitive dysfunction due to aging in adults. It was also suggested that this work be hypothesis-testing, with thought given toward a possible intervention that could be tested if the proposed study yields positive results. The panel suggested that this study have a study population that represents underserved populations and include different levels of analysis, to find risk and resilience factors that are not just personal but also interpersonal, familial, and/or environmental. The panel discussed the importance of crafting the study with an appropriate comparison group to help identify effects due to diabetes versus those due to puberty, and that the neurocognitive effects of interest be adequately defined (*e.g.*, resilience, memory, attention, developmental deficits, *etc.*). Also mentioned was the advantage of linking the proposed study with a neurocognitive ancillary study to the DCCT-EDIC study, to determine whether duration of type 1 diabetes also plays a role in neurocognitive effects.

Biomarkers for Diabetic Foot Ulcers through the Diabetic Foot Consortium
Primary discussants: Dr. Ann Marie Schmidt, Dr. Katherine Tuttle

Diabetic foot ulcers (DFUs) are a frequent, devastating, and costly complication of diabetes. Each year in the United States, about 100,000 lower extremity amputations occur in people living with diabetes, including an estimated 5,000-10,000 amputations in people with type 1 diabetes. Most of these amputations are due to DFUs that develop a serious infection or do not heal. For ulcers that do heal, the median time to healing is 12 weeks. To date, clinical trials have not yielded any significant improvements in outcome. The last U.S. Food and Drug Administration (FDA) approval for a pharmacological agent to treat DFUs occurred in 1997. The lack of validated biomarkers impairs progress at every stage of drug development. There are no qualified biomarkers for DFUs, though recent studies have revealed many potential biomarker and therapeutic targets. Advancement of these findings requires the study of human tissues that encompass skin and microbiome changes due to long-term diabetes, the unique features of plantar skin and foot pressure, and the inflammation of chronic wounds. However, obtaining an adequate number of high-quality biosamples from well-characterized patients is a significant challenge for individual investigators.

This initiative would seek to support early analytical and clinical validation of biomarkers for diabetic wound healing to encourage innovative research. The initiative would leverage the resources of the NIDDK's existing Diabetic Foot Consortium and advance the research findings from the proposed Diabetic Foot Ulcer Niche program (see "Building a Cellular and Molecular Atlas of the Diabetic Foot Ulcer Niche"). The goal of this initiative would be to identify successful biomarker candidates that could undergo more extensive validation studies through the Diabetic Foot Consortium and receive approval from the FDA Biomarker Qualification Program for a context of use important for therapy development. These validated biomarkers

would be expected to help people with type 1 diabetes in the prevention and healing of foot ulcers through individualized therapies that could be based on these biomarkers.

The panel commented that DFUs are an important problem and a huge unmet need in diabetes treatment. The panel applauded the proposed approach as having several strengths, including a strong existing network of investigators, a milestone-driven approach, and the proven track record of the Diabetic Foot Consortium, which has already identified three strong candidate biomarkers. The panel encouraged consideration going forward of whether the biomarkers being investigated and vetted were meant to be prognostic (*i.e.*, to stratify the risk associated with certain wounds), predictive (*i.e.*, to predict a safe/efficacious response to treatment), or actionable (*i.e.*, to monitor mechanistic processes, for example during treatment), as the context in which a biomarker is expected to be used can help guide research. The panel had high hopes that this proposal could stimulate high-quality science in this area and help increase understanding of both host and microbial factors that affect this problem.

Building a Cellular and Molecular Atlas of the Diabetic Foot Ulcer Niche
Primary discussants: Dr. Michael German, Dr. Junhyong Kim, Dr. Ann Marie Schmidt

DFUs are a frequent, devastating, and costly complication of diabetes. Each year in the United States, about 100,000 lower extremity amputations occur in people living with diabetes, including an estimated 5,000-10,000 amputations in people with type 1 diabetes. Most of these amputations are due to DFUs that develop a serious infection or do not heal. For ulcers that do heal, the median time to healing is 12 weeks. To date, clinical trials have not yielded any significant improvements in DFU treatment outcome. The last FDA approval for a pharmacological agent to treat DFUs occurred in 1997. In addition to the lack of biomarkers that impedes drug development (see "Biomarkers for Diabetic Foot Ulcers through the Diabetic Foot Consortium"), this paucity of effective treatments is also reflective of a poor understanding of the microstructural, cellular, and molecular changes that underlie the inability of DFUs to heal. Research has tended to focus tightly on a limited number of pathways within a single or a few elements of the wound niche and to be conducted in relatively small numbers of patients. Thus, a significant gap in our understanding of the inability of DFUs to heal is a detailed, non-biased knowledge base of the effects of long-term diabetes on the cells and extracellular proteins of the skin, its structures, and the microenvironment prior to and during wound healing.

This initiative would seek to build upon foundational studies from the NIDDK's existing "Exploration of the Diabetic Foot Ulcer Niche" pilot program to provide an unparalleled spatiotemporal atlas of DFUs. This atlas would capture states across the development, persistence, and healing/non-healing spectrum of DFUs at the microstructural, cellular, and molecular levels. It would serve as a long-lasting community resource to enable assessment of the similarities and differences in microstructural, cellular, proteomic, microbiological, metabolic, and molecular alterations underlying DFUs to help identify novel potential biomarkers. This atlas would also enable the development of therapeutics for DFU prevention and treatment, as well as the development of new research models of DFUs.

The panel commented that this proposal is an important resource that is needed to drive progress toward advances in diagnosis and treatment of DFUs. The panel noted that single-cell biology is

particularly useful for this sort of atlas, where individual cell variation can be studied and contribute to the overall picture of the cells' ecological niche. Though the panelists did not think that this effort overlapped with other atlas projects that focus more on healthy tissues, they did encourage reviewing other atlas efforts to see what can be learned from similar projects, particularly in the area of analytic software tools that could be repurposed rather than developed anew. The panel also encouraged the proposal's focus on informatics that is specific to the diabetic foot wound niche, rather than a more generalized approach, so that the informatics data can be useful to inform that specific niche's research. The panel further encouraged this effort to have a strong immunological component, as well as microbial analyses, and for it to also consider whole genome/exome sequencing.

TOPIC 6: AUTOIMMUNE ETIOLOGY, CLINICAL TRIALS, AND EPIDEMIOLOGY

Current Efforts in Autoimmune Etiology, Clinical Trials, and Epidemiology
Dr. Smith provided an overview of the current autoimmune etiology, clinical trials, and epidemiology research portfolio, including discussion of ongoing programs in which funding decisions have already been made—"Programs to Standardize C-peptide and HbA1c Assays." Dr. Smith also noted that ongoing investigator-initiated grants supported by the Program include six awards made under "Mechanisms Underlying the Contribution of Type 1 Diabetes Risk-Associated Variants" (RFA-DK-15-025); one award under "Type 1 Diabetes Pathfinder Award" (RFA-DK-15-030); one award under "Immune System Engineering for Targeted Tolerance in Type 1 Diabetes" (RFA-DK-17-020); and one award under "The Characterization and Discovery of Novel Autoantigens and Epitopes in Type 1 Diabetes" (RFA-DK-17-031). Both RFA-DK-17-020 and RFA-DK-17-031 had two receipt dates, thus it is possible that additional awards will be funded under the second receipt date. In addition, new awards are expected to be made under "Mass Spectrometric Assays for the Reliable and Reproducible Detection of Proteins/Peptides of Importance in Type 1 Diabetes Research" (RFA-DK-17-019); "Funding for Collaborative Clinical Research in Type 1 Diabetes: Living Biobank" (RFA-DK-17-032); and "Mechanisms Underlying the Contribution of Type 1 Diabetes Disease-associated Variants" (RFA-DK-18-005).

Mechanisms Underlying the Contribution of Type 1 Diabetes Disease-associated Variants
Primary discussants: Dr. Rama Natarajan, Dr. John Rioux

Type 1 diabetes arises from the action of multiple genetic and environmental risk factors, and it has been estimated that the familial (heritable) risk for type 1 diabetes is ~40 percent, with the remainder due to non-genetic causes. Currently, more than 50 genetic loci have been identified to contribute to type 1 diabetes susceptibility, accounting for nearly 90 percent of the genetic risk in the Caucasian population. However, it remains challenging to pinpoint the causative genes and variants located in most of these regions. Furthermore, most of the lead genome-wide association study single-nucleotide polymorphisms for autoimmune diseases, including type 1 diabetes, are in noncoding, rather than protein-coding, regions of the genome, and their functions in disease pathogenesis are largely unknown. In parallel with advances in tools to highlight likely causal variants and effectors, the introduction of CRISPR/Cas9 genome editing is providing new opportunities for the direct functional interrogation of non-coding variants of

interest and the effector genes through which they are presumed to operate. The new technologies being developed will help us connect the many millions of non-coding variants revealed by whole genome sequencing to disease risk, increase our understanding of the biological pathways underlying disease and the specific biological targets that can alter disease, and provide opportunities for the development of new therapeutics and biomarkers.

The goal of this proposal is to support research to determine the mechanisms underlying the contribution of the disease-associated variants for type 1 diabetes. This proposal would recruit integrative teams and individual investigators to identify causal genetic variants and elucidate the mechanisms whereby changes in the function or regulation of these variants are likely to affect risk of type 1 diabetes.

The panel commented that this is the right time for this type of initiative due to advances in technology and knowledge generated thus far. One panelist encouraged research on epigenetics and studies looking at cell type-specific variants. The panel noted the similarities between this effort and the Accelerating Medicine Partnership-Type 2 Diabetes (AMP-T2D) project and felt that there could be efforts made to have these groups of scientists work together with respect to the portal to leverage the work being done by the AMP-T2D. A suggestion was made that this proposal could also include the opportunity to study the genetic risk of non-Caucasian populations, noting the recent rise of type 1 diabetes in Hispanic populations.

The Autoantigens and Neoantigens Role in the Etiology and Pathophysiology of Type 1 Diabetes

Primary discussants: Dr. John Rioux, Dr. Jane Salmon

Often, early stages of type 1 diabetes (pre-clinical) are indicated by the presence (in blood) of two or more autoantibodies with different specificities, including insulin, GAD65, IA-2, and ZnT8. Even though these major specificities have been known for many years and are used in the diagnosis of the disease, we still do not know what leads to the breakdown of immune tolerance, and we have a poor understanding of type 1 diabetes etiology and pathophysiology. Several new autoantigens and neoepitopes have been discovered using innovative technologies, and unbiased approaches to neoepitope identification are likely to continue to identify new specificities that could add to our ability to identify the disease in its earliest stages. A better characterization of the epitopes involved in the autoimmune response in different people could differentiate endotypes of type 1 diabetes, and lead to effective and safe, personalized therapies.

The main goal of this initiative is to characterize the function that autoantigens and neoantigens (including post-translationally modified proteins) play in the etiology and pathophysiology of type 1 diabetes toward the development of future therapeutics and to inform the use of autoantigens for monitoring disease progression and treatment. Examples of responsive projects could include: 1) discovery and analysis of antigens and epitopes in type 1 diabetes, especially related to identifying subgroups of patients and associated with clinical or other features, such as age, human leukocyte antigen (HLA) type, etc.; 2) studies of mechanisms of post-translational modifications during type 1 diabetes pathogenesis, especially at early stages; 3) approaches for the identification and discrimination of pathogenic responses from bystander or regulatory responses; and 4) development of model systems to allow the pathogenicity of epitopes to be

directly measured.

The panel commented that this was a strong and important proposal that would build on discoveries in other autoimmune diseases. One panelist commented that this research could identify new mechanistic targets to broaden understanding of the mechanism of disease and has great potential to expand the way we understand the generation and progression of autoimmunity. The same panelist noted that combining this research with current at-risk, longitudinal type 1 diabetes cohort studies offers great opportunity to generate new information about neoepitopes. Another panelist suggested that the HLA components could have a more prominent role in this proposal to prioritize discovery of neoantigens presented by specific *HLA* alleles. Similarly, another panelist commented that pairing discovery of neoantigens with detection of the antigen-specific T cell could give information on how relevant these neoantigens are in the T cell-mediated response and felt that this was important to include in the proposal.

Type 1 Diabetes TrialNet
Primary discussants: Dr. Betty Diamond, Dr. Maria Grazia Roncarolo, Dr. Jane Salmon

NIDDK's Type 1 Diabetes TrialNet (TrialNet) is an international consortium for clinical trials of disease-modifying therapy to delay or prevent disease progression. A few of TrialNet's accomplishments include: performing unique clinical trials, defining the stages of type 1 diabetes through natural history studies, demonstrating the impact of age on disease progression, and generating other mechanistic insights into the natural history of the disease and its response to therapy. All five of the immune agents now known to alter new-onset disease course through preservation of insulin secretion were tested in TrialNet or in conjunction with the Immune Tolerance Network (ITN), and two of those agents are now being tested by TrialNet in earlier stages of disease. TrialNet screens over 15,000 people annually, providing a critical and unique pathway for the identification of individuals for enrollment in type 1 diabetes prevention and progression trials. TrialNet has completed three multi-year prevention trials.

This proposal would seek to support new and ongoing activities of TrialNet. TrialNet's main goals would be: 1) to conduct clinical trials of disease-modifying therapy in those at high risk of developing type 1 diabetes and those newly diagnosed; 2) to discover mechanisms of disease, validate biomarkers, and identify therapeutic targets for type 1 diabetes; and 3) to describe the natural history of type 1 diabetes progression from antibody positivity until loss of insulin secretion. This proposed support would allow TrialNet to continue its efforts to address important questions, advance innovative trial designs, and improve upon the significant progress to date in bringing disease-modifying therapy forward.

The panelists commented that TrialNet is a unique and valuable program for its accomplishments, its level of engagement with the community, and its sharing of resources with the scientific community. The panel encouraged TrialNet to continue to focus on making recruitment more efficient and to fully utilize TrialNet samples as a resource for mechanistic studies of type 1 diabetes (*e.g.*, for epigenetic studies). Also discussed was the importance of continuing TrialNet so that participants can be followed for years after their trial to examine long-term effects of treatments. Finally, the panel noted that TrialNet is unique in its ability and

willingness to study combination therapies for type 1 diabetes, which are not often studied by industry.

Immune Tolerance Network
Primary discussants: Dr. John Buse, Dr. Maria Grazia Roncarolo, Dr. Jane Salmon
The ITN is an NIAID-led consortium dedicated to the advancement of tolerance-inducing therapies for the treatment of autoimmune diseases, asthma and allergic diseases, and for the prevention of graft rejection after kidney, liver, and pancreatic islet transplantation. The goals of the ITN with respect to type 1 diabetes are to: 1) develop and test novel immune therapies to prevent and treat type 1 diabetes through the induction of robust and long-lasting immunological tolerance, 2) develop and validate assays to monitor the impact of these therapies on type 1 diabetes disease progression, 3) gain new understanding of the immunologic mechanisms involved in the natural history and progression of type 1 diabetes and to use such information to formulate new treatment approaches, 4) develop bioinformatics and data analysis strategies for the interpretation of complex clinical and mechanistic data across type 1 diabetes trials and to define common features of immunity that may be shared between this and other autoimmune disorders, and 5) encourage and provide open access for the biomedical community to ITN's type 1 diabetes trial data.

This proposal would continue support for ITN studies specifically directed towards achieving clinical and mechanistic goals in immune tolerance in type 1 diabetes. These studies would build upon knowledge gained from previous trials and the ITN strategy of testing tolerance-inducing approaches in combination with in-depth phenotyping of immune responses.

The panel commented that the investment of *Special Diabetes Program* funds in ITN is an incredible value and the participation of the diabetes community in ITN allows investigators to leverage what is learned in other diseases. One panelist thought ITN has several unique strengths that bring value to the diabetes community, including ITN's focus on tolerance towards a cure and its solid network of investigators and standardized assays to perform mechanistic studies. Multiple panelists encouraged continued coordination and synergy between ITN and TrialNet.

Collaborative Research Using Subjects from Type 1 Diabetes Clinical Studies
Primary discussants: Dr. John Rioux, Dr. Jane Salmon

Ancillary studies to type 1 diabetes clinical studies enhance the value of large investments in NIH-funded clinical studies and repositories. Over time, new type 1 diabetes trials and studies are completed, and observational studies are expanded, resulting in the addition of samples to the collections and new opportunities for research in well-characterized participants. In addition, new mechanistic questions and novel technologies provide new research opportunities.

This proposal is intended to encourage projects requesting access to well-characterized and willing study participants in clinical studies—a "Living Biobank"—to accelerate the pace of scientific research towards more effective treatment and prevention of type 1 diabetes and its complications. Because specimens obtained through this initiative are obtained on demand, they are "replenishable," allowing exploratory research. Examples of participating studies include

TrialNet's Pathway to Prevention and the DCCT-EDIC study. Other studies could be included as well, such as artificial pancreas clinical trials. The supported ancillary studies would be expected to generate scientific discoveries to identify biomarkers that can be used as surrogate endpoints in clinical trials, to understand the disease course, and to understand pathogenic mechanisms. Where appropriate, a strong emphasis would be placed on highly collaborative, cooperative projects, designed to bring new topic experts to the parent consortium.

The panel commented that this proposal enriches a valuable resource, brings additional value to studies, and recruits new investigators and expertise to type 1 diabetes research. One panelist remarked that this initiative is an essential piece that compliments clinical trials and longitudinal cohorts and suggested that NIDDK ensure that it is broadly publicized.

Exploring Vaccination to Prevent Type 1 Diabetes
Primary discussants: Dr. Betty Diamond, Dr. Maria Grazia Roncarolo, Dr. Jane Salmon

It is possible that vaccines, normally used to stimulate immune responses and prevent specific infections, could be re-designed to down-regulate or re-direct the pathogenic immune response and prevent type 1 diabetes. A portfolio analysis of currently active (earliest award date 2015) NIH grants revealed that there are no grants with both "immune tolerance" and "vaccine" in the abstract or title, indicating a need for research in this area to increase the understanding, development, and validation of materials and processes that could be used in vaccines to induce tolerance or to redirect the immune response in type 1 diabetes.

The goal of this proposal is to support mechanistic and translational research toward the development and validation of materials and processes that induce antigen-specific immune tolerance or redirect the immune response in type 1 diabetes. Major interests include: 1) discovery and optimization of novel tolerogenic or immune-deviating adjuvants, tolerogenic pathways or combinations of tolerogenic compounds that that can be used with multiple autoantigens to suppress autoimmune responses in type 1 diabetes; 2) exploration of various delivery methods (nanoparticles, liposome, or covalent linkage) to optimize tolerogenic potential in the context of type 1 diabetes; and 3) evaluation of mechanisms of action using reproducible and robust preclinical models of tolerance induction in type 1 diabetes.

The panel commented that this proposal is an important and exciting area of research. One panelist suggested coordinating with NIAID's adjuvant research as well as with researchers investigating novel antigens to build synergies. Another noted that developing animal models that better replicate human disease would be extremely valuable for testing these concepts and paving the way to clinical application.

The Environmental Determinants of Diabetes in the Young
Primary discussants: Dr. Betty Diamond, Dr. Junhyong Kim, Dr. James Meigs

The Environmental Determinants of Diabetes in the Young (TEDDY) is an NIDDK-led observational cohort study with the goal of identifying environmental triggers of type 1 diabetes, such as infectious agents, dietary factors, and/or psychosocial factors, in genetically susceptible individuals. Identification of such factors will lead to a better understanding of disease etiology

and pathogenesis and may result in new strategies to prevent, delay, or reverse type 1 diabetes. TEDDY's international consortium of six Clinical Centers and a Data Coordinating Center completed recruitment in 2010. The study was designed to follow participants for 15 years, collecting data and biosamples, to accrue approximately 800 participants who develop autoantibodies and 400 participants who develop type 1 diabetes. As of December 2018, 797 participants have reached the primary endpoint (*i.e.*, appearance of one or more islet autoantibodies confirmed at two consecutive visits), and 334 participants have reached the second primary outcome (*i.e.*, development of type 1 diabetes).

Sub-proposal A: Continued Follow-up of TEDDY Subjects and Initiation of a Second Case-control Cohort Study

The purpose of this proposal is to support the continued follow-up of TEDDY participants and to initiate a second case-control cohort to replicate the findings and find triggers for later disease onset. Continued follow-up is needed to achieve the overall goals of TEDDY and to build on the investment to date. TEDDY plans to conduct analyses from participant samples in two phases. TEDDY has initiated the first phase of analysis of specific demographic, genetic, genomic, epigenetic, psychosocial, dietary, infectious agent, environmental, metabolomic, transcriptomic, and proteomic data and will relate these measures to the development of islet autoimmunity and type 1 diabetes, respectively. TEDDY intends to initiate the second phase in participants who have reached the endpoints at a later age, thus potentially representing a different phenotype of disease. The continued follow-up could lead to validation of the findings observed from the analysis of the case-control study, allow testing for other hypotheses for which additional power is needed, and identify heterogeneity in diabetes by studying participants who develop the disease at a much later point in their childhood.

Sub-proposal B: Follow-up of TEDDY Participants with Persistent Islet Autoimmunity Beyond Age 15 Years

The purpose of this proposal is to extend the scope of TEDDY to type 1 diabetes cases expected between ages 15-20 years—an age-range previously not studied using prospective cohorts. During the proposed follow-up, ~50 percent of the study participants who developed persistent islet autoantibodies will achieve 20 years of age. Late-onset islet autoimmunity, slowly progressing to diabetes, may lead to overt diabetes in adults, including classical type 1 diabetes, latent autoimmune diabetes, gestational diabetes mellitus, and phenotypes masquerading as type 2 diabetes. It is unknown what proportion of adult diabetes represents slowly progressing or transient islet autoimmunity. The heterogeneity of diabetes in young adults poses a perplexing research and clinical challenge. Extended follow-up of TEDDY participants for dysglycemia and diabetes could help to improve classification, diagnosis, and possibly therapeutic targets for these patients.

The panel commented that TEDDY is an important flagship program and that long-term follow up is critical and of scientific value. Panelists encouraged coordination and collaboration among TEDDY and other NIH-supported studies to improve validity and robustness of findings and to maximize the value of these studies. Panelists also urged greater coordination of bioinformatics across studies of type 1 and type 2 diabetes and encouraged ancillary studies using TEDDY data. They also noted the value of the TEDDY participants that have not developed autoimmunity for searching for protective factors.

SEARCH for Diabetes in Youth
Primary discussants: Dr. James Meigs, Dr. Elizabeth Selvin

SEARCH for Diabetes in Youth (SEARCH) is an NIDDK- and CDC-led, multi-center, epidemiological study conducted in geographically dispersed populations that encompass the racial/ethnic diversity of the United States. SEARCH is designed to characterize the epidemiology of both type 1 and type 2 diabetes in the population aged < 20 years, along with the associated complications, quality of diabetes care, and the quality of life of children and youth with diabetes. Scientifically, SEARCH includes two components: a registry and a cohort component. In 2015, for administrative purposes, the Registry and Cohort were separated into two separately funded entities. The *Special Diabetes Program* funds have been used to fund continued follow-up of the SEARCH cohort. Funds from NIDDK and the CDC have been used for ongoing surveillance to determine trends in diabetes incidence. Despite the two funding streams, the study remains one unified entity and has reported important findings. For example, SEARCH has highlighted the increasing burden of type 1 diabetes in minority youth. SEARCH has also demonstrated that approximately 1 in 3 teenagers and young adults with type 1 diabetes had at least one complication or co-morbidity at a mean age of 17.9 years and a mean diabetes duration of 7.9 years.

The goal of this initiative is to continue longitudinal follow-up of the SEARCH cohort. Focus areas in a new project period could include continued tracking of the evolution of complications as the cohort ages, which could provide valuable information to inform health system needs; continued and more in-depth study of the transition from pediatric to adult care and into young adulthood to better understand potential factors underlying the known decline in glycemic control associated with this transition and young adulthood; and conducting an in-depth study of health disparities and how they relate to health outcomes.

The panel commented that SEARCH is a landmark epidemiological study of diabetes in youth. They were supportive of the focus areas proposed for a new project period described above. The panel had concerns about the loss of minority youth over time and noted that this adversely affects the generalizability of the study's results. The panel was also concerned that the loss of minorities could make it more difficult to understand health services outcomes that would be a focus of the next project period. The panel also suggested that consideration should be given as to how SEARCH findings could be validated. Finally, the panel felt that, while the proposed topics areas for the next funding period were of interest, the proposal could be more ambitious and innovative. The panel also encouraged SEARCH to consider novel ways to collaborate with other research efforts that could analyze valuable SEARCH samples.

Enhanced Surveillance of Diabetes among Children, Adolescents and Young Adults through Measurement of Diabetes Autoantibodies and Genetic Risk Score: Supplement to CDC Surveillance Efforts
Primary discussants: Dr. James Meigs, Dr. Elizabeth Selvin

Public health surveillance of diabetes and its complications is crucial to track and characterize the burden of the disease, identify high-risk groups, develop strategies to reduce the burden of

this disease, formulate health care policy, and monitor progress of primary and secondary prevention programs. Accurate data is paramount to these activities. Type 1 diabetes is one of the most common chronic diseases of childhood, whereas type 2 diabetes is typically diagnosed in adults. Although type 1 and type 2 diabetes differ in their pathophysiologic process, the increased occurrence of type 2 diabetes in adolescence and the fact that type 1 diabetes can also arise in adulthood complicates the determination of diabetes type. Surveillance systems should be capable of distinguishing between these two major forms of diabetes. Previous research by SEARCH demonstrated that diabetes type can be classified by the presence of diabetes autoantibodies, and other research has demonstrated the ability of a genetic risk score to differentiate type 1 and type 2 diabetes in an adult population, suggesting strategies to produce more accurate diabetes surveillance data. Additionally, temporal changes in the way health care providers diagnose diabetes type may occur and it is therefore necessary to track over time how provider typing agrees with markers of diabetes etiology.

This initiative proposes to add measures of diabetes autoantibodies and genetic risk profile to diabetes surveillance efforts in the United States youth and young adult population. This approach would allow researchers to assess temporal trends in diabetes autoantibodies at the onset of diabetes in both youth and young adults, as well as to determine the degree of agreement between provider type and biomarkers/genetic profiling of diabetes type in this group. These measurements, combined with clinical features, will help with discriminating type 1 from type 2 diabetes in newly diagnosed diabetes cases across all U.S. major racial/ethnic groups.

The panel commented that progress still needs to be made in type 1 diabetes surveillance, though they questioned if the use of genetic risk scores would add useful information beyond the analysis of diabetes autoantigen status already in use. They noted that genetic risk scores are generally correlated and associated with disease outcome, but that such analyses do not usually change the classification of a person's diabetes type. There were also concerns that the current genetic risk scores (developed using data gathered predominantly from Caucasian people with type 1 diabetes) would require more development before being applied to a more racially/ethnically mixed population. The panel also noted that this proposal could confirm identified type 1 diabetes cases but would not help detect new type 1 diabetes cases, which might be a more prominent need.

Incidence of Type 1 Diabetes Among Young Adults: Diabetes in Young Adults Study
Primary discussants: Dr. James Meigs, Dr. Elizabeth Selvin

Half of the cases of type 1 diabetes occur in adulthood, but there are very limited data on the incidence of type 1 diabetes in the U.S. adult population. This is due partially to the difficulty in distinguishing between type 1 and type 2 diabetes in this segment of the population and in performing complete case ascertainment in fragmented health care systems. The CDC's Diabetes in Young Adults (DiYA) study filled these gaps by assessing the performance of a surveillance system for type 1 diabetes in a unique racially/ethnically diverse cohort of young adults. The main objectives were to: 1) develop and implement a case ascertainment strategy for the identification of new-onset diabetes cases among young adults; 2) develop and implement procedures for measurement of diabetes autoantibodies at time of diabetes diagnosis; 3) establish a diverse, population-based registry of incident cases among young adults; and 4) determine the

incidence of type 1 diabetes in this population. However, several questions remain, including how the clinical course of diabetes may or may not differ by diabetes autoantibody status, treatment, or demographic factors, and whether use of a genetic risk score for diabetes can assist in identifying individuals requiring insulin early in diabetes in a racially/ethnically mixed young adult population.

This proposal would support follow-up of the young adults with incident diabetes identified as part of DiYA for patterns in clinical care and treatment and health outcomes using data from electronic health records. Additionally, the proposal would support further analysis of stored blood samples for additional markers of autoimmune diseases, *HLA*, and/or genetic risk score. These additional analyses would allow DiYA researchers to investigate what factors affect the clinical course of diabetes and to further refine the utility of a genetic risk score for type 1 diabetes in determining clinical care.

The panel commented that accurate determination of type 1 diabetes incidence is an important topic and that more information is needed on how well type 1 diabetes cases are being identified in young adults. They questioned if the current diabetes genetic risk score field is mature enough for these risk scores to be useful in this population. The panel was concerned that the study's low response rate could affect the generalizability of the results, and that the healthcare system being studied might not accurately reflect most health care systems in America. Additionally, the panel noted that many young adults studied in DiYA will likely be diagnosed with type 2 diabetes, which would be useful data, but would offer limited insight into type 1 diabetes.

Support for Small Business Innovation Research to Develop New Methods and Technologies for Assessment of Risk and for Early Diagnosis and Prognosis of Type 1 Diabetes
Primary discussants: Dr. Betty Diamond, Dr. Jane Salmon

Early identification of type 1 diabetes risk and the onset of autoimmunity provides the basis for a variety of major ongoing studies seeking to prevent or delay the disease. Investigators have used a combination of islet autoantibody positivity, autoantibody seroconversion, biomarkers of genetic susceptibility, and beta cell functional assays as criteria to identify individuals at high risk of developing type 1 diabetes. However, current technology for identification of at-risk individuals is costly, requires the participation of research laboratories, and may not be suitable for public health screening that would ensue should effective preventative interventions be established. Methods for more efficient identification of individuals at risk of type 1 diabetes who may be eligible for preventative intervention would include low-cost, high-throughput, accurate and predictive assays/devices that could be used at the point of care level. A reissue of a previous initiative is considered important to continue promoting and supporting novel developments in this field as new biomarkers/assays/devices are needed.

The main goals of this initiative are for small businesses to create new technology resources to improve the identification of individuals at risk of developing type 1 diabetes, predict prognosis and monitor disease progression, and assess the efficacy of therapeutic interventions.

The panel commented that this research area was critically important, especially in light of progress toward identifying possible approaches to prevent or delay type 1 diabetes in high-risk

persons. They also suggested making TEDDY and TrialNet samples available to scientists conducting these studies, although it is not yet known if those samples would be representative of people in the general population. The panel thought that NIDDK could also try to attract companies that are developing epigenetic assays to quantify different immune cell types, as those assays are very sensitive and require a small volume of blood, and so could potentially be useful for this area.

ADDITIONAL DISCUSSION

The expert panel also identified topic areas in type 1 diabetes research that were not addressed in the proposals presented at the workshop. Fostering research in these areas could accelerate progress on the understanding, prevention, and treatment of type 1 diabetes and its complications. Areas of opportunity identified by the panel included:

- Learn how best to treat older adults with type 1 diabetes: Panelists discussed the gap in knowledge of how to best treat older people with type 1 diabetes who have no complications. The panelists noted that more research would help to determine whether intensive glycemic control will improve or worsen outcomes in these individuals.
- Investigate type 1 diabetes and pregnancy: Panelists noted that studies of the effects of pregnancy on people with type 1 diabetes and vice versa are needed. These areas, the panel felt, could be investigated through ancillary studies to existing cohorts.
- Study the effects of nutrition and diet in type 1 diabetes: Panelists noted that research is needed in this area. Additionally, obesity in type 1 diabetes was identified as an emerging clinical problem, and the panel stated that the effect of obesity on the risk of type 1 diabetes complications is still unknown.
- Advance understanding of beta cell biology: Stem cell maturation was identified as an area with great promise that would benefit from more detailed studies into how the islet supports maturation and what prevents laboratory-derived beta cells from becoming fully functional. It is also not known whether currently available strategies for producing beta cells in the laboratory from induced pluripotent stem cells are applicable across a variety of people with type 1 diabetes.
- Continue support for islet transplantation research: The panel noted that islet transplantation is a middle ground between high-risk/high-reward discovery research and more commercialized mature technologies such as the artificial pancreas, and that making islet transplantation available to people with type 1 diabetes would be a significant step forward. Towards that goal, the panel noted that continued efforts toward FDA approval of islet transplantation are important. Additionally, some panel members suggested that research in animal models to determine the best site for cell replacement therapies would be useful, as would advances in immunosuppression drugs.
- Support research on neurocognitive complications: The panel emphasized that neurocognitive complications of type 1 diabetes in adults are a concern and encouraged support of neurocognitive ancillary studies in existing cohorts, as well as studies of basic discovery research in this area.
- Leverage ongoing efforts to advance research on diabetic neuropathy: Panel members suggested that NIDDK consider ways to leverage ongoing NIH efforts to propel progress in combating diabetic neuropathy. For example, one possibility is to partner with scientists who are working to turn stem cells into neurons—an area that has seen progress—and develop

assays that can assess neuronal damage in diabetes, which could speed testing of new neuropathy drugs.

- Encourage research in cardiovascular disease: Panelists noted that this is a gap in the diabetes research portfolio that, despite challenges, still needs addressing. In particular, research is needed to determine whether mechanisms in cardiovascular disease are similar in type 1 and type 2 diabetes. If there are differences, then treatment strategies might need to differ.
- Utilize opportunities in type 1 diabetes genetics research: More information is needed on the epigenetics of type 1 diabetes, and large-scale studies of biobanked samples, monogenic diabetes, and/or drug-induced diabetes cases could be useful in understanding this phenomenon. Twin studies were mentioned as an opportunity to study the genetics and epigenetics of type 1 diabetes.
- Support research to refine risk scores: Panelists further felt that the various genetic risk score algorithms are promising but that there is still a need for rigorous evaluation before they are used on a larger scale. The panel also urged continued attention to engaging diverse populations in type 1 diabetes studies, including underserved minority populations, especially in type 1 diabetes genetics. As genetic risk scores and other genetic algorithms mature as a field, ensuring that those are useful in all racial/ethnic groups will be important.
- Determine a window of opportunity for interventions: For prevention studies, it remains to be determined whether there are critical periods of disease progression during which application of a short-term intervention might have a long-term effect.
- Understand rise in diabetic ketoacidosis (DKA): A panel member commented that DKA has become more common, particularly in older adults with type 1 diabetes. Thus, a research opportunity exists to study DKA in older adults and to find ways to prevent it in this population and thus improve health outcomes.
- Use system biology tools in type 1 diabetes research: The panel encouraged use of systems biology approaches similar to the National Cancer Institute's Cancer Systems Biology Consortium to examine the complex interactive effects of type 1 diabetes.
- Enhance patient engagement in type 1 diabetes research: The panel advised that more patient engagement is needed. For example, people with type 1 diabetes may find reduced glycemic variability, as opposed to complete insulin independence, a worthy endpoint for scientific success. Scientists were encouraged to seek the patient perspective when designing and recruiting for research studies.
- Recruit new talent to type 1 diabetes: The panel commented that fostering the recruitment of new researchers into the type 1 diabetes research field is important. Panelists felt that strategies such as making available funding for ancillary studies, pilot projects, and/or preliminary data-gathering opportunities in existing networks, studies, and consortia were a critical investment to encourage young investigators to enter the type 1 diabetes field and thus to ensure a strong pipeline of research talent for the future.
- Support collaboration: The panel encouraged collaboration in several different areas to derive the most scientific value from existing resources. First, the panel encouraged maximizing collaboration and coordination among different type 1 diabetes research networks, studies, cohorts, and repositories, so that common data sets could be crafted, biosamples and other resources could be shared, and operational and financial efficiency could be improved. Second, continued collaboration was encouraged between NIH Institutes, where overlap in research mission would facilitate partnerships (*e.g.*, in studies of type 1 diabetes during pregnancy and in cardiovascular complications of type 1 diabetes). Third, enhanced

collaboration was encouraged between type 1 diabetes and type 2 diabetes efforts, particularly in areas such as bioinformatics and "omics" efforts, where large numbers of participants are needed. Finally, strengthening collaborations and cooperative efforts, the panel felt, would be particularly useful in the area of type 1 diabetes complications, where study participants might have several complications that could be studied in parallel.

APPENDIX 1: PANEL MEMBERS

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APPENDIX 2: ACRONYMS

AMP-T2D	Accelerating Medicine Partnerships-Type 2 Diabetes
CDC	Centers for Disease Control and Prevention
CGMs	continuous glucose monitors
DCCT-EDIC	Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications
DFU	diabetic foot ulcer
DiYA	Diabetes in Young Adults
DKA	diabetic ketoacidosis
DKD	diabetic kidney disease
DME	diabetic macular edema
DMICC	Diabetes Mellitus Interagency Coordinating Committee
DR	diabetic retinopathy
EV	extracellular vesicle
FDA	U.S. Food and Drug Administration
FOA	Funding Opportunity Announcement
FY	fiscal year(s)
HAAF	hypoglycemia-associated autonomic failure
HHS	U.S. Department of Health and Human Services
HIRN	Human Islet Research Network
HIRN-CBDS	Human Islet Research Network-Consortium on Beta Cell Death and Survival
HIRN-CHIB	Human Islet Research Network-Consortium on Human Islet Biomimetics
HIRN-CMAI	Human Islet Research Network-Consortium on Modeling Autoimmune Interactions
HIRN-CTAR	Human Islet Research Network-Consortium on Targeting and Regeneration
HIRN-HPAC	Human Iselt Research Network-Human Pancreas Analysis Consortium
HLA	human leukocyte antigen
IIDP	Integrated Islet Distribution Program
ITN	Immune Tolerance Network
IXCRP	Immunobiology of Xenotransplantation Cooperative Research Program
NEI	National Eye Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
nPOD	Network for Pancreatic Organ Donors with Diabetes
PERL	Preventing Early Renal Loss in diabetes study
RFA	Request for Applications
SBIR	Small Business Innovation Research
SEARCH	SEARCH for Diabetes in Youth
TEDDY	The Environmental Determinants of Diabetes in the Young
VEGF	vascular endothelial growth factor