APPENDIX F

ADVANCES AND EMERGING OPPORTUNITIES IN DIABETES RESEARCH: A STRATEGIC PLANNING REPORT OF THE DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE

The statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC), with leadership from NIDDK, developed a Diabetes Research Strategic Plan to serve as a scientific guidepost to NIH, other federal agencies, and to the investigative and lay community by identifying compelling research opportunities. These scientific opportunities will inform the priority-setting process for the diabetes research field and propel research progress on the understanding, prevention, treatment, and cure of diabetes and its complications. It will also serve as an important guide for research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*. The Plan addresses extraordinary opportunities in 10 major diabetes research areas listed below.

- Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications
- Type 1 Diabetes and Autoimmunity
- The Beta Cell
- Type 2 Diabetes as a Multi-Dimensional Disease
- Obesity
- Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia
- Clinical Research and Clinical Trials
- Special Needs for Special Populations
- Diabetes Complications
- Clinical Research to Practice: Translational Research

The Strategic Plan also includes a chapter that outlines resource and infrastructure development needs to support the implementation of the future directions for diabetes research identified in the Plan.

This Appendix includes specific research questions and future research directions that have been excerpted from the Strategic Plan. Included are chapters with relevance to type 1 diabetes and its complications. Therefore, chapters on "Type 2 Diabetes as a Multi-Dimensional Disease" and "Obesity" are excluded; some sections from other chapters are also excluded if they are not relevant to type 1 diabetes. Some sections cover both type 1 and type 2 diabetes and were included in their entirety. The key questions and future directions, listed under the chapter subheadings, were identified in the strategic planning process as being critically important for overcoming current barriers and achieving progress in diabetes research relative to the chapter's area of focus over the next 10 years. For the complete Plan, please see: http://diabetesplan.niddk.nih.gov.

Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications

Genes and Pathways

Key Questions:

- What are the causal genes and variants influencing or residing within each candidate susceptibility locus?
- Are the candidate genes/regions identified in European-origin populations (where most of the studies have been performed) also operative in other, ethnically diverse populations?
- Do candidate genes/risk variants interact to modify risk, and how is the penetrance of disease alleles affected by environmental factors?
- Are there subsets of genes that, taken together, represent a causal pathway that could define a therapeutic target?

- What are the effects of identified genetic variants on integration of genomic, expression, and proteomic profiling on disease risk?
- Can genetic variation be coupled with gene expression profiles at the RNA and protein levels to catalog target tissues at the population, individual, and cellular levels for both humans and animal models?
- Can model organisms be utilized to advance research from human genetic studies, and can results from model organisms direct targeted human studies?

Future Directions:

- ➢ Develop standardized and emergent protocols for assessing phenotypic characteristics of populations, both clinical and epidemiologic, for use in genetic studies.
- ➢ Understand how candidate genes contribute to disease risk.
- ➢ Elucidate the interactions among genes at the cellular level and discover common pathways of risk.

Detection of Rare Variants

Key Questions:

- How can sequence variation that is rare in populations, yet accounts for familial risk of disease, be identified?
- Can genomic sequence data from many individuals with known phenotypes provide insight into the effect that natural variation in genome structure has on susceptibility to diabetes and obesity?
- What is "normal" sequence variation compared to "risk" variation in the context of environmental triggers that lead to diabetes and obesity?
- Can population-specific DNA sequences be identified that are associated with disease risk and that are predictive of response to therapies?

Future Directions:

- ➢ Perform DNA sequencing in tens of thousands of participants with type 1 diabetes, type 2 diabetes, and obesity to detect all sequence variants that may be associated with risk of these conditions.
- ➢ Correlate sequence variants with the level of risk for development of diabetes, obesity, and their complications.

Gene-Environment Interactions

Key Questions:

- What kinds of sample and data resources are needed for analyzing genetic variation in groups of participants with diabetes and obesity or in healthy populations before they develop complications, so that environmental triggers can be identified in those at high genetic risk?
- How and to what extent will information be collected on environmental triggers, especially unknown/potential triggers for diabetes, obesity, and their complications?
- Can research tools used in mouse models of disease be used to identify potential modifier effects in human genetic data?
- How can genetically determined epidemiologic risk factors be identified and monitored as biomarkers of exposures that interact with genetic risk variants?
- What recent changes in human exposures, diets, or social and behavioral activities contribute to onset of disease in genetically predisposed individuals? Can any of these factors be modified to lower risk?

Future Directions:

- ➢ Determine how candidate genes or sequence variants interact with environmental risk factors that can lead to disease outcome.
- ➢ Develop resources and technologies to study gene-environment interactions.

Epigenetic Contributions to Risk

Key Questions:

- Do DNA methylation and other aspects of epigenetic modification contribute to inter-individual variation in the risk of diabetes, obesity, and diabetes complications?
- Do epigenetic mechanisms correlate with risk and serve as therapeutic targets?
- What is the potential interaction between epigenetic modification and a pro-inflammatory environment and oxidative stress, and how does this interaction affect the risk of diabetes and obesity?

Future Directions:

- ➢ Identify epigenetic markers that influence susceptibility to diabetes, obesity, and/or diabetes complications.

Translation of Genetic Research from Bench to Bedside

Key Questions:

- How can the development of diabetes and obesity investigators who are well-trained, multidisciplinary and interdisciplinary, and able to form research teams be fostered?
- Can an incubator be created for innovative research tools and information technologies focused on translational and behavioral research in diabetes and obesity?
- Will current guidelines on human participants research permit synergism of multidisciplinary and interdisciplinary clinical and translational research to facilitate the application of new knowledge and techniques in clinical practice?
- Can opportunities be developed to bring physiologists (both animal and human) into a productive collaboration with geneticists to bridge research gaps?
- What methods can be developed to translate novel techniques of prediction, prevention, and treatment into the general community?

Future Directions:

- ➢ Optimize the use of genetic and environmental risk factor data in the design of translational and clinical research programs for diabetes and obesity.

Type 1 Diabetes and Autoimmunity

Human Type 1 Diabetes Trials (Prevention/ Reversal/Transplantation)

Key Questions:

- Will additional information about genetic underpinnings of type 1 diabetes allow therapies to be targeted to homogeneous populations, thus increasing their effectiveness?
- Will antigen-specific versus non-specific tolerance induction protocols be safe and effective in preventing progression to overt type 1 diabetes in individuals deemed to be at high future disease risk?
- How can combination therapies using short-course immunosuppressants, cellular mobilization agents, insulin sensitizers, anti-inflammatories, islet antigens,

and/or molecules capable of inducing beta cell replication *in vivo* be tested?

- How can multi-center, international collaborative trials that support biomarker and discovery studies best be accomplished?
- How can very long-term follow-up (*i.e.*, beyond the 1 to 2 year standard for current studies), including metabolic and mechanistic studies, as well as monitoring of adverse events of patients in trials for the prevention of beta cell loss, be accomplished?
- Can biomarkers be developed to stratify patients for trials and to obtain an early indication of therapeutic effectiveness?
- Will drugs designed for the treatment of other disorders, especially autoimmune disorders, and possessing a highly favorable safety profile, prove efficacious as treatment(s) for type 1 diabetes?
- Is it possible that intervention may provide a clinical benefit in patients months or even years after diagnosis?
- Could the principles of "disease staging," often used in oncology, be applied to settings of type 1 diabetes both prior to and well beyond the diagnosis of this disease?

Future Directions:

➢ Conduct coordinated clinical trials to test therapies to prevent or reverse type 1 diabetes.

Natural History and Pathogenesis of Human Type 1 Diabetes

Key Questions:

- What is the natural history of type 1 diabetes, including the precise sequence of events leading to the initiation of insulitis, and continuing on to clinical diabetes?
- Why is type 1 diabetes increasing in incidence and occurring more often at younger ages?
- What is the basis of the observed heterogeneity in type 1 diabetes and is there additional heterogeneity yet to be discovered?
- Is noninvasive imaging of beta cell mass and associated insulitis achievable?
- Can autoimmune pathogenesis at the islet, whether in people in pre-clinical stages of pathology or in autoimmune recurrence in transplant recipients, be measured indirectly in the blood, for example by a measurement of T cell responses to diabetes-relevant antigens? Can such biomarker assays be developed to enhance prediction of type 1 diabetes, facilitate studies of natural history, and serve as surrogate markers in therapeutic trials?
- What is the role of the gut microbiome in disease etiology?

Future Directions:

➢ Discover triggering factors for islet autoimmunity and environmental factors responsible for the recent increase in incidence of type 1 diabetes.

➢ Better define the heterogeneity and diagnosis of type 1 diabetes and foster the development of therapies specific to different forms of the disease.

➢ Delineate the natural history, or histories, of type 1 diabetes.

➢ Elucidate the impact of environmental or other non-genetic factors on development of type 1 diabetes.

➢ Study role of innate immunity in diabetes.

Animal Models/Translational Efforts from Pathogenesis to Therapy

Key Questions:

- Can higher fidelity mouse models of human disease be developed that will improve the ability to predict the efficacy of new therapies in patients?
- Can non-obese diabetic (NOD) mice (and/or higher fidelity mouse models of human disease) be used to:
  - Perform systematic screening of small molecules or other potential therapies for prevention or reversal of type 1 diabetes?
  - Identify environmental agents that precipitate or prevent type 1 diabetes?
  - Identify biomarkers in the blood that can monitor islet cell mass or autoimmunity?
- Can the function of human diabetes susceptibility or protective genes be effectively studied in mouse models?
- Can common pathogenic mechanisms be identified among different autoimmune diseases and in different disease models that may inform the search for new therapeutic targets and strategies?

Future Directions:

- ➢ Rapidly translate new findings on disease pathogenesis in animal models into potential therapies.
- ➢ Use animal models to identify and validate biomarkers of type 1 diabetes.
- ➢ Develop a higher fidelity mouse model of human disease that develops type 1 diabetes.
- ➢ Develop *in silico* models for type 1 diabetes.

Beta Cell Function in Type 1 Diabetes: Autoimmune Attack and Prospects for Recovery

Key Questions:

- What is the beta cell mass/function at onset of type 1 diabetes?
- How much residual beta cell mass/function is required for reversal after immunotherapy? Does it differ with different treatments?
- Can mechanisms that protect mouse cells from autoimmune destruction also protect human islets from autoimmune attack?
- Why is pancreas volume greatly reduced in people with type 1 diabetes? Does this reduction have an influence on disease parameters? Can it be used as a biomarker of disease development or potential for success in therapeutic intervention?
- Are there diabetes-susceptibility genetic variants that determine the ability of beta cells to resist autoimmune attack, or to regenerate or recover function once autoimmunity is controlled?

Future Directions:

- ➢ Develop metabolic tests to detect early signs of beta cell dysfunction.
- ➢ Examine the effect of insulin resistance on the development of type 1 diabetes.
- ➢ Identify genes and mechanisms that protect beta cells from autoimmune dysfunction and/or destruction, in animal models or in humans when possible.

- Define specific and sensitive surrogate markers of physical and/or functional beta cell recovery in response to immunotherapy and determine if beta cell mass can regenerate without reactivating autoimmunity.

Immune Mechanisms of Pancreatic Pathology

Key Questions:

- How diverse are the T and B cell responses to individual diabetogenic antigens, and how can the dominant effect of major histocompatibility complex (MHC) sequence on diabetes susceptibility be explained?
- What are the respective roles of $CD4^+$ and $CD8^+$ T cells, as well as other immune cell subsets (*e.g.*, B cells, NK cells, dendritic cells, and mast cells), in pathogenesis?
- What is the role of regulatory cell populations in diabetes pathogenesis or protection?
- What is the relationship between autoimmunity and inflammation in type 1 diabetes, and what are the roles of other organs such as gut, liver, fat, or others?
- What underlies the variability of attack on different islets within the same pancreas, and can that understanding be used to interdict the disease process?

Future Directions:

- Identify the range of tolerance mechanisms defective in type 1 diabetes models and patients (*e.g.*, genetic polymorphisms in immune system genes) and delineate precisely where the cellular and molecular defects lie.
- Define how auto-inflammatory infiltrates and beta cells communicate with each other in controlling type 1 diabetes progression.
- Understand the repertoires of responding lymphocytes, including T cells and B cells.
- Identify the range of regulatory cell populations potentially defective in type 1 diabetes and learn which regulatory populations—defective or not—provide good therapeutic opportunities.
- Define which pathways are shared by different autoimmune diseases and which are disease-specific.
- Extend and preserve existing pancreas repositories and data banks, which are critical for direct examination of pancreatic pathology.

The Beta Cell

Integrated Islet Physiology

Key Questions:

- What is the full communication network that exists between the five endocrine cell types regulated in the islet? What is its role in disease progression?
- Are novel receptors and paracrine factors present in the endocrine pancreas?
- What are the functional interactions among the exocrine, ductal, and endocrine cell types?
- How does islet vasculature affect islet function and engraftment after transplant?
- How is islet innervation established? Does it change over time and/or in response to physiological cues and disease states? How does it affect islet function?
- What is the integrated physiology of the human islet? How does this differ from regulation in rodent islets?

Future Directions:

- Investigate integrated islet paracrine regulation.
- Develop drug therapies targeting islet signaling pathways.
- Develop scaffolds and other support systems for beta cells.
- Increase understanding of human (versus rodent) islet physiology.
- Determine the influence of the intrauterine environment on islet development and function.

Beta Cell Dysfunction and Failure

Key Questions:

- What are critical steps of unfolded protein response (UPR) that could be manipulated to improve beta cell function and survival?
- Which of the nutrient sensing pathways contribute to beta cell loss?
- Which of the intracellular signaling pathways can be manipulated to preserve beta cell function and mass?
- What are the initiating events, participating cells, and destructive processes underlying the intra-islet inflammatory response?
- What are common features of immune-mediated damage in type 1 and type 2 diabetes, and how might this potential mechanistic overlap inform the development of new therapeutic approaches for both diseases?

Future Directions:

- Discover ways of modulating intra-islet inflammatory mediators in order to prevent insulitis in type 2 diabetes.
- Develop pharmacological agents to modify key signaling molecules to preserve and protect beta cell function.

Cellular Replacement Therapies for Diabetes

Key Questions:

- Are there ways to promote successful islet engraftment and survival so that people require fewer islets and/or transplants to produce sufficient amounts of insulin?
- Can researchers harness the information from a fundamental understanding of the developmental biology of the endocrine pancreas to generate fully functional beta cells from stem cells *in vitro*?
- Can induced pluripotent stem (iPS) cells be generated safely for patient-specific cell replacement therapy, eliminating the concern of genome integration by the associated viral vectors?
- What are the underlying principles of cellular reprogramming, and under what physiological or pathophysiological conditions will transdifferentiation, transdetermination, and reprogramming occur?
- What are developmental and/or epigenetic factors that affect pancreatic endocrine fate?
- Given the number of ways to increase beta cell mass in rodent models, can these findings be translated into increasing beta cell mass in humans?
- What are common features in beta cell replication between rodents and humans at the physiological periods when replication is known to take place (neonate, puberty, and pregnancy)?

Future Directions:

- Improve islet transplant procedures by determining the optimal sites for islet transplantation and developing novel islet survival strategies.
- Define a molecular signature for endogenous human beta cells, as well as for human stem cell-derived beta cells, and their progenitors.
- Discover late developmental pro-beta cell signals and use these signals to produce large numbers of functional human beta cells from stem/progenitor cells.
- Generate large quantities of fully functional beta cells through the transdifferentiation or direct reprogramming of other adult or progenitor cell types *in vitro* and/or *in vivo*.
- Develop animal models to test the engraftment, survival, and metabolic impact of human beta cells or islets derived in culture from stem/progenitor cells.
- Create new animal models of human diabetes.
- Understand the cell types, signaling pathways, and genes that control islet cell mass and beta cell replication and are relevant to the regenerative capacity of the human islet.

Imaging the Pancreatic Islet

Key questions:

- What are the best technologies, reagents, and targets for noninvasive imaging of pancreatic beta cell mass and function? For islet inflammation?
- How best can transplanted islets be monitored *in vivo*? Can angiogenesis and neurogenesis in these islets be visualized directly, and can imaging be used to monitor the life cycle and common causes of loss of the transplanted tissues?
- How does beta cell mass change throughout the normal human lifespan? What are the effectors and natural history of cell loss in diabetes? What is the relationship between mass and function in health, pregnancy, obesity, insulin resistance, etc.?

Future Directions:

- Assemble interdisciplinary environments and teams to work on imaging the beta cell, and invite cross-pollination from related fields such as cancer and neuroimaging.
- Identify cell-specific beta cell surface proteins as molecular imaging targets and use high-throughput methods to find or produce highly specific, tight-binding, small molecule or peptide imaging agents.
- Recruit chemists to design imaging agents for beta cell targets, or to improve the kinetic and imaging properties of existing promising agents.
- Develop novel, noninvasive technologies to monitor islet cell function, islet angiogenesis, nerve function and growth, and inflammation.
- Define the biology of promising imaging agents and their cell targets, such as the expression in development and islet life cycle, cellular location during function, and other fundamental properties.

Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia

Glucose Sensors

Key Questions:

- Can accuracy and reliability of glucose sensors be improved?

- Can new glucose-sensing technologies be developed?
- Will the incorporation of nanotechnology strategies and the use of smart biomaterials be able to improve reliability and durability of sensors?
- Will it be possible to develop a reliable and durable implantable sensor?
- Will it be possible to develop new technologies/strategies for a noninvasive, reliable, low cost, continuous glucose sensor?
- Will universal design strategies for sensor development be applied to facilitate use by people with diabetes?

Future Directions:

- ➢ Develop improved glucose sensors.
- ➢ Validate glucose-sensing technologies.
- ➢ Translation.

Algorithm Development—*In Silico*/Simulation Models

Key Questions:

- What outcome measures are suitable for judging the effectiveness of closed-loop control in relatively short-duration clinical trials? What would be the "standard" performance criteria? What degree of control error is acceptable?
- What are the requirements for designing control modules?
- Can *in silico* models of human metabolism be improved by making them more powerful in terms of generating "virtual participants" for *in silico* trials? Can a rich tracer database on type 1 diabetes (adult and children) be developed? Can counter-regulation and exercise be incorporated? Can a type 2 diabetes simulator be developed?
- What safety features can be incorporated into controllers?

Future Directions:

- ➢ Using system biology approaches, develop a comprehensive computer simulation environment allowing for efficient and cost effective *in silico* experiments with diabetes treatments.
- ➢ Develop effective closed-loop algorithms for clinical and outpatient use.

Insulin—Improving Delivery and Formulation

Key Questions:

- Which insulin delivery approaches result in clinically relevant improvements and are acceptable to the user?
- How do market-specific cost constraints influence the optimization of novel delivery methods, devices, and insulins?
- What changes in insulin chemistry and/or physical properties would most likely improve its use in alternative delivery routes, devices, and/or materials?
- How can the potential risk of alternative delivery sites and insulin chemistries to produce unwanted metabolic, toxic, or immunogenic effects be quantified and reduced?
- How may the automated delivery of insulin counter-regulatory hormones such as glucagon be integrated into current or future closed-loop systems? What changes in glucagon chemistry and/or physical properties are needed to have more effective and stable glucagon formulations for delivery by pumps?

Future Directions:

- Establish standardized pre-clinical models for safety and efficacy testing of alternative insulin delivery methods, materials, and devices that dependably predict their potential clinical utility.
- Develop integrated insulin delivery systems that improve the quality of life.
- Develop failsafe devices or biomaterials that respond based on low glucose levels to release glucagon or other insulin-counteractive therapeutics to prevent hypoglycemia.
- Reduce immune responses to facilitate alternative site and/or long-acting polymeric insulin delivery systems.
- Develop new insulins with increased stability at high concentrations and minimal, reproducible subcutaneous absorption delay time.
- Develop a family of non-toxic, non-antigenic, low molecular weight molecules that effectively and specifically bind glucose in the presence of serum components and across the physiological range of glucose concentrations, from hypoglycemic to hyperglycemic levels.

Telemedicine

Key Questions:

- What are the best technological solutions (both hardware and decision-support software) to best enable telemedicine to be easily and effectively applied in clinical practice?
- What types of behavioral modification tools or incentives can be developed to facilitate communication and adherence to telemedicine-generated instructions?
- Can high blood glucose or low blood glucose alerts be sent automatically from a glucose meter to a health care provider by way of a Web server to elicit an immediate assistance response that could reduce emergency room visits?
- Can personal digital assistant (PDA) applications ("apps") for diabetes management, which track blood glucose, food intake, insulin, and exercise, improve outcomes?
- How can telemedicine platforms be integrated into an automated closed-loop system?

Future Directions:

- Develop telemedicine approaches that can be incorporated as components and/or adjuvants of an artificial pancreas.
- Determine whether online peer-to-peer management can improve diabetes outcomes.

Tissue Engineering for Replacement of Pancreatic Islets

Key Questions:

- Will the development of novel biomaterials contribute to more effective immunobarrier/encapsulation methods to establish and maintain a functional bioartificial pancreas using transplanted islets from different sources?
- What methods can be developed for effective vascularization of islets after implantation?

Future Directions:

- Improve perfusion of islet cells within a graft site.
- Develop new biomaterials and immunobarrier protection for transplanted islets.

- Pursue approaches to scale up and commercialize production.

Impact of Closed-Loop Control on the Pathophysiology of Diabetes

Key Questions:

- Can an artificial mechanical pancreas or islet replacement restore glucose counter-regulation and hypoglycemia awareness and preserve brain function in people with type 1 diabetes, especially young children?
- Can early intensive insulin therapy increase beta cell survival and prevent the loss of the glucagon response to hypoglycemia in people with new-onset of type 1 diabetes?
- What are the short- and long-term consequences of the route of delivery of insulin on glycemic outcome, vascular complications, and body weight?
- Is glucose the only target that should be used in developing closed-loop systems? Should additional compounds be measured online, *e.g.* insulin, glucagon, other metabolites?
- Are the differences between systemic and portal administration significant enough to favor technologies (mechanical or cellular) that deliver insulin to the liver—its primary site of action?
- Can incorporation of automated glucagon delivery increase defenses against hypoglycemia without excessively raising blood glucose?

Future Directions:

- Determine the impact of an artificial mechanical pancreas on brain function, fuel metabolism, and structure, especially in children.
- Determine if a closed-loop system artificial mechanical pancreas is sufficient to restore normal glucose counter-regulation and reverse hypoglycemia unawareness.
- Determine whether an artificial mechanical pancreas (or implanted engineered islets) can preserve beta cells and maintain alpha cell responses to hypoglycemia in type 1 diabetes if given early, when some insulin secretion is still present.
- Determine whether insulin delivery via the portal vein will be more effective in achieving normoglycemia by reducing insulin resistance and enhancing portal sensing of glucose and gut peptides.
- Develop methods to measure insulin levels in real time, to provide input to closed-loop feedback algorithms.

Behavioral Aspects

Key Questions

- What are the challenges and benefits of new diabetes technologies for individuals with the disease, including physical (*e.g.*, complexity of use, ease of availability), behavioral (*e.g.*, cognitive load, adherence, time requirements), psychological (*e.g.*, quality of life, fear of hypoglycemia), and social (vocational and family functioning) impacts?
- What factors contraindicate the use of specific diabetes technologies for individuals with diabetes (*e.g.*, age, knowledge, psychological status, cognitive development, functional status, treatment regimen, type and stage of diabetes, and home environment and disease management support)? How can accessibility and usability be increased across populations?

- How can these technologies be more accessible to people from different backgrounds and those with educational, sensory, motor, and cognitive limitations? Has the human/technology interface been designed to be easy to use for people with limited literacy and numeracy skills?
- What are the most effective ways for health care providers to incorporate new technologies and the data they produce into practice?

Future Directions:

- ➢ Quantify the broad-ranging impact of new diabetes technologies on people with diabetes.
- ➢ Increase accessibility and usability of technologies by people with diabetes-related (and non-diabetes-related) functional impairments and disabilities.
- ➢ Increase adoption and effective use of technologies across the lifespan.
- ➢ Increase employment of generic new technologies to promote positive health behavior change in people with diabetes.
- ➢ Develop more effective information and educational and training methods for health care providers in use of diabetes technological advancements.

Design of Clinical Trials and Clinical Outcomes

Key Questions:

- What are appropriate outcome measures (*e.g.*, HbA1c, reduction in hypoglycemia, reduction in glycemic variability) for clinical trials of artificial mechanical pancreas technologies in people with type 1 or type 2 diabetes?
- Can continuous glucose monitors (CGM) or an artificial mechanical pancreas be used successfully in insulin-requiring patients with type 2 diabetes to maintain HbA1c targets with less hypoglycemia?
- Can reduction of glycemic variability in people with type 2 diabetes who are insulin-dependent lead to improved outcomes, such as reduced diabetic nephropathy, reduction in cardiac arrhythmias in people at high risk for cardiac mortality, and/or reduction of systemic inflammation and oxidative stress?
- What is the value of CGM and/or closed-loop insulin delivery devices in the intensive care unit?
- Can an artificial mechanical pancreas prevent hypoglycemia and/or diabetic micro- and macrovascular complications?
- Should the measurement of vital signs such as heart rate, temperature, and breathing rate be monitored together with glucose monitoring in clinical studies to prevent hypoglycemia and excessive glycemic postprandial excursions?

Future Directions:

- ➢ Study the impact of closed-loop glucose control on exercise and nocturnal hypoglycemia.
- ➢ Determine the efficacy of CGMs and eventually of closed-loop glucose control to improve disordered fuel metabolism and reduce hypoglycemia and diabetic complications in people with type 2 diabetes who require insulin treatment.
- ➢ Determine whether closed-loop glucose control can preserve beta cell function in people with new-onset type 1 diabetes or with type 2 diabetes.

- Conduct long-term studies of closed-loop glucose control in children and adolescents.
- Study use of continuous glucose monitoring and closed-loop insulin delivery systems in people with gastroparesis.
- Study use of closed-loop technologies in the intensive care unit (ICU).

Clinical Research and Clinical Trials

Treatment

Key Questions:

- Are there approaches to the initial treatment of type 2 diabetes that will reverse or slow the decline in beta cell function that has been shown to occur over time?
- What is the optimal timing for diabetes interventions? Do specific treatments have maximum benefit at different stages of the disease?
- What genetic factors or other patient characteristics influence the choice of initial therapy for individuals?
- How can adherence to diabetes treatments be improved?

Future Directions:

- Conduct studies to preserve endogenous insulin secretion or induce "remissions" of diabetes.
- Determine whether preventing or delaying diabetes can also delay or prevent the chronic complications of the disease.
- Evaluate the effect of bariatric surgery procedures on obesity, diabetes, and underlying pathophysiology.
- Evaluate early effects and duration of action of commonly used anti-diabetic drugs for the initial treatment of early type 2 diabetes.
- Identify biomarkers.
- Design well-powered, comprehensive clinical trials aimed at individualizing therapy of type 2 diabetes.
- Examine the causes of and means of improving poor adherence to diabetes treatment regimens.
- Describe the epidemiology of hypoglycemia.
- Determine whether hypoglycemia unawareness can be prevented or reversed.

Etiology of Diabetes and Its Complications

Key Questions:

- Can genetic information improve disease prediction over currently available clinical markers?
- Can genetic information predict response to lifestyle or pharmacological interventions in disease prevention or treatment?
- Can genetic information predict the development of diabetic complications? For instance, do genetic predictors of hyperglycemia also influence risk of coronary heart disease?
- What are the etiologic factors that explain clinical heterogeneity and provide a rational molecular basis for disease taxonomy, particularly in type 2 diabetes?
- What are the mechanisms underlying the impact of intrauterine exposures or diet and exercise on the risk of developing type 2 diabetes?
- What is the impact of environmental exposures on the risk of developing type 1 diabetes?
- What is the role of sleep disturbances in increasing the risk of type 2 diabetes? What is the effect of treating obstructive sleep apnea in the prevention and therapy of type 2 diabetes?

Future Directions:

- Continue to expand knowledge of the genetic basis for type 1 and type 2 diabetes.
- Continue to incorporate newly discovered variants into genetic prediction models using existing prospective population cohorts.
- Conduct studies to assess how environmental and genetic factors interact to produce type 2 diabetes and affect responses to interventions.
- Identify factors that influence the evolution of type 1 diabetes.
- Harness genetic information to characterize individual susceptibility to diabetic complications.
- Conduct studies to improve understanding of both the relative importance and the mechanism(s) by which sleep disturbances increase the risk of type 2 diabetes.
- Evaluate whether treating obstructive sleep apnea has an effect on the prevention and treatment of type 2 diabetes.

Complications

Key Questions:

- How does the pathophysiology of atherosclerosis differ in people with type 1 diabetes, in people with type 2 diabetes, and in non-diabetic populations?
- How important is insulin resistance in the development of macrovascular complications in people with type 1 diabetes?
- What are the principal mediators of atherosclerosis in people with type 2 diabetes and can specific targeted interventions be developed?
- How important is aggressive and sustained blood pressure and lipid lowering in reducing the risks of micro- and macrovascular complications in people with type 1 diabetes, and when should they be implemented in the course of the disease?
- What is the mechanism of the adverse impact of renal disease on cardiovascular disease (CVD) in individuals with type 1 and type 2 diabetes?
- Can reliable biomarkers of disease, including the long-term microvascular and cardiovascular complications, be identified to make clinical trials more efficient and guide therapy?

Future Directions:

- Define optimal treatment to reduce CVD risk in people with type 1 diabetes.
- Assess the rate of development of atherosclerosis in people with type 1 diabetes and investigate which interventions will have the most salutary effects and when they should be applied.
- Examine the role of coagulation abnormalities as risk factors for CVD in type 1 and type 2 diabetes patients.
- Assess how neuropathy contributes to unique CVD risk in people with diabetes.
- Examine the role of nephropathy in contributing to CVD in people with diabetes.
- Develop surrogate end points and biomarkers that can be used in studying interventions to decrease vascular complications in diabetes.
- Study the effect of glycemia and insulin resistance on cognitive function.

Special Needs for Special Populations

Pregnancy and the Intrauterine Environment

Key Questions:

- What are the immediate- and long-term health outcomes for offspring of women treated for diabetes or placed on weight maintenance or weight loss regimens during pregnancy?
- What noninvasive fetal measurements can be used to quantify diabetic "fetopathy" *in utero*? How can such measurement(s) be applied clinically to identify pregnancies in need of intensified maternal glucose control?
- Which anti-diabetic treatments work to mitigate perinatal and/or long-term complications in such pregnancies?
- By what mechanisms does the intrauterine environment increase the risk of the offspring developing obesity and diabetes?
- What biomarkers can be used to monitor women who have had gestational diabetes to determine if their glucose homeostasis is deteriorating, even before glucose levels become impaired? What interventions can actually stop progression to diabetes?

Future Directions:

- ➢ Identify the safest and most effective approaches to achieve optimal glycemic control during pregnancy.
- ➢ Determine the effects that different interventions for diabetes and/or obesity in mothers have on the long-term health outcomes for offspring.
- ➢ Develop new approaches to antepartum monitoring and management of gestational diabetes.
- ➢ Develop effective clinical approaches to prevent birth defects in diabetic pregnancies.
- ➢ Investigate the progression to type 2 diabetes and its mitigation in women with prior gestational diabetes.

Diabetes in Children and Youth

Key Questions:

- What is the role of overweight and obesity in the development of diabetes—including hybrid diabetes—in children and youth? Are there racial and ethnic differences?
- How does the development of overweight/obesity in children or youth affect diabetes management and outcomes, and contribute to patterns of disordered eating?
- Do children with hybrid diabetes have the same genetic, environmental, and cultural risk factors as those with type 1 diabetes?
- How can children and youth be more successfully transitioned to adult management of diabetes? What are the most effective and affordable ways for parents, caregivers, and individuals with diabetes to become motivated and competent to manage diabetes?
- How can children and youth with diabetes obtain optimal support for their diabetes care from environments outside the home (*e.g.*, day care, schools, colleges, community organizations)?
- What complications and risk factors for complications are present in youth with diabetes?
- Can diabetic ketoacidosis (DKA) rates be significantly reduced in the United States, at presentation and over the course of childhood diabetes?

- How can the interactions between the four main modifiable parameters influencing glucose control (insulin administration, diet, physical activity, and stress) be better understood? What types of interventions would be successful and cost effective at achieving optimal glycemic control and improving quality of life?
- Can pre-diabetes be identified (by a cost effective strategy) and the development of type 2 diabetes in children and adolescents be delayed or prevented?

Future Directions:

- ➢ Determine whether the increase in type 1 diabetes in younger children is due to increases in obesity/overweight.
- ➢ Characterize the role of obesity in contributing to inflammation and insulin resistance in all forms of childhood diabetes.
- ➢ Develop effective weight loss strategies, in the context of the growing and developing child, for children with all forms of diabetes who are overweight.
- ➢ Develop cost effective methods for assessing and tracking diabetes complications and risk factors for complications in children and youth with diabetes.
- ➢ Study behavioral methods to improve treatment adherence in the context of a chronic disease, including a better understanding of the way treatment approaches need to evolve with the maturation of the child.
- ➢ Determine risk factors for the development of DKA and establish approaches to reduce rates of DKA in the United States.

Diabetes in Older Adults

Key Questions:

- What are the optimal strategies for motivating older people to improve and sustain lifestyle changes that can help prevent or control diabetes?
- What are the appropriate (optimal) glycemic, blood pressure, and cholesterol targets across the spectrum of health for older adults to help prevent diabetes complications (and maintain quality of life)?
- If it is not feasible to reach targets for all three risk factors (glycemia, blood pressure, and cholesterol) due to therapeutic complexity, polypharmacy, costs, and/or competing medical conditions, how should risk factor control be prioritized to limit morbidity and mortality in older adults?
- How does diabetes and its treatment affect other health issues faced during aging, such as falling, osteoporosis, incontinence, polypharmacy, and declines in functional status?
- For the frail, older adult with diabetes and limited life expectancy, what are the most important treatment priorities if the goal is to maintain quality of life and decrease the risk of the geriatric syndromes?

Future Directions:

- ➢ Determine how to activate older adults with or at risk for diabetes to improve and sustain lifestyle modification.
- ➢ Determine the optimal strategy to manage hyperglycemia and minimize cardiovascular risk in older adults with diabetes.
- ➢ Study differential drug clearance in older adults, as well as across the lifespan and across different races and ethnicities.

Diabetes Complications

Metabolic, Biochemical, and Signaling Pathways

Key Questions:

- How do the identified molecular pathways associated with diabetes interact within the cell and does this vary for different cell types?
- Are there undiscovered molecular pathways that contribute to diabetes complications?
- What protective pathways are present and how do they interact with other pathways? Do complications arise from an imbalance of maladaptive to adaptive responses?
- What are the relative contributions of hyperglycemia versus impaired insulin and other growth factor signaling in the development of diabetes complications?
- What is the effect of large dynamic changes in the levels of glucose and other metabolites in comparison to sustained elevations?
- Why do cells exposed to the same systemic factors have different pathologies? Why does the apparently global pathogenic mechanism of increased mitochondrial activity have variable consequences in different cell types?
- What is the clinical significance of the identified biochemical changes in the cell induced by diabetes?

Future Directions:

- ➢ Develop better tools to assess mitochondrial function, transport, number, fission/fusion states, transcription factors, and DNA.
- ➢ Improve mitochondrial function in tissues in which mitochondrial dysfunction contributes to complications.
- ➢ Develop a better understanding of the immunologic pathways common to type 1 and type 2 diabetes and diabetes complications.
- ➢ Develop better tools to study glycation and lipoxidation of proteins.
- ➢ Determine if modulators of autophagy affect diabetes complications.
- ➢ Develop tools and approaches that produce a more global understanding of the cellular effects of diabetes and a more specific understanding of the effects of diabetes on individuals.

Genetics and Epigenetics

Key Questions:

- What are the genes that predispose or protect people from developing end-stage renal disease, diabetic retinopathy, neuropathy, and other diabetes-associated complications?
- How do candidate genes identified by genome-wide studies contribute to the pathogenesis of diabetic complications?
- How do epigenetic mechanisms fit within the context of other known cellular mechanisms for diabetes complications?
- Are epigenetic changes in chromatin responsible for metabolic memory? How do they interact with other persistent effects of glucose control, such as glycation and oxidation of long-lived macromolecules?
- Is epigenetics the mechanism by which birth weight determines adult susceptibility to diabetes and coronary heart disease?
- What is the role of small regulatory RNA, in particular the microRNA, in the development of diabetes complications?

Future Directions:

- Identify the key genetic factors predisposing to or protecting from diabetic complications and define the population genetic architecture underlying this risk.
- Test the role of genes identified from genome-wide association studies (GWAS).
- Incorporate new genomic and epigenomic technologies to evaluate diabetic complications.
- Characterize epigenetic changes or patterns of changes that can be used in population studies to probe the questions of metabolic memory.
- Investigate the changes in microRNA profiles associated with diabetes complications and the downstream effects of identified microRNA.

Tissue and Organ System Injury

Key Questions:

- How does systemic inflammation from dysregulation of the innate and adaptive immune systems affect specific tissues, such as the periodontium, bone and endothelium?
- What are the mechanisms of injury in specialized cells, such as podocytes, pericytes, Müller cells and interstitial cells of Cajal?
- What distinguishes cardiovascular, kidney, and urologic disease associated with diabetes from non-diabetes related forms of these diseases? Does diabetes accelerate the same pathologic processes or have unique components?
- What mechanisms are responsible for the increased mortality in people with diabetes and end-stage renal failure?
- Is there a point in the progression of diabetes complications when the pathologic process becomes relatively independent of the diabetes-related factors that initiate it? Is there a point when the progression becomes irreversible?
- What are the pathological and molecular correlates of autonomic neuropathy? What are the biologic mechanisms involved in the bi-directional associations of depression and diabetes and Alzheimer's disease and diabetes?
- To what extent does the pain associated with diabetes reflect peripheral tissue injury versus altered central nervous system (CNS) processing and perception of pain?

Future Directions:

- Develop *in vitro* models to study vascular complications.
- Establish bio-repositories of human cells and tissues.
- Determine the mediators of dyslipidemia-induced renal and neuronal injury.
- Pursue cross-disciplinary research to understand the basic science for neurovascular disease related to diabetes.
- Understand the mechanisms by which diabetes affects the enteric nervous system and related elements in the gastrointestinal system.
- Explore the "temporal theory" of urinary incontinence and diabetic uropathy.
- Incorporate measures of depression, cognitive impairment, brain vascular lesions, and Alzheimer's disease in longitudinal studies of diabetes complications.

Tissue Repair and Regeneration

Key Questions:

- Can the complications of diabetes be reversed by stimulating formation of normal new vessels and re-growth of nerves? Is this possible despite continued hyperglycemia?
- How do the various pathways leading to abnormal vascular proliferation, loss, and permeability contribute to complications in different tissues?
- Can restoration of the regulation and oxygen sensing of hypoxia inducible factor (HIF)-1 alpha rescue the diabetic impairments in neovasacularization?
- How do dysfunctional repair mechanisms contribute to poor recovery from maternal injuries of childbirth and the resultant increased risk of stress incontinence and female pelvic floor disorders?
- How are specific populations of stem/progenitor cells affected by diabetes? Are these abnormalities reversible through optimal diabetes treatment or therapies targeted to stem/progenitor cells?
- Will new cell reprogramming techniques, such as induced pluripotent stem (iPS) cells, lead to individualized cell therapy?

Future Directions:

- ➢ Elucidate the mechanisms underlying the poor revascularization response to ischemia in diabetes.
- ➢ Characterize the impairments in stem and progenitor cell populations.
- ➢ Develop cell-based therapies.

Biomarkers, Imaging, and Bioinformatics

Key Questions:

- Can early diabetes-induced changes in tissues and organs be detected by noninvasive imaging?
- Will computational models that incorporate several biomarkers and imaging results create a composite analysis that is a better measure of disease progression than the individual components?
- What are the indicators that predict an irreversible step in the progression of diabetes complications such as the identification of a vulnerable atherosclerotic plaque that is likely to rupture?
- Why do agents that prevent the onset of diabetes complications in rodent models not prevent complications progression in humans? Are intermediate models such as swine or nonhuman primates key steps in paths to translation?
- How can the large amount of data generated by genomic, epigenomic, and high-throughput screening experiments be synthesized into new, testable hypotheses on diabetes complications?

Future Directions:

- ➢ Develop biomarkers for diabetes complications.
- ➢ Leverage technological advances in noninvasive imaging.
- ➢ Improve animal and cell models.
- ➢ Transform high-throughput screening to elucidate the complexity of diabetes complications.
- ➢ Apply systems biology and bioinformatics tools to the analysis of data generated on human samples and experimental models.

Therapeutic and Preventive Strategies

Key Questions:

- Do treatments that prevent the development of complications also prevent the progression of complications?
- What is the impact of diabetes duration and pre-existing tissue damage on the ability to respond to therapies?
- What behavioral interventions improve diabetes self-management and prevent complications?
- Will combination therapies be more effective than single therapies? Can mechanisms for testing combination therapies be developed?
- What are approaches that will lead to individualizing therapies? For example, which diabetic individuals will benefit from a therapy that uncouples oxidant and carbonyl stress from hyperglycemia?
- How can therapies be targeted to specific tissues?

Future Directions:

- ➢ Personalize drug development and treatment.
- ➢ Improve behavioral approaches to treating co-morbid depression and diabetes.
- ➢ Identify novel therapeutic targets and develop more effective approaches for the prevention and treatment of diabetic complications.
- ➢ Target therapies to specific compartments.
- ➢ Establish a mechanism for early evaluation of therapeutic agents parallel to the pharmaceutical industry.

Clinical Research to Practice: Translational Research

Diabetes Clinical Care

Key Questions:

- What are the best approaches to optimize cardiometabolic risk reduction in diverse populations with pre-diabetes or type 2 diabetes?
- How can diabetes management and outcomes be improved in older persons with diabetes who often have serious comorbidities?
- How can diabetes management processes be improved to alleviate the burden of disease in younger people with diabetes?
- What is the most appropriate sequence, rate of intensification, and tailoring of therapeutic goals to individual patient characteristics to optimize health outcomes and safety?

Future Directions:

- ➢ Develop individualized care approaches to optimize outcomes.
- ➢ Identify methods to improve the quality of life and outcomes of older persons with diabetes.
- ➢ Identify strategies for attaining optimal health outcomes in youth with type 1 diabetes.
- ➢ Determine systems of care that optimize processes and improve outcomes for people with diabetes.
- ➢ Find ways to make clinical trials more generalizable to diverse populations in different settings.

Patient-Centered Care

Key Questions:

- What self-management approaches support clinical care and ensure better outcomes for those whose diabetes is accompanied by multiple comorbidities?
- Which factors unique to the individual with diabetes, intervention, health care system, and context outside of the health care setting contribute to the success of self-management approaches?
- How can people with diabetes become more effectively engaged in the self-management of their disease in concert with their health care provider's efforts?
- How can evidence-based self-management interventions, using cognitive behavioral approaches, be incorporated into clinical and community-based care?

Future Directions:

- ➢ Identify a concise, practical set of behavioral and psychosocial factors, including both process and outcome measures, that can be collected and used on a routine basis to inform patient-centered care.
- ➢ Understand the long-term effects of diabetes interventions with regard to sustained behavioral change (patient and/or provider) and diabetes health outcomes.
- ➢ Understand how to increase diabetes self-management.

Systems of Care

Key Questions:

- How can multi-level interventions, combining policy/marketing, community, organization, delivery system, provider, and patient/family components, be implemented and sustained to improve diabetes care and outcomes?
- What are the key principles for adapting evidence-based interventions to real world settings in ways that make them locally relevant, preserve their effectiveness, and expand their reach to a higher proportion of people with diabetes?
- How do novel mechanisms for payment of health care services impact the process and outcomes of diabetes care?
- How can interventions to control diabetes be cost effective for society and financially feasible from the perspective of individual payers and health care organizations?
- What practical measures of the quality/processes of diabetes care bear the strongest relationship with better downstream outcomes? Can reporting of such measures and novel methods of payment improve these outcomes?
- Can decision support tools or other health information technologies be used to facilitate breakthroughs in clinical performance related to diabetes care and quality improvement?

Future Directions:

- ➢ Understand how changes in the structure of health care delivery systems can lead to improvements in diabetes care and prevention.

- Develop strategies to implement and sustain organizational efforts to improve diabetes care and outcomes.
- Integrate multi-level interventions (combined policy/marketing, organization, provider, patient/family, community) synergistically to enhance the likelihood of success and sustainability.
- Identify optimal settings for delivery of diabetes interventions.
- Evaluate "natural experiments" that occur when policy or care changes are instituted in health care settings that impact large numbers of people with diabetes.
- Develop new approaches to study the impact of system- and policy-level interventions on diabetes control and prevention.
- Identify promising strategies, such as pay-for-performance and public reporting of performance measures, to bridge the persistent gap in quality of diabetes care and outcomes.
- Identify new uses of health information technology to improve diabetes care.

Resource and Infrastructure Needs for Diabetes Research

Research Training and Human Resource Development

Key Questions:

- How can training and career development in all aspects of diabetes research be enhanced?
- What programs can be developed to train multidisciplinary researchers capable of examining interactions among biological, psychological, behavioral, social, and environmental factors that impact diabetes and obesity?
- How can biomedical engineers, computational biologists, mathematicians, and experts in disciplines not traditionally applied to the problems of diabetes, obesity, and complications be encouraged to pursue research on these diseases?
- How can training of physician-scientists be supported in critical areas such as genetics/genomics and biostatistics, population-based methods, and interventional research?
- How can investigators from underrepresented minority groups be more effectively encouraged to pursue research careers that are focused on diabetes and obesity?
- What educational opportunities can be developed for clinical practitioners and for the general public to encourage participation in clinical research?

Future Directions:

- Incorporate transdisciplinary research opportunities into training programs related to diabetes and obesity.
- Create training programs that encourage the application of new fields of study to key problems in diabetes.
- Enhance training opportunities for basic and clinical investigators and establish opportunities for translational research in all aspects of diabetes and obesity research.
- Develop programs to educate the medical community and the general public on clinical research.

Diabetes Research Resources

Key Questions:

- How can access to high-quality human islets and pancreatic tissue for research be improved?
- What data registries or biobanks of human tissues and cell lines from people with and without diabetes would best support diabetes research?
- How can long-term studies of diabetes and its complications be optimized to provide research data and resources to the diabetes research community?
- How can transdisciplinary research and collaboration be encouraged, publicized, and supported across departments, institutions, and methodological fields?

Future Directions:

- ➢ Establish biobanks of annotated human tissue samples related to diabetes and obesity etiology and diabetic complications.
- ➢ Follow cohorts of individuals with type 1 diabetes and youth with type 2 diabetes longitudinally.
- ➢ Develop mechanisms to foster communication and collaboration among researchers and clinicians with an interest in diabetes and obesity.
- ➢ Promote interactions between NIH-supported Centers for diabetes and obesity research and other research institutions to maximize access to state-of-the-art resources and training.

New Technologies, Methodologies, and Measurements for Research

Key Questions:

- What DNA/RNA/protein sequencing and other technologies are needed to identify and study diabetes candidate genes and to better correlate genotypes with phenotypes in humans?
- How can mouse or cellular models be developed that are informative about the functional consequences of genetic differences associated with diabetes or obesity?
- How should evolving proteomic and metabolomic approaches be harnessed for diabetes research?
- What imaging technologies and resources are needed to advance research on diabetes, obesity, and related complications in humans?
- What bioinformatics resources and statistical approaches need to be developed or made more accessible to facilitate diabetes research?
- What tools are needed to measure energy balance in free-living humans?
- What new analytic methods or tools are needed to study complex, multi-level interactions within populations that impact obesity?
- Can standardized methods be developed for assessing predisposing behaviors and outcomes in human obesity trials?
- How well do self-reported and observational measurements correlate with biological markers?
- What are the best research designs to study causality in sociological systems?
- Can new instruments be developed to measure health promotion outcomes across communities and populations?
- How can more efficient communication be encouraged between people with diabetes and health care providers?

Future Directions:

- ➢ Develop and make available advanced technologies for discovering diabetes genes in humans.

- Develop analytical methods for epigenetic processes and other resources to study the relationships among genotypes and phenotypes in humans.
- Establish banks of monoclonal antibodies specific for diabetes-associated proteins.
- Create novel cell lines and related resources for diabetes and obesity research.
- Encourage new approaches to diabetes research and treatment based on stem cell technology.
- Make new technologies available as they arise, including stem cell resources.
- Apply proteomic and metabolomic methodologies to research on diabetes and obesity.
- Develop advanced, noninvasive imaging techniques that can be used in living humans.
- Develop statistical and bioinformatical methods and resources for integrating and analyzing large datasets generated by state-of-the-art technologies.
- Design innovative tools for studying energy balance under real-world conditions.
- Develop new methods for studying the impact of the environment on obesity.
- Improve and standardize measurements for translational research.
- Develop new methodologies for comparative effectiveness research.
- Develop advanced web-based and mobile technologies for capturing clinical data, enhancing education, and facilitating data management.

Animal Models for the Study of Diabetes and Obesity

Key Questions:

- What new small and large animal models are needed to accelerate research on type 1 and type 2 diabetes?
- Can animal models be developed that mimic human obesity etiology and treatment outcomes?
- Can animal models be developed that better simulate complications of human diabetes? Can new biomarkers be defined for complications in both animal models and humans?
- How can functional brain imaging techniques be improved for use in animal models?
- What new resources are needed to improve the phenotyping of animal models for diabetes and obesity?

Future Directions:

- Develop new small and large animal models that better represent the pathology and treatment of human diabetes and obesity.
- Develop *in silico* models of disease pathogenesis in type 1 and type 2 diabetes.
- Standardize research protocols involving diabetes-related mouse models.
- Develop standard definitions of abnormalities in mouse models of diabetes and obesity.
- Develop improved methods and technologies for phenotyping of mouse models.

Distribution and Sharing of Human Data and Biosamples

Key Questions:

- How can communication be fostered between basic scientists and clinical investigators conducting clinical studies and trials?
- How can awareness of and access to human biosamples and data from clinical trials be enhanced in order to facilitate biomarker discovery?
- How can awareness and use of new diabetes and obesity intervention programs and research tools be enhanced?
- What mechanisms or resources are needed to make datasets of de-identified medical records available to researchers?
- How can universal electronic medical records be made accessible for research while safeguarding patient and provider privacy?

Future Directions:

- ➢ Communicate the availability of datasets and biosample repositories and improve access to these resources by qualified diabetes researchers.
- ➢ Improve technology capabilities for dissemination of intervention programs.
- ➢ Develop policies that facilitate research using electronic medical records while protecting individuals' right to privacy.

Public-Private and International Partnerships

Key Questions:

- How can NIH collaborate with clinical care providers and payers to conduct clinical research in real-world settings and to conduct comparative effectiveness research more efficiently?
- How can policies for protecting the privacy of research participants be updated to foster multi-center clinical trials, associated biomarker studies, and the sharing of genetic materials between the public and private research sectors and internationally?
- What new NIH policies are needed to facilitate international collaborations?
- How can regulatory and financial issues be resolved in order to support the development of glucose management technologies, new therapeutics for microvascular complications, agents for glycemic control with adequate information on cardiovascular and other risks, and combination therapies for diabetes and obesity?
- How can NIH support and encourage partnerships between researchers and their local communities?

Future Directions:

- ➢ Build or strengthen partnerships between NIH and other government agencies, the pharmaceutical industry, the health insurance industry, and private foundations with an interest in diabetes and obesity research.
- ➢ Foster practice-based and community-based participatory research to promote the prevention and control of diabetes in vulnerable populations.