PATHWAYS TO HEALTH FOR ALL

Heterogeneity of Diabetes

Final Report

Report of the
Working Group of the
NIDDK Advisory Council

National Institute of Diabetes and Digestive and Kidney Diseases

Colleagues and Friends,

During 2025, we at NIDDK celebrated our 75th Anniversary and, as has been the case over our storied history, we remain committed to our mission. NIDDK's mission is to conduct and support medical research, research training, and to disseminate science-based information on diabetes and other endocrine and metabolic diseases, digestive diseases, nutritional disorders, obesity, and kidney, urologic, and hematologic diseases to improve the health and quality of life of all individuals. The diseases of interest in our mission are some of the most common, chronic, consequential diseases and conditions affecting people in this country.

These diseases of interest to NIDDK are very costly at an individual and national level given the enormous physical and mental burden associated with the diseases. Diabetes, in particular, carries an unsustainable economic cost. In 2022, the total estimated cost of diagnosed diabetes in the U.S. was $412.9 billion, including $306.6 billion in direct medical costs and $106.3 billion in other costs attributable to diabetes. This was an increase of over $80 billion since 2017!

To ensure that NIDDK research is pursuing pathways to health for all individuals and addressing the diabetes burden, it is paramount that we develop innovative ways to improve health for those at risk as well as those who have diabetes. To achieve this goal, we need continued research that would allow more targeted and efficient approaches to prevention, diagnosis and management of diabetes and its complications. This is a challenging task, particularly as significant heterogeneity of diabetes exists within our nation as well as in countries across the globe. There are multiple metabolic pathways that contribute to risk of diabetes and these pathways are not captured in the current definitions of diabetes. We also recognize that a major limitation to advancing precision diabetes medicine by addressing heterogeneity of diabetes is the reliance on a single clinical marker (elevated glucose) for diagnosis and management of risk and disease.

To address the complex issue of how diabetes develops and the paths to implementing precision diabetes medicine to improve health for all, we need to acquire a better understanding of the current state of diabetes in research and clinical practice. We want to insure that NIDDK scientific staff will be equipped with a clear understanding of the gaps in knowledge as well as the research opportunities that can be used to achieve a better understanding of heterogeneity of diabetes. In order to attain our goal of implementing precision diabetes medicine, the Heterogeneity of Diabetes Working Group of the NIDDK Advisory Council was formed in January 2023.

Since approval, Working Group members have developed a comprehensive set of Recommendations and Opportunities across all phases of research that are required to fully elucidate and understand heterogeneity of diabetes. I am pleased to share that NIDDK is implementing programs to advance our understanding of heterogeneity of diabetes. These programs, along with past research efforts, will provide impactful data that will be leveraged by new research based upon the Recommendations of this Working Group. Together, the research supported by the NIDDK will continue to accelerate progress on understanding and developing new approaches to address the heterogeneity of diabetes.

I thank the Working Group on behalf of NIDDK for their outstanding work and tireless efforts for this report. The NIDDK is optimistic that, with continued research investment in diabetes heterogeneity, successful achievement of many of the Opportunities presented under each Recommendation will be actionable and will lead to meaningful reclassification of diabetes in the future and advancements in precision diabetes medicine.

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Table of Contents

Introduction

NIDDK MISSION AND STATUTORY AUTHORITY

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was established in 1950 as part of the National Institutes of Health (NIH) and acquired its current name in 1986. As authorized by Sections 426-434A of the Public Health Service Act [42 U.S.C. 285c – 285c-9], the mission of the NIDDK is to conduct and support medical research and research training and to disseminate science-based information on the following topics to improve people's health and quality of life: diabetes and other endocrine and metabolic diseases; digestive diseases, nutritional disorders, and obesity; and kidney, urologic, and hematologic diseases.

This Report outlines research Recommendations from the NIDDK's Working Group of Council on Heterogeneity of Diabetes, a result of tremendous effort and significant contributions from global investigators and NIDDK staff. This Report complements and builds on opportunities outlined in NIDDK's 2021 Strategic Plan for Research. The Strategic Plan elaborates on specific research needs and opportunities that NIDDK could pursue to accelerate research into the causes, treatment, and prevention of diseases and conditions under the Institute's mission. Along with other strategic planning efforts, it also guides the Institute's approaches to build on scientific discoveries, pursue promising research avenues, and maximize the public investment in research. A scientific goal in the 2021 NIDDK Strategic Plan for Research is to *"Advance understanding of biological pathways and environmental contributors to health and disease."* Thus, the Recommendations from the Working Group complement the NIDDK Strategic Plan for Research and provide research opportunities to advance the Institute's mission and to further understanding of biological pathways and environmental contributors to health and disease particularly as it relates to diabetes.

Framing of this Report

The current classification of diabetes had its genesis over 85 years ago, when individuals with diabetes were first subclassified into insulin sensitive and insulin insensitive states based on the response to an oral glucose tolerance test. The classifications of type 1 diabetes and type 2 diabetes in use today were coined over 35 years ago. However, it is well recognized that even within these conventional classifications significant heterogeneity of disease exists across individuals and across the world's diverse populations. Moreover, our current understanding of the pathophysiology of diabetes and the contributions of multiple metabolic pathways are not captured in the current diabetes classifications.

Although it is recognized that certain classifications of diabetes such as type 1 diabetes and monogenic diabetes may be associated with specific biomarkers (e.g., islet autoantibodies, genetic variants), the major limitation of these broad classifications remains over-reliance on a single clinical marker (i.e., elevated glucose) for diagnosis and management. We now know, however, that multiple etiologic and pathogenic processes lead to both type 1 diabetes and type 2 diabetes, reflecting significant heterogeneity in factors associated with initiation, progression, and clinical presentation. Thus, increasing our understanding of heterogeneity of diabetes across the global scientific community and the diabetes ecosystem will greatly inform progress in diabetes care *per se* and especially in the emerging domain of precision diabetes medicine.

Statement of the Problem to be Addressed

Conceptually, and as a broad overview of the topic, one may suggest that the future of research on stratified diabetes medicine (i.e., precision diabetology) may rely on a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human genome and phenome, as outlined elsewhere (Figure 1).[1] Understanding these complex interactions in the context of the environment in which the individual lives (e.g., social and community context, health care access and quality, economic stability) holds the key to unlocking the tremendous potential of precision medicine. In moving forward, it is envisioned that precision medicine approaches will yield: 1) validated biomarkers to inform on diabetes subtypes and improve diagnosis and classification; 2) more precise and targeted therapeutic, behavioral and technology driven strategies for management; 3) earlier identification and more effective prevention of complications; and 4) optimization of interventions for prevention across the world's diverse populations. However, a major barrier to achieving these goals and in fulfilling the promise of precision diabetes medicine is to adequately elucidate the disease's heterogeneity and to recognize that diabetes is a multifaceted condition, representing the outcomes of numerous related disorders with varying causes and manifestations. Improving understanding of the factors contributing to heterogeneity within and between diabetes types will enable the scientific community to develop treatment approaches that more effectively target specific patient subgroups, improve patient outcomes and potentially lead to new therapies. In this regard, there has been significant interest in this area and significant progress and advances recently reported.[2]

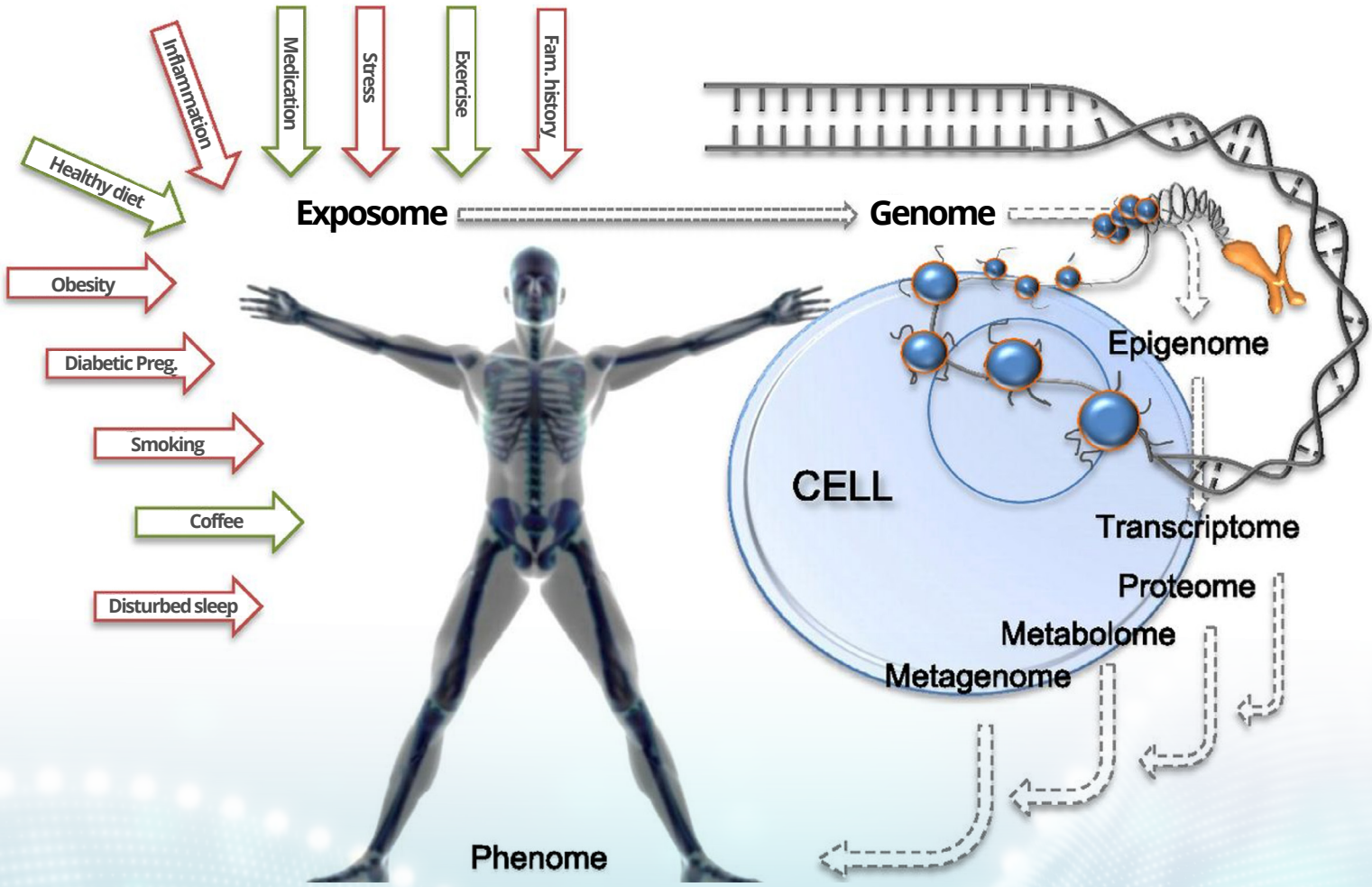

Figure 1: Future of research on stratified diabetes medicine. From Franks PW et al[1]

To gain a deeper understanding of heterogeneity of diabetes and use this to strengthen clinical care, we must first consider current management approaches in practice. Examples of current management approaches were recently reviewed by the Executive Committee of the Working Group of Council (WGOC) for both monogenic diabetes and for type 2 diabetes.[3] Specifically, in monogenic diabetes, a collection of single gene disorders, the specific subtypes can be accurately diagnosed using gene sequencing and often managed with specific pharmacological agents, thereby exemplifying precision medicine through a granular stratification of the diagnosis and optimization of diabetes care.[4] However, in type 2 diabetes, a highly complex trait, individuals present with heterogeneous phenotypes and different degrees of abnormalities based on multi-system contributions to the pathophysiology. Specifically, in any given individual with type 2 diabetes, hyperglycemia may be attributable to a combination of etiological characteristics, typically involving deficiencies in insulin secretion and quality, excessive hepatic glucose production, peripheral insulin resistance, and deficient gut-brain signaling, which exist in the context of different environmental factors.[4] In many, but not all, people with type 2 diabetes, excess adiposity is a key driver of many of these metabolic abnormalities.

An important limitation of current diabetes standards-of-care is that, despite the widely recognized diversity in etiology, presentation, treatment requirements and prognosis, the foundational evidence relies on population-average risk factor susceptibility and treatment response. Understanding and leveraging this heterogeneity will require separating "signal" from "noise," a major challenge as the heterogeneity spans etiology, clinical presentation, and prognosis.[2] Key sources of heterogeneity of diabetes were elegantly reviewed in a recent International Consensus Report that identified gaps and opportunities for the clinical translation of precision diabetes medicine.[2] Within each of these domains, sources of heterogeneity are identified by discovering markers of causal processes that distinguish variation in (1) diabetes susceptibility and (2) response to therapies (Figure 2).

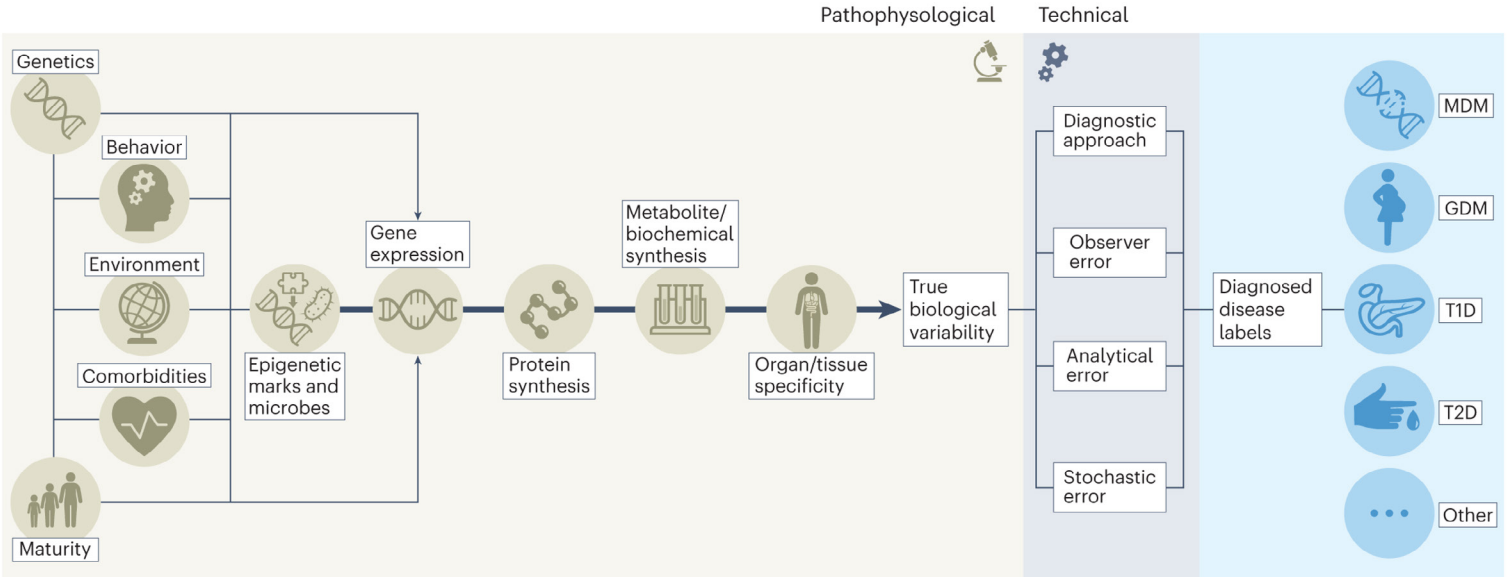

Figure 2: The success of precision diabetes medicine will be enhanced by successfully leveraging heterogeneity of diabetes. To do so will require parsing "signal" from "noise"; the figure illustrates the key sources of heterogeneity within each of these domains. From Tobias DK et al[2]

Key: Monogenic diabetes mellitus (MDM), Gestational Diabetes Mellitus (GDM), Type 1 diabetes (T1D) and Type 2 diabetes (T2D)

Progress to Date

Clinical Subtypes

The many known challenges that confront our ability to meaningfully address diabetes heterogeneity have motivated global efforts to develop sub-classification approaches for type 2 diabetes prediction, prevention, and care, with particular focus on subclassification using a range of analytical methods. Several recent reviews overview the range of available analytical approaches, including the use of simple criteria based on categorization of clinical features, biomarkers, imaging, and other parameters rather than approaches that use machine learning incorporating clinical data and/or genomic data.[5] Many simple approaches to subclassification have been tried but replication remains a concern, and it is unclear which of these approaches are likely to advance clinical care. More complex stratification, using machine learning applied to clinical variables, yield reproducible subtypes of type 2 diabetes, each conveying different relationships with major clinical outcomes. However, both approaches still require a higher grade of evidence. Proof-of-concept data have been reported from studies designed to demonstrate that pathophysiologic heterogeneity exists before diagnosis of type 2 diabetes. The report highlighted groups of individuals who have increased rates of progression to overt type 2 diabetes and risk of complications.[6]

Other major advances in diabetes subclassification over the last decade were based on the analysis of data from 8,980 Swedish patients with newly diagnosed diabetes that used a "hard (k-means) clustering" machine learning approach for a data-driven classification of diabetes subtypes ("Ahlqvist" clusters).[7] These clusters were derived based on six variables: GAD antibodies, age at diagnosis, body mass index, HbA1c, and Homeostasis Model Assessment 2 estimates of beta-cell function and insulin resistance. The five replicable clusters of individuals with diabetes obtained from this approach were reported to have significantly different clinical characteristics and complications risk. In addition, the relationship between the five subtypes and incident events (e.g., use of hypoglycemic medication, achievement of treatment goals, and diabetes complications) was determined and validated in independent cohorts. Since the publication of the Ahlqvist clusters, more than 30 replication studies have been published in epidemiological cohorts and cardiovascular outcome trials (i.e., ORIGIN, DEVOTE, LEADER, and SUSTAIN-6).[5, 8-10] However, these studies do not provide basic, but essential, comparisons against standard prediction models.[2]

Recognizing that variables may change with disease progression and treatment (i.e., cluster migration), genetic data have been used to assign diabetes into plausible etiological subtypes using the pPRS (partitioned polygenic risk scores) approach with five clusters identified, two related to insulin deficiency and three to insulin resistance.[11] In an independent study, similar analyses were undertaken and these pPRS clusters validated.[12] More recently, the pPRS method was extended to incorporate multiethnic data, resulting in the expansion of the number of diabetes subtypes from 5 to 12.[13]

Molecular Signatures for Diabetes Subtypes

Given the advances and observations to date in diabetes subtyping outlined above, an important research goal would be identifying the molecular signature for each individual subtype. In this regard, and as recently reviewed by the Executive Committee, significant progress has been made in elucidating the molecular etiology of individual subtypes that included genetic approaches as well as ongoing molecular research using cell lines, organoids, and model systems.[13] For example, a recent report applied the k-means hard-clustering method to 650 genetic variants associated with type 2 diabetes and another 110 genetic variants in diabetes-related traits (e.g., fasting insulin, fasting glucose) in ~1.4 million participants of diverse genetic ancestry.[13] It was reported that twelve genetically informed clusters were enriched for specific single-cell regulatory regions, consistent with most type 2 diabetes-associated variants residing in enhancer regions, that differ in distribution by genetic ancestry, reflecting the ancestral diversity of the cohorts included in the analysis. In addition, the overlap in the genetic composition of scores in type 2 diabetes with other traits (e.g., higher proportion of lipodystrophy-related risk in East Asian ancestry) suggested that the genetic clusters could provide insights into potential biological mechanisms underlying disease heterogeneity.

Clustering has been used to assess multi-omic contributions to diabetes heterogeneity. A subset of individuals were clustered on five clinical characteristics and evaluated using genetic, metabolomic, lipidomic, and proteomic approaches.[14] Individual clusters did appear to have specific molecular multi-omic signatures. An insulin-resistant cluster exhibited the most distinct molecular signature (i.e., higher branched-chain amino acid, diacylglycerol, and triacylglycerol levels) while the obesity cluster exhibited higher levels of cytokines. Furthermore, individuals that were identified in the mild diabetes cluster were characterized by elevated high-density lipoprotein levels, and had levels of biomarkers associated with reduced diabetes risk, in contrast to those in the insulin-resistance cluster. Taken together, the clustering and multi-omic membership in the clusters were reported to provide insights into possible molecular mechanisms of diabetes heterogeneity related to pancreatic islets, liver, and adipose tissue metabolism.[3] Collectively, these and other reports continue to inform the field by providing evidence that type 2 diabetes subtypes may have specific molecular etiologies contributing to the clinical presentation of disease and its apparent heterogeneity. However, further work is needed to reconcile and determine how to utilize the various approaches that have been described. Many of the research opportunities presented in this Report should enhance our understanding of the molecular foundation of diabetes subtypes.

Ongoing and Planned Research Efforts

This Report from NIDDK's WGOC represents a logical progression of past research activities and currently funded research programs that will continue to advance our understanding of heterogeneity of diabetes. Specifically, the following key initiatives were reported by the Executive Committee as having significantly influenced the development of NIDDK's Working Group Report on the heterogeneity of diabetes.

Precision Medicine in Diabetes Initiative (PMDI)

Precision Medicine in Diabetes Initiative (PMDI) launched the ADA/EASD Precision Medicine in Diabetes Initiative (PMDI) in January 2018. The PMDI established a mandate to develop consensus on the viability and ultimate clinical implementation of precision medicine for the diagnosis, prevention, treatment, prognosis, and monitoring of diabetes. In October 2019, a global consensus meeting involving various stakeholders from academia, industry, funders, and people with diabetes was held, which helped inform the First ADA/EASD Consensus Report on Precision Diabetes Medicine.[15] The report provided common language to describe precision diabetes medicine through which five core "pillars" were described: diagnostics, prevention, therapeutics, prognostics, and monitoring. Critical gaps in knowledge were identified, as well as the evidence required for the scientific advancement, implementation, and ongoing evaluation of precision medicine in diabetes. The PMDI launched an evidence-based, systematic review of the scientific literature in 2020 on precision diabetes medicine across four of the five pillars (excluding monitoring) in monogenic diabetes, type 1 diabetes, type 2 diabetes, and gestational diabetes that was conducted by over 200 investigators from 28 countries worldwide. Systematic literature reviews continued across 15 working groups (published as a collection), with the Second Consensus Report describing the need for common standards for clinical readiness, consideration of cost-effectiveness, health equity, predictive accuracy, and liability and accessibility of technologies and biomarkers, with key milestones for clinical implementation outlined.[2]

All of Us Research Program

The National Institutes of Health created the All of Us Research Program to improve individualized (precision) health care by collecting existing data from electronic health records and generating new data on 1 million participants in the United States. The All of Us Research Program is dedicated to building a database of varied individuals at many levels related to lifestyle, environment, and biology. Data are available through the All of Us Researcher Workbench. All of Us protocols have generated extensive data related to diabetes and obesity, with reports that illustrate the use of family history information for prevention of diabetes, obesity, and heart and blood disorders and the utility of treatment with sodium glucose co-transport 2 inhibitors and glucagon-like peptide-1 receptor agonists in underrepresented populations.[16,17] Whole genome sequence data and genome-wide genotyping data are available in the All of Us Researcher Workbench on study participants, nearly all of whom also have linked electronic health records (EHR) data or survey data, through a higher tier of controlled certification for researcher use.[18]

Rare and Atypical DIAbetes Network (RADIANT)

Rare and Atypical DIAbetes Network (RADIANT) is a network of universities, hospitals, and clinics in the United States, supported by the NIDDK, established to better understand atypical diabetes. Atypical diabetes includes some features seen in type 1 and type 2 diabetes but also lacks other characteristics of those common diabetes types, with many uncharacterized forms. The RADIANT investigators have a systematic approach to participant ascertainment, enrollment, and evaluation, including biochemical analyses, autoantibody testing, and DNA and RNA extraction and sequencing.[19,20] RADIANT uses a data-mining approach to identify and cluster phenotypes of atypical diabetes that can be used to establish likely patterns of clinical and biological data with discrete subtypes of atypical diabetes.[21,22]

Diabetes Related to Acute Pancreatitis and its Mechanisms (DREAM)

The NIDDK supported the Type 1 Diabetes in Acute Pancreatitis Consortium (T1DAPC) in 2020 and subsequently launched the Diabetes Related to Acute pancreatitis and its Mechanisms (DREAM) study to address knowledge gaps through an observational cohort study design.[23] The incidence of acute pancreatitis is increasing in the United States, with health care costs approaching $2B with complications including development of type 2 diabetes in ~25% of cases. DREAM study recruitment was initiated in 2021 and completed in 2024.[24] DREAM is designed to address knowledge gaps to provide the evidence needed to screen for, prevent, and treat diabetes following acute pancreatitis. In addition, it will focus on discovery of genetic and other factors associated with acute pancreatitis to advance prediction, treatment, and prognosis of disease.

COVID-19 and Diabetes Assessment (CODA) Study

In people who had COVID-19, there has been ~50% increase in risk for new-onset diabetes (usually type 2 diabetes) compared with people who never had COVID-19, although the range in risk varies by studies, suggesting multiple factors may explain the heterogeneity of response to exposure.[25,26] The length of time that diabetes remains post-COVID-19 infection is uncertain, with some studies suggesting that diabetes is transient while others suggest it is persistent; the risk may also depend on genetic or other risk factors.[27] CODA aims to answer important questions about the link between diabetes and COVID-19. The study will support research on studies of adults and children to characterize onset, clinical course, and mechanisms of new-onset diabetes after COVID-19 infection. It is unknown whether diabetes post-COVID is new-onset disease or secondary unmasking due to COVID-19 infection.

DEFINE T2D—Definition, Etiology, Function: INtegration to Enhance Type 2 Diabetes

Sub-classification approaches for classification of type 2 diabetes and prognosis (aspects of precision medicine) underscore the existence of distinct and heterogeneous etiologies in type 2 diabetes, but additional unexplored data types and data from varied populations could refine these definitions.[5,11,28] This consortium will capture and integrate various data types (e.g., markers of organ and tissue function, additional molecular and social/behavioral/environmental data) with artificial intelligence/machine learning to inform heterogeneity and motivate the development of novel precision medicine approaches. The consortium's aims are (1) identification and collection of data types and markers that can be analyzed across large cohorts; and (2) implementation of data analysis to identify clusters or subgroups of individuals with type 2 diabetes based on the data types and markers selected. This effort launched in 2024 and is expected to improve understanding of heterogeneity of type 2 diabetes, with the goal to develop more precise and accurate definitions of the disease.

Envisioning a Comprehensive Approach to Addressing Heterogeneity of Diabetes

In 2021, a symposium celebrating the 100th anniversary of the discovery of insulin, supported in part by the NIDDK, brought together researchers to discuss the heterogeneity of diabetes and highlight critical knowledge gaps and innovative research opportunities.[29-31] Given the interest in heterogeneity as outlined in NIDDK's Strategic Plan, the NIDDK recognized that it needed a long-term plan to address heterogeneity of diabetes that would allow for more accurate stratification for diagnosis, prevention, and management (i.e., precision medicine). The proposed plan (e.g., a "Research Roadmap") would permit NIDDK to target research investment and provide funding opportunities for pre-clinical, clinical, diagnostic, therapeutic, dissemination, and translation research to address heterogeneity (Figure 3).[3] Addressing the roadmap objectives would provide the necessary data to inform on a reclassification of type 2 diabetes based on advanced understanding of pathophysiology and natural history of the disease and, ultimately, its complications.

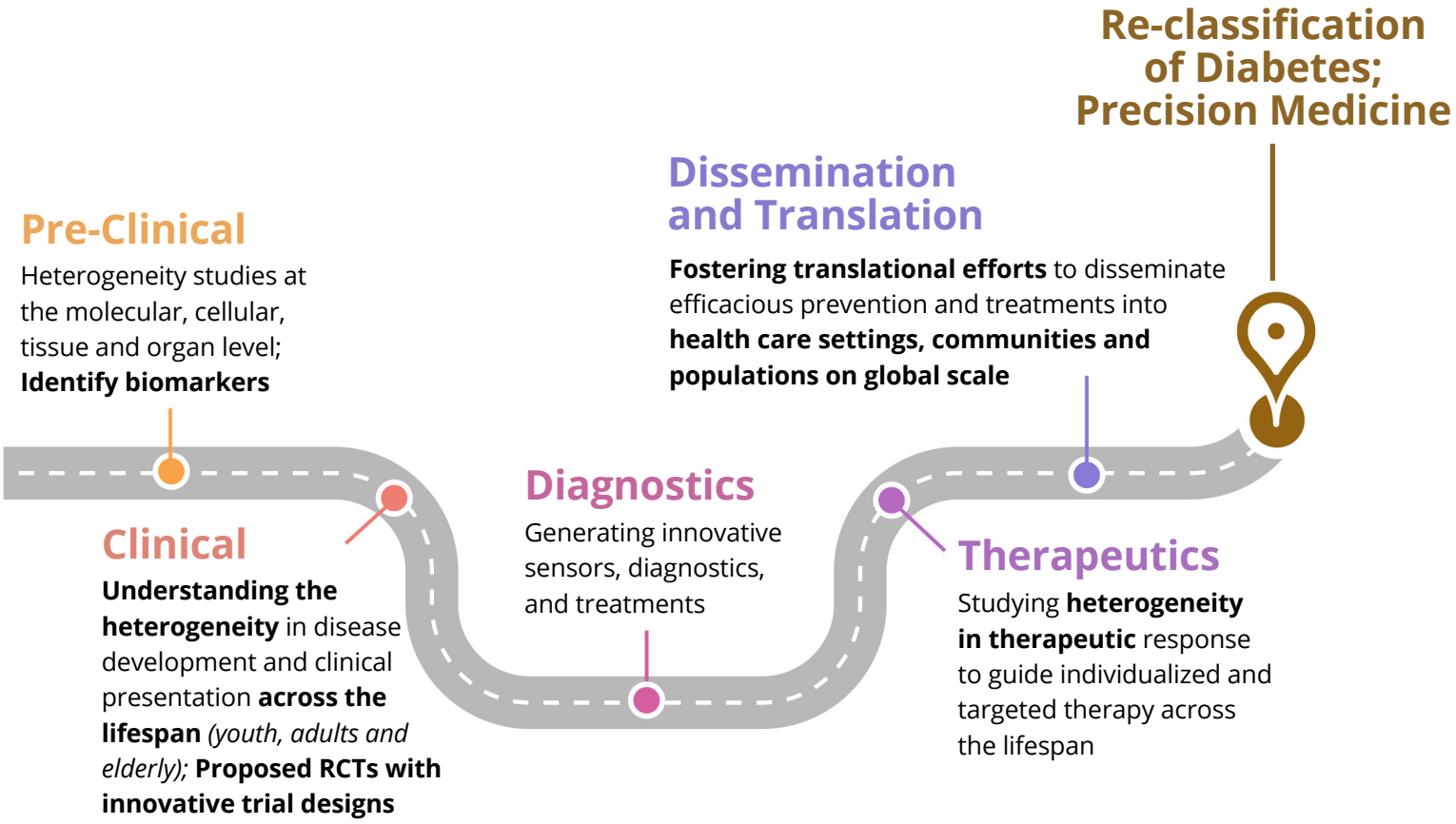

Figure 3: A "Research Roadmap" envisioned to address heterogeneity of diabetes . Adapted from Franks PW et al[3]

Leveraging of Research Resources and Studies

Given the above overarching goal of a comprehensive heterogeneity of diabetes initiative, the WGOC Report represents a long-term plan for NIDDK research opportunities that may take decades to complete. More importantly, as written, the Report provides Recommendations and Opportunities that can be initiated and addressed in the short- or medium-term, whereas other Recommendations are envisioned to be addressed well into the future after additional data, new methods, and new cohort studies are available. In addition, it is proposed that for the initiative to be successful, NIDDK must not only commit to fund new research programs and initiatives, but also allow for investment in research that leverages completed studies so as to "mine" available data that will continue to accelerate progress on heterogeneity of diabetes. In this regard, several research Opportunities outlined in this Report could be accomplished by accessing repository data and biospecimens from previously completed NIDDK clinical studies. NIDDK has a storied history of conducting long-running landmark studies involving populations with pre-diabetes, type 1 diabetes, type 2 diabetes, and youth and adolescent type 2 diabetes. A major advantage of this approach is having access to disease populations across the lifespan; in addition, investigators can take advantage of data collected from human cadaveric samples or from Pre-Clinical models as a result of the NIDDK investment (Table 1). Examples of past NIDDK investment that may provide data from these samples and animal models are outlined in the below table:

Table 1: NIDDK investment in Ongoing and Completed Studies, Trials and Programs

Study Population	Study Name	Identifying Logo
Pre-diabetes (T2D)	Diabetes Prevention Program/Diabetes Prevention Program Outcome Studies (DPP/DPPOS) (Ongoing)	
Pre-diabetes (T2D)	Vitamin D and type 2 Diabetes (D2d) study (Completed)	
Type 2 Diabetes	Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study (Completed)	
Type 1 Diabetes (Pre-diabetes/Diabetes)	The Environmental Determinants of Diabetes in the Young (TEDDY) (Ongoing)	
Type 1 Diabetes (Pre-diabetes/Diabetes)	Type 1 Diabetes (TrialNet) (Ongoing)	
Youth onset Type 2 Diabetes/ Pre-diabetes	Restoring Insulin Secretion (RISE) Study (Completed); The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) (Completed)	
High Risk individuals, Youth and Adolescent Type 2 Diabetes	The DISCOVERY of Risk Factors for Type 2 Diabetes in Youth Study (Ongoing)	
Type 1 Diabetes/Type 2 Diabetes: Cadaveric Specimens	Human Islet Research Network-Human Pancreas Analysis Program (Ongoing)	
Type 1 Diabetes, Type 2 Diabetes, cardiovascular disease, obesity, kidney disease, liver disease	Accelerating Medicines Partnership® Program for Common Metabolic Diseases (AMP® CMD) (Ongoing)	
Basic Science: Animal Models	Mouse Metabolic Phenotyping Center in Live Models (Ongoing)	

As envisioned, a comprehensive *umbrella* program for NIDDK to address heterogeneity of diabetes would span from pre-clinical research to clinical and translational studies through dissemination and implementation research. Such a program would require successfully completing the current ongoing studies addressing heterogeneity of diabetes (See *"Ongoing and Planned Research Efforts"* and Table 1) but would also leverage previously completed clinical trial and studies. These data will be integrated with findings from genetic, functional genomic, and multi-omic data and from mechanistic studies generated from pre-clinical models. The concept of a proposed comprehensive *umbrella* initiative with the above approach to address heterogeneity of diabetes envisioned by NIDDK is outlined in Figure 4.

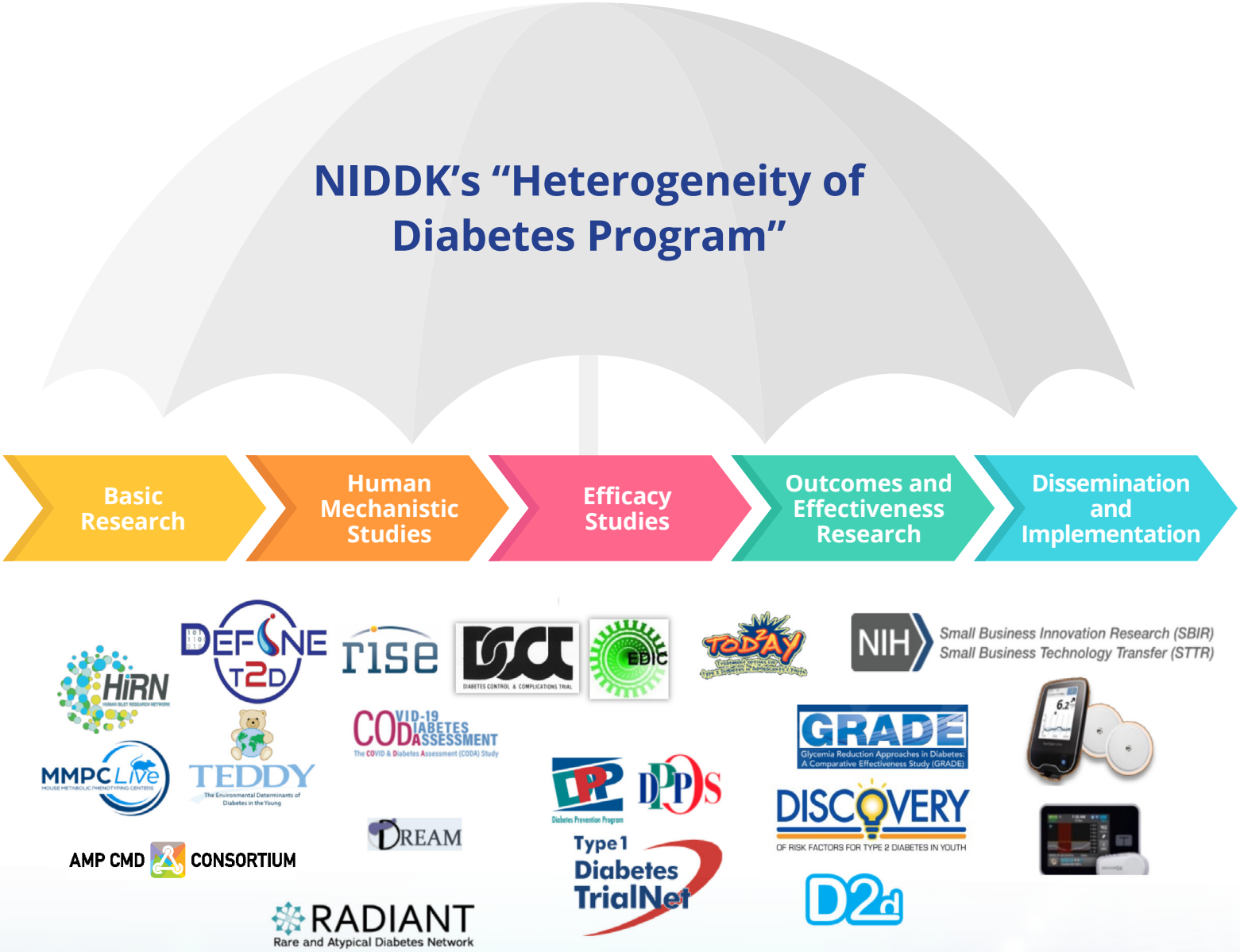

Figure 4: An envisioned comprehensive *umbrella* program for NIDDK which complements current ongoing and planned studies in heterogeneity of diabetes by leveraging completed NIDDK studies and other resources

Development of This Report

Establishing the Working Group of Council (WGOC)

Given the need for a comprehensive program, the NIDDK established a Working Group of the Advisory Council (WGOC) on Heterogeneity of Diabetes in January 2023. Building on the networks and efforts of the ADA/EASD PMDI, the NIDDK WGOC convened thought-leaders in diabetes to provide a detailed and expert overview of the current state of knowledge on diabetes heterogeneity and inform NIDDK scientific staff about recognized gaps and opportunities that should be considered for future research funding. As outlined in this Report, the WGOC identified five areas of emphasis for which SubGroups were formed, distinct from the PMDI pillars through emphasis on translation from basic research to clinical implementation. The WGOC SubGroup areas consist of Pre-Clinical, Clinical, Lifestyle, Innovation, and Engagement, with Cross-Cutting Themes identified as common features of SubGroups—Health for All and Data-Science. SubGroup and Cross-Cutting Theme teams were led by global investigators with expertise in heterogeneity and precision medicine and were staffed by NIDDK program leads. Thus, each SubGroup was comprised of multiple experts well versed in the topic of interest (See *"Executive Committee and Working Group Composition"*).

Charge of Each WGOC Subgroup

Pre-Clinical: The Pre-Clinical SubGroup was tasked to evaluate biological mechanisms and causal processes that underlie diabetes heterogeneity, as well as mechanistic pathways and biomarkers that require evaluation in Pre-Clinical models (e.g., cells, animals, virtual patient simulations) across multiple systems before translation to human studies and potential implementation in the clinic.

Clinical: The Clinical SubGroup was tasked to consider how to leverage knowledge about physiologic and environmental drivers of disease for defining diabetes heterogeneity and establishing clinically actionable approaches, including strategies for assessment and optimization of precision diabetes medicine (prediction, prevention, diagnosis, treatment) in practice across various populations.

Lifestyle: The Lifestyle SubGroup was tasked with assessing approaches to understand the contribution of lifestyle factors to diabetes heterogeneity and the application of lifestyle interventions that may be effective in clinical trials yet require novel approaches to maximize tailoring and adherence to recommendations related to heterogeneity of diabetes in various populations.

Innovation: The Innovation SubGroup consisted of three major areas for defining the heterogeneity of diabetes and implementing the principles of precision diabetes medicine: technology, biomarker development, and innovative study design. These areas require novel methods for collecting and analyzing physiological, biological, and environmental factors contributing to diabetes heterogeneity, and the discovery and utility of new biomarkers of the disease process.

Engagement: The Engagement SubGroup was tasked with evaluating barriers to recruitment into clinical studies and clinical trials to define diabetes heterogeneity across the lifespan and for subsequent implementation of prediction, prevention, diagnosis, and treatment of diabetes based upon precision approaches in varied populations. In addition, the SubGroup was tasked to provide solutions to overcome those barriers and optimize applications of precision diabetes medicine through engagement with external stakeholders.

Cross-Cutting Themes: The Health for All Cross-Cutting Theme represents an extension of NIDDK's prior reports, while the Data-Science Cross-Cutting Theme builds upon NIDDK's dkNET Pilot Funding Program in "AI Models to Accelerate Diabetes Heterogeneity Research."[32] This Report aims to provide Recommendations and Opportunities for research in diabetes heterogeneity across the domains and interests of each SubGroup.

Research Recommendations and Opportunities

Over the course of more than two years, the five SubGroups developed overarching research Recommendations for each SubGroup's focus area that provided a "Research Roadmap" for the NIDDK moving forward. In addition, the two Cross-Cutting Teams provided broad Recommendations in Data-Science and Health for All across the SubGroups. With this Report, the NIDDK will now consider the following Recommendations from each SubGroup as a blueprint to help prioritize the most compelling Opportunities to address diabetes heterogeneity within its mission.

SubGroup Recommendations and Opportunities

Pre-Clinical SubGroup Recommendations

Pre-Clinical investigation is often key to understanding the biologic processes and mechanisms underlying diabetes heterogeneity across cells, tissues, organs, whole organisms, and human populations. To optimize this interpretation, models used for Pre-Clinical understanding should reflect human physiology in healthy and disease states. There is a need to enhance understanding of diabetes heterogeneity by expanding genetic variety in animal and human cell models, standardizing metabolic assays across research settings, and characterizing diabetes-relevant tissues as well as benchmarking against human induced pluripotent stem-cell (iPSC) models. These are crucial approaches given the complex heterogeneity of diabetes etiology and the limitations of currently narrow research models. Implementation of these Recommendations would advance our understanding of diabetes pathophysiology through genetically diverse and genetically modified models, standardized measurements, and complementary tissue analysis methods. Increased support of broadly shared and curated resources will accelerate the discovery of novel disease mechanisms, identify diabetes subtypes, and develop targeted therapeutic approaches.

Recommendation 1:

Increase the genetic diversity of animal and human models to study diabetes and make these available through repositories that are broadly accessible to the research community

Over the past decade, meta-analyses of genome-wide association studies (GWAS) in European-ancestry cohort collections (1.34 million participants) and in collections of diverse genetic ancestries (~2.5 million participants) have discovered 611 loci and 1,289 statistically independent genetic variants for type 2 diabetes.[12,33,34] In parallel, GWAS for type 2 diabetes in populations of East Asian, South Asian, Hispanic/Latino, or African ancestries, as well as their trans-ancestry meta-analyses, have identified dozens of additional genetic variants, some that are unique or have higher risk allele frequencies than those in European-ancestry populations.[12,35,36] These results point to multiple biological pathways and genes previously unsuspected of contributing to the pathogenesis of type 2 diabetes. Despite this evidence of genetic diversity in type 2 diabetes risk, most pre-clinical models lack genetic diversity and fail to adequately

capture disease heterogeneity.[37] In addition, current human cell models are not widely available, are often prohibitively expensive, and are limited to a small donor pool. Existing production and in vivo phenotyping capabilities make functional characterization of mouse models faster and more straightforward than in the past. However, the requirement for material transfer agreements (MTAs) between institutions can hinder access, consequently limiting their adoption. Notably, the development of the Diversity Outbred (DO) mouse program that captures the genetic diversity in this experimental model has provided an attractive alternative to decades of work on inbred mouse lines (e.g., the C57BL/6 mouse).[38-40]

Opportunity 1-1: Build on existing efforts to establish induced pluripotent stem cells (iPSC) biobanks from patients of diverse genetic ancestry with diabetes and obesity.

Opportunity 1-2: Use existing human organoid platforms to functionally identify the impact of genetic variants that alter the risk of diabetes.

Opportunity 1-3: Increase the use of DO mice for both genetic discovery and disease modeling of metabolic and glycemic traits.

Opportunity 1-4: Use current phenotyping platforms to execute rapid in vivo functional characterization of mouse models.

Opportunity 1-5: Improve cataloging and aggregating existing data on authentic human cell models and Diversity Outbred mice with centralized user access.

Opportunity 1-6: Accelerate and increase the availability of Pre-Clinical human model data for a wide variety of relevant tissues for diabetes, beyond islets, and data types (e.g., omics technologies, imaging, and functional assays) to the community.

Opportunity 1-7: Develop analytical methods that maximize the use of varied 'omic' datasets to identify continuums of physiological states and their relationships to diabetes subtypes.

Opportunity 1-8: Establish a panel of human iPSC lines derived from diverse genetic ancestries and differentiate them into multiple metabolic cell types, with data and cell lines widely available to the community.

Opportunity 1-9: Support the development of "off the shelf" human stem cell-derived organoid products of relevance to diabetes, pancreatic islet organoids with endocrine, ductal, and exocrine compartments, gastrointestinal (stomach, intestine), liver, adipose, muscle, and brain.

Opportunity 1-10: Support the development of high-throughput organoid systems to study the impact of environmental factors on cell and tissue function at different stages of diabetes.

Opportunity 1-11: Screen DO mice with multi-omics technologies to discover loci controlling intermediate phenotypes to understand diabetes heterogeneity.

Opportunity 1-12: Perform comprehensive multi-omic mapping and single-cell analysis in diabetes-relevant tissues in multiple diabetes models using novel technologies coupled with emergent data analytics.

Opportunity 1-13: Encourage systems biology approaches for data integration and analysis by the creation of a public repository for mouse study data.

Opportunity 1-14: Invest in data-science infrastructure to facilitate data access, integration, and visualization, ensuring the wide use and reuse of complex human and model systems data in diabetes.

Recommendation 2:

Standardize and benchmark assays that are widely used for metabolic phenotyping

To bridge Pre-Clinical models (clinical, primary cells, organoids, animals), validated measurements of cell and tissue metabolic outputs and responses to multiple perturbations are required. Standardization of assays is critical, particularly in the context of diabetes heterogeneity where phenotypic readouts are necessary to detect subtle changes resulting from modest genetic variation effects. Currently, there is a lack of interoperability between datasets as measurements differ across models and laboratories, which limits data integration. In addition, some tissues (e.g., adipose and muscle) require technological advancements to enable comprehensive phenotyping at both functional and molecular levels.

Opportunity 2-1: Establish international working groups (including academia and industry) to reach consensus on the metabolic assays and functional assessments necessary to qualify each diabetes tissue type and its iPSC organoid counterpart, and create open-access reference databases for each assay.

Opportunity 2-2: Encourage academia and industry experts to develop guidelines for phenotyping approaches that are widely used in diabetes.

Opportunity 2-3: Support automation of phenotypic assay techniques and standardized protocols to reduce technical variation and encourage adoption by the research community.

Opportunity 2-4: Create representative and accessible datasets of spatial biology profiling across key metabolic tissues (e.g., islets, adipose) as a comparator to animal and in vitro model systems.

Opportunity 2-5: Support technical developments in functional and molecular assays in primary metabolic tissues (e.g., adipocytes) to integrate with omics data and high-content imaging to inform on cellular phenotypes at the single-cell level.

Opportunity 2-6: Convene a consortium of investigators to establish cross-laboratory assay qualification and comparability approaches (similar to the Islet Autoantibody Standardization Program, IASP) to evaluate and benchmark assays.[41,42]

Recommendation 3:

Characterize diabetes-relevant tissues from the same individuals and benchmark against human iPSC models

Much can be learned about diabetes heterogeneity by studying clinical samples; however, their limited expansion, functional maintenance, variable quality, and restricted accessibility for some tissues prevents extensive mechanistic studies. Using human iPSC-derived organoid models can fill this gap and complement studies using individual primary tissues. Validating these models through benchmarking against primary tissue samples will establish their research value.

Opportunity 3-1: Leverage existing tissue collections by expanding to include diabetes-relevant tissues and cell types (e.g., exocrine pancreas, gut, brain) and refine functional, single-cell, and molecular phenotyping efforts from the same individual.

Opportunity 3-2: Support pilot programs to establish feasibility and infrastructure to benchmark human iPSC-derived organoids against primary tissues.

Opportunity 3-3: Assess the contribution of various fat depots to diabetes heterogeneity with single adipocyte sequencing across genetically diverse populations of donors with integration of dense image analysis.

Clinical SubGroup Recommendations

This section provides key Recommendations to transform the approach to clinical diabetes research and care by establishing robust international collaborations for data harmonization, elucidating pathophysiologically distinct diabetes subtypes, developing targeted interventions for high-risk individuals, and designing innovative clinical trials that account for treatment effect heterogeneity. These Recommendations aim to advance precision diabetes medicine, enabling more personalized prevention and treatment strategies that address the complex interplay of genetic, metabolic, environmental, and social and structural determinants across the diabetes spectrum, ultimately improving outcomes for global populations affected by diabetes.

Recommendation 1:

Support international collaborations to enable data harmonization, linkage, and sharing across existing multi-population datasets

Diabetes is a common disease globally, but there are significant differences in epidemiology, clinical manifestations, and disease progression across geographical regions and ancestral groups.[43] These differences are related to variations in genetic, environmental, and cultural influences. The potential to leverage these variations to develop more accurate clinical guidelines for diverse populations has not been fully realized due, in part, to the lack of comprehensive, standardized, and harmonized comparative datasets across geographic regions and ancestral populations globally.

Opportunity 1-1: Implement data harmonization, which may include definitions for equivalences between measures.

Opportunity 1-2: Support initiatives that maximize international collaboration by developing equitable guidelines on international data and biospecimen access.

Opportunity 1-3: Support initiatives that achieve consensus in research guidelines for harmonization of data related to diabetes heterogeneity (e.g., minimum variables datasets, standardized phenotypes, agreement on objective endpoints) that can be translated into clinical practice.

Recommendation 2:

Elucidate pathophysiologically distinct diabetes subtypes and define their diagnostic and therapeutic strategies by generating datasets that integrate clinical data, environmental exposures, and multi-omic biomarkers from diverse, longitudinal cohorts

Current recommendations for diabetes management continue to be based on the average glycemic treatment effect from clinical trials that fail to account for diabetes heterogeneity. Existing datasets lack essential measures, such as insulin secretion and insulin sensitivity, which are often not systematically measured. Additionally, there is a gap in environmental exposure data that modify the development and progression of diabetes. Few studies consider crosstalk between tissues and organs involved in the pathogenesis of diabetes and most lack integration of clinical characteristics with multi-omics data. Without comprehensive data collection, our understanding of how key factors interact to influence diabetes outcomes remains incomplete.

Subtyping diabetes using clustering approaches may lead to more accurate treatment strategies based upon research studies conducted in various settings over the past decade.[5] These studies suggest that progression to diabetic complications varies between clusters and sub-phenotypes. Data are needed to determine if insights regarding diabetes heterogeneity can be used to improve clinical outcomes.

Several barriers have been identified that limit the ability to conduct new clinical trials and studies. Clinical trials are often expensive, limiting the number of trials with an appropriate, well-powered study design in presence of treatment-effect heterogeneity. Furthermore, most clinical trials are designed for internally valid estimation of an average treatment effect rather than subgroup effects. Few examples of interventional trials related to diabetes prevention or treatment have used phenotypic heterogeneity to inform stratification.[44-46] Finally, large sets of clinical data derived from EHR have examined the selected population of individuals receiving clinical care, for whom treatment choices may be biased.

Opportunity 2-1: Support initiatives to encourage collaboration between holders of large existing datasets (obtained from clinical cohorts and clinical trials) with deep phenotyping with relevant variables (e.g., insulin secretion, insulin resistance, and other diabetes-related endpoints) to afford greater statistical power and the ability to examine diabetes subtypes.

Opportunity 2-2: Support initiatives to encourage collaboration between clinical research and basic research to increase integration between clustering of 'simple' clinical variables and clustering that employs genetic, multi-omic, and molecular biomarkers.

Opportunity 2-3: Measure variables important for defining diabetes heterogeneity across existing repositories with biobanked samples (e.g., https://repository.niddk.nih.gov/home/) and establish repositories with increased access and limited restrictions on data sharing with accessible tissues.[47]

Opportunity 2-4: Create large, new longitudinal cohorts that capture the natural history of diabetes development, diagnosis, progression, and treatment with sample collection to capture multi-omic and biomarkers for integration of clinical and environmental data.

Opportunity 2-5: Support research on clinical trial design and methodology for determining the necessary sample size and design for detecting differences in treatment response based on physiological heterogeneity and/or clinical subtyping.

Opportunity 2-6: Conduct clinical trials designed to evaluate treatment response heterogeneity to interventions to delay or treat diabetes and establish clinically actionable subtypes.

Recommendation 3:

Investigate approaches for supporting research to understand heterogeneity of diabetes prevention, progression and treatment globally

Individuals in low- and middle-income countries (LMICs), children, and individuals of non-European ancestry remain understudied. Heterogeneity in clinical presentation, disease course, and epidemiological findings suggests that diabetes may have etiological differences and pathogenic mechanisms in different populations, which affect its development, progression, and response to treatment. The lack of detailed data to explain differences in diabetes incidence is a major gap in knowledge. Strategies need to be developed to accurately map risk factors and epidemiological determinants to better understand diabetes heterogeneity across populations for improved prevention and treatment of diabetes globally.

Opportunity 3-1: Develop high-throughput methods for collecting standardized longitudinal environmental and behavioral data, including physical activity, diet, sleep, stress measures, toxin exposure, and data from wearable technologies.

Opportunity 3-2: Develop methods to obtain multi-omics data in countries and regions where standard technologies are currently unavailable.

Opportunity 3-3: Identify and/or develop point-of-care diagnostic tests for any identified clinically useful novel biomarkers related to diagnosis or prognosis to facilitate clinical implementation.

Opportunity 3-4: Develop screening tools adapted to all populations through creation of culturally sensitive and translated questionnaires, "apps," digital tools, laboratory testing with minimal participant burden (e.g., metabolic testing), and technologically advanced tests that are accessible and provide accurate data in the absence of large academic centers.

Opportunity 3-5: Conduct research to compare clinically accessible tests, including those accessible in LMICs, against gold-standard research tests.

Opportunity 3-6: Develop measures, currently lacking, that provide pediatric normative data in early stages of diabetes.

Opportunity 3-7: Develop diabetes-relevant genetic testing methods and clinical tools to be used by all end-users for patient care decisions that are affordable and accurate, that will be accessible and promote health for all.

Opportunity 3-8: Advance research and build data collection capacity on biomarkers of diabetes risk (e.g., genetic and other omic) for use across populations. For biomarkers that do not perform accurately across all groups, population-specific thresholds of biomarkers should be developed.

Opportunity 3-9: Support research on the use of telemedicine to expand access to diabetes research, clinical care, and prevention programs in remote areas.

Opportunity 3-10: Support initiatives to develop and implement strategies to increase public trust in diabetes research.

Opportunity 3-11: Facilitate use of existing cohorts and databases through incentives to combine diabetes-relevant data and increase sample size toward the goal of health for all.

Lifestyle SubGroup Recommendations

Embedded into a rapidly evolving environment, lifestyle behavior factors such as diet, physical activity, and sleep contribute to the heterogeneity of diabetes development and progression. These Recommendations highlight the need for targeted research across life-course transitions, including puberty, pregnancy, menopause, and aging, to address responses to lifestyle modifications among individuals with pre-diabetes and diabetes. These Recommendations also emphasize exploring intergenerational effects of interventions, developing precision medicine approaches to assess risk factors and treatment response heterogeneity, implementing multi-level interventions that address environmental and social influences beyond individual behaviors, and considering the unique challenges faced by populations with cognitive dysfunction, neurodiversity, and mental health conditions.

Recommendation 1:

Support clinical trials that target behavioral approaches during key life-course periods to address the heterogeneity of individual responses to lifestyle interventions for the prevention and treatment of diabetes

Motivation for behavior change can differ across the lifespan. Challenges in adolescence include psychological desire to achieve independence, while pregnancy-related periods (before, during, and after) include competing demands, short parental leave, and sleep disruption. Challenges in older individuals include risk of falls, loss of taste and appetite, and cognitive decline. Age may influence how lifestyle interventions can be implemented and how people respond to modifications in diet and exercise. Lifestyle interventions for people with pre-diabetes or diabetes are rarely designed to address challenges unique to a specific life-course period.

Opportunity 1-1: Support clinical trials targeting key transition periods in the life-course to optimize response to lifestyle interventions in people with pre-diabetes and diabetes (puberty, pregnancy, midlife, menopause, and older age).[48-50]

Opportunity 1-2: Evaluate the implementation and response to lifestyle interventions in pre-diabetes and diabetes through building partnerships with established life-stage programs.

Opportunity 1-3: Conduct clinical trials to develop and evaluate lifestyle interventions for people with pre-diabetes and diabetes that incorporate life-stage-specific social network support and account for the variability in individual responses to these interventions.

Opportunity 1-4: Initiate clinical trials to develop and evaluate interventions that are sustainable across the lifespan and to understand response heterogeneity to achieve health for all.

Opportunity 1-5: Conduct clinical trials to determine optimal physical activity levels for diabetes prevention and treatment across life stages.

Recommendation 2:

Support research on the interplay between lifestyle and pathophysiologic factors in pre-diabetes and diabetes across life-stage transitions

Glucose/insulin regulation is physiologically modified during key life stages, and studying these transitional periods may help optimize lifestyle interventions. For example, higher insulin resistance and increased hormones are observed during puberty.[51] During pregnancy, there is a temporary increase in insulin secretion, insulin resistance, and subsequent reversal.[52] The menopause transition is associated with changes in body composition and a decline in estrogen levels.[53] Older individuals may be affected by loss of lean mass and changing circadian rhythm/sleep patterns. The extent to which physiological changes during life transition periods contribute to the response variation associated with lifestyle interventions for people with pre-diabetes or diabetes is currently unknown.

Opportunity 2-1: Support research to determine whether pathophysiological subtypes of diabetes (and pre-diabetes) change during key life transition periods.

Opportunity 2-2: Determine whether lifestyle modifications (e.g., dietary patterns, physical activities, sleep) during key life transition periods affect the progression from pre-diabetes to diabetes or the shift between diabetes subtypes, specifically insulin resistance to insulin deficiency.

Recommendation 3:

Support research to investigate the intergenerational response to lifestyle interventions for people with pre-diabetes and diabetes and their family members

There is limited evidence that a lifestyle intervention in individuals with pre-diabetes or diabetes can directly influence the health of other family members (e.g., modifying epigenetics in offspring) or indirectly (e.g., modifying the home food environment).[54]

Opportunity 3-1: Design clinical trials to investigate whether people are more motivated to change their own behavior if this stands to benefit family members' health.

Opportunity 3-2: Promote studies investigating how lifestyle interventions during pregnancy affect fetal programming mechanisms, including epigenetics.

Recommendation 4:

Support research in use of technology to assess the heterogeneity of response to lifestyle interventions for people with pre-diabetes or diabetes

Disparities in assessing new technologies and information continue to hinder the advancement of precision health lifestyle interventions aimed at preventing diabetes for all.[55,56] This area of research should include technologies tailored to specific communities to ensure broad adoption and sustainability.

Opportunity 4-1: Invest in research programs that combine modern technologies for monitoring individual physiologic responses and behavior change in response to lifestyle interventions in people at risk of diabetes.

Opportunity 4-2: Prioritize research programs to improve assessment of adherence to, and efficacy of, lifestyle interventions across populations at risk of diabetes.

Opportunity 4-3: Explore variability of behavioral responses using real-world implementation of lifestyle interventions for people at risk of diabetes using existing data or innovative passive data collection methods (e.g., grocery purchases, built environment).

Recommendation 5:

Support research projects testing multi-level (the individual, neighborhood, community, region) interventions that target lifestyle behaviors and social drivers of health with respect to heterogeneity of diabetes

Effectiveness of diabetes prevention interventions is lower among populations experiencing greater social adversity. Social needs are major drivers of health disparities and risk factors for diabetes. Heterogeneity of diabetes may be attributable, in part, to environmental and/or social factors. It is unknown whether intervening on these factors at the population level (e.g., improving the quality of local stores or parks) or at the individual level (e.g., healthy food delivery) can improve responses to lifestyle interventions in a specific diabetes subtype.

Opportunity 5-1: Conduct research to determine whether multi-level interventions addressing environmental or social influences (e.g., building safer bike lanes) and individual lifestyle behaviors (e.g., personalized health coaching to support physical activity) simultaneously yield greater improvements in diabetes prevention or treatment outcomes than each intervention in isolation.

Opportunity 5-2: Perform research utilizing natural experiments or policy changes that impact social factors and lifestyle behaviors to study heterogeneity of intervention responses in individuals with pre-diabetes or diabetes.

Opportunity 5-3: Study implementation of lifestyle interventions in low socioeconomic communities through development of partnerships and engagement with community-based organizations to obtain data from those who would be the targets of the interventions.

Recommendation 6:

Support research that investigates the impact of lifestyle behaviors and the capacity to initiate and sustain behavior change on heterogeneity of diabetes in vulnerable populations

There is a lack of knowledge about the efficacy of diabetes prevention and lifestyle interventions in vulnerable populations, where the adoption and/or efficacy of behavioral/lifestyle changes may be especially challenging. Studies examining diabetes heterogeneity should be conducted in individuals with dementia, as they often encounter substantial challenges in implementing and maintaining lifestyle modifications. Individuals with severe mental illnesses are usually managed by medications that influence metabolism and can promote weight gain and glycemic disorders. Psychological distress, including post-traumatic stress disorder, anxiety and chronic stress, and neurodiversity (e.g., attention deficit and hyperactivity disorder) are associated with the development of diabetes through multiple pathways. These populations are less likely to adhere to medications (including diabetes medications and those used for other co-morbidities) secondary to their cognitive functioning and are associated with adverse behavioral coping, substance use disorder, prolonged sedentary behavior, poor quality and insufficient sleep.

Opportunity 6-1: Investigate the heterogeneity of lifestyle behaviors and diabetes outcomes among individuals with cognitive dysfunction, substance use disorders, depression, and severe mental illnesses by leveraging existing longitudinal cohort studies of administrative data sources.

Opportunity 6-2: Identify whether unhealthy lifestyle behaviors or other characteristics associated with heterogeneity of diabetes are over-represented in vulnerable populations due to brain or mental health conditions.

Opportunity 6-3: Conduct research to study the implementation and dissemination of evidence-based lifestyle interventions in individuals vulnerable to cognitive dysfunction or severe mental illness.

Recommendation 7:

Encourage and foster academic-community partnerships to optimize behavioral interventions among people with diabetes and/or pre-diabetes

Community organizations serve individuals at high risk of developing, or affected by, diabetes. These organizations are often more trusted than academic institutions, large health care systems, or hospital-based researchers. Partnering with community organizations to design, develop, and implement lifestyle interventions may increase the potential impact of interventions for target people/populations and enable early integration of interventions within a community infrastructure.

Opportunity 7-1: Propose funding opportunities that encourage and support collaborations between academic researchers and the community to advance community-engaged research on the heterogeneity of diabetes and lifestyle intervention responses.

Opportunity 7-2: Create and clearly state a standard definition of 'community engagement' to emphasize the collaboration between academic researchers and communities in health research as a "mutually beneficial exchange of knowledge and resources in the context of partnership and reciprocity.[57]

Opportunity 7-3: Minimize barriers to academic-community partnerships by increasing access to community organizations to permit them to be full research partners.

This could include changes to the NIH application and review process and/or funding requirements to provide infrastructure support to engage in grant writing, time for developing partnerships ahead of research study design, and reimbursement for community partners' time and effort (creating a new 'category' of partners in research that is neither "academic sub-award" nor "vendors").

Recommendation 8:

Support research that fosters multi-sector partnership(s) with organizations that share similar goals, missions, and objectives related to lifestyle approaches

Complementary strengths and skills exist in multi-sector partnerships, allowing each organization to contribute uniquely. These partnerships can help researchers investigate how various lifestyles impact the heterogeneity of diabetes and treatment outcomes by combining resources and data from both sectors.

Opportunity 8-1: Develop funding opportunities for planning grants to encourage and support the development of multi-sector partners to engage in research related to lifestyle approaches to addressing the heterogeneity of diabetes.

Opportunity 8-2: Support funding opportunities for studies that use multi-sector partners to engage in research related to lifestyle approaches to addressing the heterogeneity of diabetes.

Opportunity 8-3: Support partnerships with industries that manufacture wearable devices to facilitate free access to raw data in a consistent, curated, and harmonized manner for future analysis, particularly across various brands of wearable devices.

Innovation SubGroup Recommendations

Beyond manifest diabetes, therapeutic options are expanding to include the potential for interventions in those at risk of diabetes as well as for maintenance of glucose homeostasis and for reduction of complications. As diabetes disproportionately impacts communities also facing health disparities, these same individuals are underrepresented in access to, and use of, technology to support diabetes research, innovation, and clinical practice. These barriers are compounded not only by rapid advancement of technology-assisted innovation but also by health and digital literacy.

To better understand and positively impact the heterogeneity of the risk, progression, and outcomes of diabetes, it will be necessary to consider single and integrated innovations in diabetes technology. In assessing the value of such novel innovations, these considerations should include determining their impact on individuals and communities with the greatest burden of diabetes, the application of multimodal longitudinal monitoring (e.g., biomarkers, digital markers, and psychosocial influences) and the emerging use of artificial intelligence (AI) approaches in multi-sourced information collection. A unique opportunity for innovation will be an expanded emphasis on both non-pharmacological as well as the continuing development of pharmacological interventions.

Recommendation 1:

Advance research to increase understanding of the diagnostic, prognostic, and therapeutic value of individual continuous glucose monitor (CGM) profiles in individuals with, or at risk of, dysglycemia

CGM is increasingly being used in individuals without diabetes, including those with pre-diabetes and also those at risk of developing diabetes (e.g., family history, very low or high birthweight, high genetic load, or other co-morbidities). Novel CGM metrics have been proposed that may help facilitate stratification into subgroups of individuals at risk of dysglycemia progression and diabetes-related complications. Changes in CGM profiles over time, or in response to intervention(s), may provide opportunities to predict and personalize behavioral and pharmacological approaches in diabetes prevention, prediction, and management. There is a need to generate evidence of the value of these metrics in attenuating diabetes risk and progression at a personal level.

Opportunity 1-1: Support research to determine predictors of CGM-based glucose profiles and meal responses in real-time and longitudinally.

Opportunity 1-2: Define digital markers to examine the heterogeneity of CGM curves stratified by patient-specific factors (e.g., age, comorbidities, social and structural determinants of health, and digital literacy).

Opportunity 1-3: Advance research to associate CGM trajectories with the development of dysglycemia, diabetes, and complications risk, as well as determining whether personalized CGM use modifies adherence with behavioral interventions.

Opportunity 1-4: Determine whether AI methods for interpreting and integrating real-time CGM and other data sources can create and assess just-in-time interventions.

Recommendation 2:

Advance the use of wearable technologies for real-time monitoring of behavioral and physiological parameters to examine diabetes heterogeneity

Beyond CGM, other wearable digital technologies can capture additional real-time data, including activity, sleep, stress, and cardiovascular status; however, barriers to wearable technology remain, including acceptability, reproducibility, and efficacy. Future research should consider how to overcome the barriers to engagement and adoption of wearable devices and increase acceptance by clinicians and individuals living with diabetes of how utilizing technology can improve diabetes care.

Opportunity 2-1: Initiate studies of digital markers of mental health (e.g., stress, impulsivity, mobility, and sociability) to increase data on behavioral influences on dysglycemia, diabetes prognosis, and therapeutic responses.

Opportunity 2-2: Develop studies of how measures obtained from wearable technology (e.g., environmental, sociological, and behavioral measures) predict diabetes risk and longitudinal changes in glycemia, risk of complications, and responses to single or combined treatments.

Opportunity 2-3: Support studies to determine whether technological automated logging of food choices and macronutrient content compares with individual logging of dietary data.

Opportunity 2-4: Support research on integrating wearable data with biomarkers and clinical parameters to facilitate precision diabetes management.

Opportunity 2-5: Evaluate technologies that include facial recognition, digital retinal imaging, and voice pitch to examine their relevance to diabetes heterogeneity.

Opportunity 2-6: Support research to assess alternate human tissues and physical sites for monitoring (e.g., retinal imaging to detect non-retinal disease) or alternate dermal locations (e.g., the foot) in individuals at risk of diabetes and its complications for those living with diabetes.

Opportunity 2-7: Support studies that examine new analytes beyond glucose (e.g., ketones, insulin, and relevant metabolites) as targets for real-time monitoring and determine their relevance to diabetes heterogeneity.

Recommendation 3:

Develop strategies to determine the clinical relevance of molecular biomarkers for understanding diabetes heterogeneity

Molecular biomarkers, specifically those derived from blood, tissue, and single-cell transcriptomics and proteomics, can be applied at a population-wide scale for precision stratification and mechanistic subtyping. With the advancement of technologies, the number of diabetes-associated biomarkers continues to increase. Which of those has causal relevance or reflects its heterogeneous subtypes remains to be established.

Opportunity 3-1: Conduct studies on molecular biomarkers that identify undetected subgroups and predict the risk of diabetes onset, prognosis, and treatment response by including data from multi-ancestry cohorts, incorporating clinical parameters and study designs to reflect potential clinical applications.

Opportunity 3-2: Conduct studies on translating molecular biomarkers to clinical practice that address cost-effective assay development, convenience of sampling, acceptable testing strategies, and societal barriers to their use.

Opportunity 3-3: Initiate studies with large multi-omic data designed to investigate diabetes heterogeneity at diagnosis for evidence of treatment response heterogeneity.

Opportunity 3-4: Implement AI approaches to aid investigation of molecular data for diabetes heterogeneity.

Opportunity 3-5: Initiate studies to address the accuracy and translation of blood-based molecular biomarkers to tissue-specific biomarkers in diabetes.

Recommendation 4:

Improve clinical relevance and validity of diabetes polygenic risk scores (PRS) for understanding mechanisms of diabetes heterogeneity

PRS represent a summation of genetic variants and their effects on the risk of diabetes, with separate scores for different sub-types of diabetes. PRS for different forms of diabetes account for different proportions of risk and vary by the amount of genetic data available to generate PRS for diverse ancestry populations. PRS are compelling as a single value that combines genome-wide variation and offer promise for understanding the heterogeneity of diabetes pathophysiology and improving precision medicine. However, the integration of PRS into clinical care remains variable by diabetes type and perceived impact. Using PRS derived from multi-ancestry populations is expected to significantly improve their accuracy and utility. Research in this area requires the active participation of populations with varying degrees of risk. Future research should ensure that strategies are implemented to educate clinicians on use of PRS and engage people living with diabetes for participation in genomic and other 'omic' research.

Opportunity 4-1: Evaluate the utility of PRS against clinical benchmarks/risk factors for prediction and biological understanding of diabetes heterogeneity.

Opportunity 4-2: Advance research on multi-ancestry genetic factors to improve diabetes PRS and understand diabetes heterogeneity across populations, including evaluation of partitioned/process-specific PRS (pPRS) to test heterogeneity in drug response, tolerability, and adverse effects.

Opportunity 4-3: Incorporate AI approaches to integrate multiple data types (e.g., single-cell and additional molecular data) for new PRS methods and innovative approaches in diabetes prediction and response to therapies.

Recommendation 5:

Promote the application of innovative omics technologies to diabetes heterogeneity across diverse populations, human tissues, and cells

Deep short- and long-read sequencing is now applied at a population scale. Analyses of transcriptomic, epigenomic, and other omics at single-cell resolution can be applied to relevant tissues and cell types to better define diabetes heterogeneity. Future research is needed to determine whether these data will provide the ability to predict the trajectory of diabetes risk and progression.

Opportunity 5-1: Conduct whole genome sequencing with respect to diabetes risk and progression in diverse populations to identify ancestry-specific variants, develop and stratify studies of diabetes risk using PRS and identify genetic variants that predict therapeutic response.

Opportunity 5-2: Promote the inclusion of tissue- and cell-type-specific relevance of gene expression (transcriptomics), chromatin accessibility (epigenomics), and proteomics mapped in extensive sample collections using single-cell approaches.

Opportunity 5-3: Evaluate differences across individuals with cell type-specific risk to physiological challenges and pharmacological interventions (e.g., through participant recall and examination).

Engagement SubGroup Recommendations

These Recommendations provide a comprehensive framework for fostering partnerships between research teams and the communities they serve. From supporting various investigator teams to establishing clear expectations for community engagement, ensuring appropriate compensation, implementing culturally sensitive data collection methods, advocating for community-level risk assessment, and enhancing capacity-building resources, these Recommendations aim to ensure inclusion of all populations in research while improving research quality and outcomes. By centering the needs, values, and perspectives of communities disproportionately affected by diabetes, we can develop more effective, ethical, and impactful research approaches that ultimately contribute to reducing health disparities and advancing diabetes care for all populations.

Recommendation 1:

Support investigator teams that demonstrate engagement with people with lived experience (PWLE) and communities impacted by diabetes

Meaningful engagement involves collaboration between community and research teams, ensuring that studies are designed and conducted with the needs, values, and perspectives of communities in mind. This approach enhances the quality of research and contributes to the broader goal of improving public health and reducing health disparities. Meaningful engagement ensures that community leaders or members from whom the data are being collected are included in all decisions about the data, such as who, what, and how the data should be collected, used, and reported. Community members should be included as decisional voices in these determinations within the research teams and regulatory bodies overseeing the research.

Community engagement is a spectrum from the 'lightest touch' to a deeply collaborative, co-ownership model. Evidence suggests that involving patients throughout the project lifecycle, from initial planning to sharing results, yields the most effective patient-centered research and community-level implementation.[58,59] Building meaningful connections throughout the period of a research project represents an ethical imperative that fosters trust, enables effective engagement with individuals, and is essential to strengthening social contracts between the community and researchers.[60,61] Sporadic or intermittent engagement during a research project should be avoided, as it fosters mistrust and disingenuous relationships, ultimately diminishing the effectiveness of interactions. Some historical engagement efforts have involved the use (or misuse/abuse) of community members who are viewed as temporary transactional resources needed strictly for data collection. This has been referred to as "helicopter research" and fails to foster relationships, mutual understanding, and shared aspirations between researchers and community members.[62] These perspectives should be kept in mind when researchers embark on current and future engagement activities.

Opportunity 1-1: Promote research teams with diverse perspectives by including researchers from varied backgrounds and fields while emphasizing the inclusion of PWLE and community members in future funding opportunities.

Opportunity 1-2: Provide support and resources to help community members overcome barriers to accessing and completing grant applications and awards. Examples of support would be providing enhanced technical assistance to community investigators navigating the application system.

Recommendation 2:

In future funding opportunities, delineate an expectation for engagement with relevant communities, which can be interrelated but is distinct from engagement with individuals from within communities

Community can be defined in several ways, which is crucial for recognizing and understanding the context of their identities and developing appropriate engagement strategies. From a big-data or biorepository perspective, the following framework has been provided for conceptualizing communities:[63]

- **Formal Communities:** These are formally constituted entities with established governance structures and often legal recognition. Examples include Tribal nations and Indigenous Peoples who maintain their own governance structures (up to and including sovereignty), as well as advocacy organizations with strong internal governance.
- **Informal Communities:** Characterized by less obvious constitutions and normative rules, informal communities include co-located people (e.g., a neighborhood or region) or those with shared lived experiences.
- **Invisible Communities:** Defined within biorepositories by researchers, invisible communities are governed externally, raising concerns about surveillance and consent.
- **Impacted Communities:** Arising in response to specific events or issues, impacted communities are dynamic and responsive, requiring rapid decision-making and governance procedures that allow for flexibility in a changing situation.

When involving formal communities, the NIDDK should only support clinical research which is the genesis of a collaborative effort between the leadership and governance of the impacted communities (where applicable) and the research teams. For example, Indigenous Peoples of the United States have Government-to-Government Relations with various legal parameters regarding human subjects research participation for these communities.[64] Regardless of formal structure, all communities have strengths and potential infrastructure that can contribute to the success of research. To fully elucidate the heterogeneity of diabetes and to achieve robust and varied participation in clinical research, identifying and harnessing these strengths by engaging the leadership and/or governance of these communities will be most impactful.

Informal communities often possess strengths, such as a sense of loyalty or commitment, or may have strength in advocacy for topics of common concern across the community, and the presence of internal knowledgeable liaisons, also known as credible messengers. Formal communities may have the infrastructure, such as appointed liaisons or review boards, to consider biomedical research within the community. These strengths can impact research goals, strengthen community relations, mitigate potential harm, and ensure adherence to legal processes. Aside from community strengths, various engagement barriers exist within communities, including funding, capacity, regulations, and challenging infrastructure hurdles. Researchers cannot overcome these hurdles without acknowledging or understanding these barriers or identifying solutions.

Engagement should be tailored to each community's specific context, recognizing both the sovereign status of Indigenous Peoples and the unique needs and structures of other communities. Research teams should prioritize building collaborative relationships with community leaders and stakeholders to ensure research projects are co-created and executed in partnership with the communities they aim to serve.

Opportunity 2-1: Establish clear expectations that funded research involving communities experiencing health disparities should demonstrate early and sustained engagement with community leaders and governance, where applicable.

Opportunity 2-2: Acknowledge and encourage the use of credible messengers within research development, execution, and dissemination for vulnerable populations included in the research.

Recommendation 3:

Investigator teams need to adequately compensate and provide necessary resources for community members and PWLE to participate in research engagement activities

Inadequate funding can lead to practices where activities are solely intended to "check the box" for engagement but do not execute genuine engagement, which should support tangible learning and collaboration with community members.[65] Additionally, engagement can be facilitated through the provision of adequate resources, including tools and infrastructure as some populations and communities at highest risk for type 2 diabetes often have less centralized access to resources.[58,61,65] The nature and amount of compensation (monetary or otherwise) should be commensurate with the local context, similar to compensation for other team members with similar roles, and provide an equal opportunity to a variety of community members. Compensation that is too high can be coercive and result in biased participation. Conversely, too low compensation will systematically bias the pool of community members, excluding individuals with less financial flexibility to participate, such as those who cannot easily afford to be away from their wage-earning activities for several hours.

Opportunity 3-1: Ensure adequate and agreed upon compensation for community partners or consultants.

This should include language in funding opportunities that communicates the expectation of appropriate engagement budget line items and the administrative review of selected awards to ensure adequate budget allotment for engagement activities.

Opportunity 3-2: Develop co-funding partnerships or cost-sharing with academic, health systems, and research institutions and organizations to facilitate community engagement.

Recommendation 4:

Require demographic and identity data collection related to diabetes heterogeneity using approaches that are advantageous to the community, and not collecting data when harm outweighs benefits

The collection of identity data provides an opportunity for visibility, and with visibility, action can be taken to eliminate health disparities. To obtain rigorous demographics and identity data, there should be active engagement efforts for all communities, especially communities impacted by health disparities. The lack of community engagement in specific sub-communities contributes to invisibility and adverse health outcomes.[66] Efforts should be made to ensure all communities are included and representative data are collected to ensure all communities are engaged. Data collection methods and decisions should be made culturally appropriate to respect all research participants' cultures. There are different health perspectives, and Western approaches to research may not match all perspectives.[67,68]

Investigators and research teams can only be held accountable for inclusive excellence when data are available to demonstrate universal inclusion (or lack thereof). The erasure of communities through specific omission of data collection and capture is inherently harmful to the human psyche and is counterproductive to the goal of achieving optimal health for all.[69] Rigorous data collection provides transparency for levels of inclusion and exclusion across communities, which is necessary to eliminate health disparities.[70,71] Mutual respect, equal participation, shared goals, and a commitment to ongoing collaboration characterize an authentic research partnership, as it fosters a dynamic relationship where all partners actively engage in the research process, leading to more relevant, impactful, and ethically conducted research.

Opportunity 4-1: Strengthen and expand partnerships with national working groups that advocate for communities impacted by health disparities.

Opportunity 4-2: Develop, review, and assist with vetting standardized wording for data collection tools that include demographic, identity, and social needs collection questions.

Opportunity 4-3: Develop educational resources, such as webpages or informational sessions, that demonstrate the critical role of social identity data collection in advancing health disparities research.

Opportunity 4-4: Require demographic data collection that is community-driven and requires researchers to promote fairness, transparency, confidentiality, and accountability in the research (including appropriate training) in future funding opportunities.

Recommendation 5:

Advocate that scientific oversight bodies, such as data and safety monitoring boards, include community-level risk evaluation in approvals and monitoring plans

Policies and processes established by scientific oversight bodies, such as institutional review boards (IRBs), can create barriers or facilitate engagement, depending on the nature and implementation of these policies and procedures. Proactively incorporating regulatory systems with engaged community partners should help facilitate meaningful collaborations and minimize barriers.

Community partners should be recognized and included as equal research partners throughout the scientific oversight process.[72] Researchers and regulatory bodies should be required to engage in cultural sensitivity training to be better informed about the population involved in research. Research regulatory training (human subjects, Collaborative Institutional Training Initiative (CITI program) should include group harm and cultural safety topics.[73-75]

Not all scientific oversight bodies understand or consider community-level impact, and this is a missed opportunity. Equal participation and an adequate community perspective are necessary to ensure that culturally and ethically appropriate guidance and decisions are implemented throughout the scientific oversight process.

Opportunity 5-1: Advocate for revision to the Federal Policy for the Protection of Human Subjects (Common Rule), delineating Criteria for IRB approval (CFR 46.111) such that not only individual-level risk and harms are evaluated, but that community-level impact is considered by scientific oversight bodies when making approval decisions.

Opportunity 5-2: Encourage or mandate that Data and Safety Monitoring Boards (DSMBs) include meaningful participation of community members from communities impacted by health disparities (from input to decision-making).

Opportunity 5-3: Include acknowledgment and encourage research teams to understand and assess the need for community consent when applicable.[76]

Opportunity 5-4: Advocate and support research institutions to provide education regarding community harm and cultural safety training to researchers, staff, and members of the scientific oversight committee.

Opportunity 5-5: Promote efforts to acknowledge and consider mandatory data repatriation, (e.g., data return to the community) while considering the privacy and anonymity of research participants.

Recommendation 6:

Provide enhanced capacity-building resources, which aim to facilitate (i) cultural sensitivity and engagement training focused on researchers, scientific oversight committees, and (ii) scientific and technical research training within communities and individuals motivated to collaborate in research

There is a clear need for bidirectional learning. NIDDK, researchers, scientific oversight committees, and regulatory bodies would benefit from an enhanced understanding of community needs, motivations, fears, strengths, and goals. Additionally, communities affected by diseases and conditions relevant to heterogeneity of diabetes would benefit from a deeper understanding of the research process, its goals, expectations, limitations, and future implications, as well as the enhanced capacity to collaborate meaningfully in research projects.

Both researchers and community members need sufficient capacity to execute effective collaborations. Increased knowledge and mutual capacity should enhance community engagement activities, leading to research studies having a greater impact on the community. Capacity-building resources include, but are not limited to, webinars, print and electronic materials, workshops, and training series.

Well-trained, competent, secure, sensitive, and respectful researchers and regulatory bodies implement techniques and tools that assess readiness, provide transparency, support sustainability, build capacity, and develop and nurture long-lasting partnerships with communities. NIDDK researchers, as well as regulators, would benefit from exploring and implementing existing tools and training that help build competency, safety, sensitivity, and respect for all those engaged in and impacted by research. One toolkit of training is the Community Health Interests for Researchers & Oversight Networks (CHIRON), which encourages researchers, ethics boards, and data access committees to consider group interests as they plan, execute, and report on big health data research.[63]

Opportunity 6-1: Require adequate expertise in engagement methodology for select funding opportunities.

Opportunity 6-2: Create funding opportunities that dedicate resources and scientific support to strengthen engagement capacity among community partners participating in diabetes-related research.

Opportunity 6-3: Support the development and dissemination of engagement tools and resources to enhance the rigor of research engagement activities.[63]

Cross-Cutting Themes Recommendations and Opportunities

Recommendations from all SubGroups were reviewed and common overarching themes were identified across all SubGroups. From these themes, global research opportunities applicable to multiple SubGroups were developed. These opportunities were identified and then removed from the individual SubGroup sections and consolidated into two Cross-Cutting Themes (Data-Science and Health for All), below.

Data-Science Cross-Cutting Theme Recommendations

The Data-Science Cross-Cutting Theme Recommendations reflect the central role of data in advancing our understanding of diabetes heterogeneity. Capturing the full complexity of diabetes requires integrating diverse and emerging data types, ranging from EHR and longitudinal cohorts to wearable sensors, imaging, and digital biomarkers, all within standardized, interoperable frameworks. Without common data and metadata standards, rigorous quality control measures, and harmonized analytic approaches, these rich but disparate resources cannot be fully leveraged. Equally essential are collaborative data-sharing and analytics platforms that overcome policy, governance, and access barriers, ensuring equitable participation and broad utility. Finally, the responsible and transparent application of AI will be key to transforming integrated datasets into robust, actionable insights for research and clinical care. Together, these Recommendations outline a coordinated strategy to build the data infrastructure, governance, and analytic capacity necessary to accelerate discovery, improve outcomes, and understand heterogeneity of diabetes.

Recommendation 1:

Support collection and standardized curation of diverse data types towards prioritizing multimodal data models for understanding diabetes heterogeneity

Understanding diabetes heterogeneity requires integration and analysis of multimodal data, including established and new data types. Examples of areas of need for new data types include data from wearable devices and EHRs, as well as adaptation of standard and novel analytic methods. When integrated with existing data types for which advanced analysis models have been developed, these data types and approaches have the potential to support powerful advances in understanding of diabetes heterogeneity.

Opportunity 1-1: Support collection of comprehensive cross-sectional and longitudinal environmental, behavioral, and lifestyle data appropriate for research in diabetes heterogeneity, including support for their standardized representation to promote incorporation into multimodal data analysis.

Opportunity 1-2: Promote research activities focused on quantifying exposure to domains not regularly captured in traditional diabetes research (e.g., microplastics, natural disasters, complex lifestyle, and exposome).

Opportunity 1-3: Conduct research studies to establish interoperable systems that integrate data from various sources, such as EHR, cohort studies, clinical trials, and real-world evidence in diabetes heterogeneity.

Opportunity 1-4: Support research to develop new data-science methods and adapt existing processes to perform optimally, enabling a robust assessment of the clinical utility and validation accuracy of candidate stratified approaches addressing diabetes heterogeneity.

Recommendation 2:

Promote data and metadata standardization across existing and new modalities to improve interoperability, enhance analysis, and support sustainability in diabetes heterogeneity

Data collected across different platforms and from different studies are often complex and heterogeneous, resulting in critical challenges in cross-study data integration and analysis. Existing data types (e.g., EHRs, longitudinal cohorts, omics data) often lack standardization and interoperability, hindering seamless integration and harmonization. New data sources, including wearable devices (e.g., smartwatches, glucose monitors), advanced imaging techniques (e.g., retinal scans), and digital biomarkers (e.g., facial and vocal expressions), may offer valuable insights into disease risk and progression, but their diverse data types require effective frameworks for their incorporation into broader studies. Variability in phenotyping assays, inconsistent reporting standards, and the absence of metadata benchmarks create barriers to data integration and reproducibility. Developing computational tools to bridge these diverse data types and integration barriers (e.g., harmonizing metadata, benchmarking models, and cross-platform compatibility) will improve the ability to derive meaningful insights into diabetes heterogeneity.

Opportunity 2-1: Promote, incentivize, and enforce current and novel standardization practices across all data types, especially for emerging data modalities and metadata, to ensure consistency and interoperability across research themes in diabetes, with automatic data governance and provenance.

Opportunity 2-2: Promote initiatives to link lifestyle factors with existing longitudinal clinical/laboratory data and comprehensive molecular phenotype data from large EHR/national health registries related to diabetes and its complications.

Opportunity 2-3: Provide training to new and established clinicians and scientists in innovative analytic methods, research study design, and data-science related to capturing lifestyle factors in the context of diabetes prevention and treatment.

Recommendation 3:

Promote standardization for data quality control and assurance, addressing the heterogeneity of diabetes, including tools to report and address bias

There is significant variability and inconsistency in data quality control across different data types. For example, while EHR and biobanks provide the largest samples of individuals with diabetes and its complications, these datasets lack representation across the natural history of diabetes and have high levels of missingness and selection bias based upon medical indication. In addition, technology-specific variability, incomplete standardization of data quality measures, and inconsistent assay protocols contribute to reduced reliability. In diabetes model systems, there is a lack of authenticity validation, limited phenotypic data, and an inadequate number of standardized assays for cellular phenotyping, further complicating cross-study integration and interpretation.

Opportunity 3-1: Data quality and assessment standardization should be established by supporting development of protocols across diabetes-related datasets to ensure reliability and accuracy.

Opportunity 3-2: Support innovative computational models to address biases present in data, such as under-representation of specific populations or structural biases inherent in diabetes data collection processes.

Opportunity 3-3: Enhance data imputation methods to account for missing or incomplete data, ensuring that data-driven insights on diabetes heterogeneity remain robust, equitable, and comprehensive.

Opportunity 3-4: Support developing and validating standardized protocols and methodologies for integrating EHR data for diabetes outcomes research.

Recommendation 4:

Support development and promotion of collaborative data-sharing platforms, including open-access databases, federated databases, and simplification of data use and informed consent

There is a need to encourage collaborative sharing of datasets, not only to address representation gaps and reduce disparities in evidence-based outcomes, but also to maximize the benefits to be gained from research datasets generated. Current challenges to this goal include restrictive Material Transfer Agreements (MTAs), inconsistent consent policies across institutions, and privacy laws that limit the ability to share data. Additionally, constraints imposed by scientific oversight bodies and local regulations further limit the accessibility and usability of models and data. Data sharing is also limited by decentralized and delayed deposition practices, inadequate metadata accompanying deposited datasets, and limited frameworks to support open-access repositories. These challenges create barriers for those researchers with fewer resources and broadly constrain data sharing needed for a comprehensive study of diabetes heterogeneity.

Opportunity 4-1: Establish researcher, user, and data identifiers to implement a standardized system of unique identifiers for researchers, data contributors, and datasets.

Opportunity 4-2: Support creation of robust, user-friendly, open-access databases and collaborative platforms that promote data, tool, and workflow sharing across research communities.

Opportunity 4-3: Support efforts to standardize and simplify data consent procedures by engaging stakeholders and research communities to streamline and standardize data consent processes, ensuring ethical adherence while minimizing administrative burdens.

Opportunity 4-4: Encourage adoption of federated database technology by promoting the development of federated database systems and federated learning models to enable secure and decentralized sharing and analysis of human diabetes data.

Opportunity 4-5: Ethics-by-design models should incorporate ethical considerations directly into the development of AI systems, ensuring alignment with health care priorities and recommendations for diabetes treatment and management.

Opportunity 4-6: Develop and expand scalable and secure data infrastructure to enhance data storage, sharing platforms, and computational resources, including cloud-based systems, related to diabetes heterogeneity.

Opportunity 4-7: Support funding of research to develop and validate shared platforms and other data resources that can handle multimodal and high-dimensional data.

Recommendation 5:

Advance the use of AI models for research and clinical practice through improvement of integrity of data and enhancing utility and operability of AI systems

Emerging AI models integrate large amounts of diverse data types to increase the understanding of diabetes heterogeneity. To fully harness this power while continuing to develop new AI capabilities, several challenges and obstacles must be addressed. AI models often reflect the biases inherent in the data on which they are trained, resulting in disparities in outcomes across various clinical and demographic groups. Protection of privacy while allowing meaningful data sharing for AI model development remains a challenge for the secure and ethical use of AI. It is important to create interpretable models and rigorous frameworks for evaluating AI performance and risks, including increasing availability and affordability for all individuals at risk for, or living with, diabetes.

Opportunity 5-1: Standardize auditing and reporting by implementing uniform processes for auditing AI models to ensure accurate and reliable interpretations, minimize errors, and improve transparency in the prediction and resolution of diabetes heterogeneity.

Opportunity 5-2: Develop models that provide interpretable and human-readable insights into their predictions of diabetes and its complications, thereby enhancing trust among researchers, clinicians, and individuals and supporting the real-world effectiveness and impact of these models.

Opportunity 5-3: Develop cloud-based infrastructure for sharing large AI models between private and public entities, create and maintain open-access models.

"Health for All" Cross-Cutting Theme Recommendations

'Health for All' is an aspirational goal that requires work in medical and non-medical settings to ensure that all residents in the U.S. have the best chance for a healthy life. It requires that disparities in health care delivery are identified and addressed where they exist among populations based on geography, income, age, ancestry, and other social factors. Health for All also means that research is needed to explore and address how social, structural, and environmental factors can promote or harm health, as well as how populations are differentially exposed to these factors. Within diabetes, there have been longstanding differences in outcomes for glycemic control, diabetic complications, and comorbid conditions among individuals with low income, living in rural areas, and socially disadvantaged. These differences include disparities in access to health care, differential health systems care, exposure to harms in the social, built and natural environment, and constrained choices for health behaviors.

Recommendation 1:

Include broad representation of those affected by diabetes in research studies

Full understanding of the depth and breadth of diabetes heterogeneity requires that the most varied population of patients be included in research studies. Currently, most new cases of diabetes are occurring in LMICs; however, most diabetes research and treatment innovations occur in high-income countries, whose populations differ significantly based on genetic ancestry, environmental exposures, and other important factors. Within high-income countries, socially and economically disadvantaged groups have been underrepresented in diabetes research. Having varied and richly representative study populations for diabetes heterogeneity requires intentional and thoughtful work to build trust with individuals and communities, ensuring the broad representation of all groups in research. Community trust is crucial when collecting sensitive personal information and biospecimens. In practice, the addition of a variety of populations necessitates addressing the differential infrastructure and resources that exist within and between countries, as well as among researchers and institutions that work with patient populations currently understudied in diabetes research.

Opportunity 1-1: Research should be supported at institutions that serve populations at high risk for developing diabetes. These institutions often have strong community ties and longstanding trusted relationships but frequently lack adequate research infrastructure.

Opportunity 1-2: Support studies to identify, investigate, and treat atypical forms of diabetes in varied groups (e.g., defined by geography, ancestry, age).

Opportunity 1-3: Conduct research to understand and address barriers to participant recruitment and retention in research studies.

Opportunity 1-4: Encourage research that builds trust with affected communities and enhances access to research teams and facilitates data collection.

Recommendation 2:

Explore potential influences of diabetes heterogeneity that extend beyond biology

There are many biological mechanisms that can lead to diabetes (e.g., immunological reponses, insulin resistance), yet less is known about how nonbiological factors interact with biological mechanisms to differentially increase the risk of diabetes, its control, and complications. It is critical to identify modifiable factors that impact the development of diabetes and the response to therapy.

Intrauterine nutrition affects the risk of developing diabetes later in life. Individuals not exposed to intrauterine undernutrition but who consume high-calorie and low-protein diets for a prolonged duration after birth may also have a higher risk of insulin resistance. Beyond intrauterine effects of nutrition on subsequent diabetes development, food insecurity has been associated with poor diabetes control and increased hospitalizations for hyperglycemia and hypoglycemia. Neighborhoods with higher ratings of vulnerability have higher rates of diabetes and complications, presumably due to factors in the built environment and social environment that have been associated with diabetes in observational studies.[77-79]

Chronic stress (including chronic exposure to neighborhood or regional violence) can lead to overactivity or underactivity of allostatic systems, resulting in subsequent inflammatory responses and stress hormone patterns that increase the risk of diabetes.[80,81] It is unclear the degree to which other environmental toxins and exposures increase the risk of developing diabetes. Research is needed to explore how these nonbiological factors contribute to diabetes heterogeneity. This type of research requires the collection of more comprehensive data on nutrition intake and physical activity, food access, the social and built environment, psychosocial measures, environmental exposures, and other relevant factors.

Opportunity 2-1: Conduct research to study the impact of exposure to neighborhood violence, pollution, and other neighborhood environmental factors on the heterogeneity of diabetes among children and adults.

Opportunity 2-2: Support research to investigate the feasibility and efficacy of strategies that impact modifiable risk factors and determine the effect on progression to diabetes and/or response to treatment, including studies that address the interplay of multiple modifiable drivers of diabetes outcomes.

Opportunity 2-3: Support research to better understand and address factors that affect adherence to diabetes prevention and management strategies and how adherence affects the heterogeneity of diabetes and the progression of complications.

Opportunity 2-4: Conduct research on the magnitude of the treatment effect difference between a healthy lifestyle program for people living in a resource-constrained neighborhood compared with a neighborhood without constraints.

Recommendation 3:

Conduct research on how best to disseminate and implement interventions and information about diabetes heterogeneity within the lay community using accessible language, trusted stakeholders, and high-impact media opportunities

Many Americans struggle with both health literacy and health numeracy, making it difficult to understand health information, including key information about diabetes. Health literacy has been associated with a range of health outcomes, including diabetes knowledge and self-management, and glycemic control.[82,83] In order to ensure that the public has an understanding of diabetes heterogeneity and what this means to individuals in their community, informational messages will need to be tailored to fit a range of audiences, considering literacy, social and cultural beliefs and norms, as well as other essential factors that influence the uptake of information. Research will need to engage a variety of stakeholders, including people with diabetes, health professionals, advocacy organizations, public health organizations, community-based groups, and other trusted brokers within community spaces.

Opportunity 3-1: Support research in the dissemination and implementation related to diabetes heterogeneity that includes collaborations with rural, low-income, and other populations with high diabetes burdens and fewer points of contact with health care systems.

Opportunity 3-2: Support research to develop best practices for communicating and translating research results effectively to the public, with particular focus on the groups who could benefit the most from the research.

Recommendation 4:

Conduct research to understand and address the ways in which innovation and technology may adversely affect health for all

Advances in health technology and medicine have the potential to improve the health, vitality, quality of life, and longevity of patients, including those with diabetes; however, technology can also lead to unintentional harm for some populations (e.g., those with limited health literacy). Many new and effective medications are expensive and accessible only through health insurance plans, making these treatments unavailable to the underinsured and uninsured for those with high morbidity and mortality from diabetes. Research is needed to understand and address differential engagement of health-promoting technologies and behaviors in people with or at risk of diabetes. AI and machine learning methods are being adapted for use in the prediction of diabetes risk and clinical applications for diagnosis, prognosis, and treatment.[84,85] Research is needed in development of principles that promote access to novel therapeutics toward the goal to improve health for all.

Opportunity 4-1: Conduct research on how to achieve greater engagement and participation in health care across populations (e.g., ancestry, socioeconomic status, access to wealth acquisition) with respect to novel digital technologies AI and machine learning approaches.

Opportunity 4-2: Support research to identify and address health care gaps that affect access to health technology and innovation.

Opportunity 4-3: Support research to develop and test practical ways to disseminate newer digital technologies across varied populations and improve digital literacy.

Conclusion

Despite the progress to date addressing heterogeneity of diabetes, much work remains to be done toward the goal of precision diabetology and the routine application of accurate, precise and stratified management approaches for subtypes of diabetes. We continue to recognize that significant heterogeneity of diabetes exists within countries and across the globe and that multiple metabolic pathways that contribute to risk of diabetes are not captured in current definitions of diabetes. We recognize that a major limitation to advancing precision medicine and addressing heterogeneity of diabetes is the reliance on a single clinical marker (i.e., elevated glucose) for diagnosis and management of disease. It is encouraging to note that significant advances have been made toward the goal of subclassifying diabetes and proposing subtypes and that data has been reported that specific subtypes may have specific molecular signatures driving the phenotype. Nonetheless, more research needs to be conducted to achieve the goal of a more accurate and precise diagnostic stratification. There is need for accumulation of data on natural history of diabetes subtypes to improve their clinical utility.

Since the approval of the Working Group formation by the NIDDK Advisory Council in 2023, the WGOC members developed a comprehensive set of Recommendations and Opportunities across all phases of research that are required to fully elucidate and understand heterogeneity of diabetes. This Report provides a detailed overview of the current state of knowledge on the heterogeneity of diabetes and has identified gaps and provided research Opportunities to address the gaps in our knowledge. This Report will inform NIDDK scientific staff of evolving concepts in this field from a global perspective and will be used to stimulate research efforts to develop more discrete definitions of subtypes of type 2 diabetes. Research Opportunities have been presented across all phases of research and across the human lifespan that, if successful, will continue to advance the field. The NIDDK is optimistic that, with continued research investment in diabetes heterogeneity, successful achievement of many of the Opportunities presented under each Recommendation will be actionable and will lead to meaningful reclassification of diabetes and advancements in precision diabetology.

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Appendices

Appendix A: Acronyms

ADA	American Diabetes Association
AI	Artificial intelligence
CGM	Continuous glucose monitor
CHIRON	Community Health Interests for Researchers & Oversight Networks
DSMB	Data and Safety Monitoring Board
EASD	European Association for the Study of Diabetes
EHR	Electronic health records
GWAS	Genome-wide association studies
IRB	Institutional review board
LMIC	Low- and middle-income countries
MTA	Material transfer agreements
NIH	National Institutes of Health
PMDI	Precision Medicine in Diabetes Initiative
PRS	Polygenic risk scores
PWLE	People with lived experience
WGOC	Working Group of Council

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