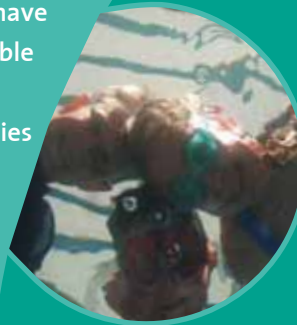


Having volunteered for the Diabetes Prevention Program (DPP) clinical trial and now participating in the DPP Outcomes Study, **Irish Stovall** says she would advise anyone interested in his or her health to take part in studies like these. Although she was at high risk for type 2 diabetes at the time she enrolled in the DPP, she says “I didn’t have diabetes at that time and, thanks to the study, I still don’t.”



Two of **Toni and Rob Berg’s** three children have type 1 diabetes, which made the family eligible to participate in the Type 1 Diabetes Genetics Consortium study. Toni encourages other families to participate in type 1 diabetes clinical research studies, saying, “The larger the pool of people they have to study, the more they can learn about combating the disease.”



Dan Lamb enrolled in the Diabetes Control and Complications Trial (DCCT) clinical trial in 1983, and participates in the Epidemiology of Diabetes Interventions and Complications (EDIC) study to this day. He says, “Had I not been part of the DCCT, I probably would not have paid attention to my diabetes as closely as I have, nor possess the same understanding of the disease and its complications that I have now. The study has been a huge part of my life, and has contributed greatly to my success as a person with diabetes.”



The NIH-supported Gestational Diabetes Mellitus (GDM) Cohort Study focused on Hispanic women who had gestational, or pregnancy-related, diabetes. This research has increased understanding of GDM and risk for subsequent type 2 diabetes. **Modesta Solórzano**

participated in the study, and says, “It’s been very helpful to me and my family.” (“Ha sido muy útil para mí y para mi familia.”)



SUMMARY AND FUTURE RESEARCH DIRECTIONS



SUMMARY AND FUTURE RESEARCH DIRECTIONS

Diabetes is a common, chronic, and costly disease that is threatening the health of generations of people in the United States and around the world. Support for biomedical research efforts that can lead to prevention, treatment, and possibly even cures for diabetes is an integral part of Federal efforts to improve public health and reduce the cost of health care in the Nation. Developed through a dynamic

planning process involving multiple stakeholders in the diabetes research enterprise, *Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee (DMICC)* is meant to serve as a guidepost for these efforts over the next decade.

BURDEN OF DIABETES IN THE UNITED STATES

Diabetes affects an estimated 25.8 million people of all ages, racial and ethnic groups, and socioeconomic status in the United States. Another 79 million Americans are estimated to be at greatly increased risk of developing diabetes in the next several years. One in three American children born in 2000 are predicted to develop diabetes at some point in their lives. Diabetes lowers life expectancy by up to 15 years and is the seventh leading cause of death. People with diabetes have a higher rate of cardiovascular disease than those without diabetes and are at increased risk for kidney failure, lower limb amputation, and blindness. Total costs of diabetes, including medical care, disability, and premature death, reached an estimated \$174 billion in 2007 in the United States.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a

hormone that helps the body absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels that, over time, damages organ systems and leads to debilitating complications.

Type 1 diabetes affects approximately 5 percent of individuals with diagnosed diabetes. While it most often develops during childhood, the disease can strike at any age. Type 1 diabetes results from an autoimmune process in which a person's immune system launches a misguided attack that destroys the insulin-producing beta cells of the pancreas. People with type 1 diabetes require daily insulin administration to regulate their blood glucose as close to normal levels as possible.

Type 2 diabetes accounts for 90 to 95 percent of diagnosed diabetes cases in the United States. Type 2

diabetes is strongly associated with obesity and aging and occurs at higher rates in certain minority populations. In type 2 diabetes, the body becomes resistant to insulin signaling, which can eventually result in impaired insulin production. Treatment approaches for type 2 diabetes include diet, exercise, orally administered medications, and, in some cases, injected insulin. Type 2 diabetes is increasingly being diagnosed in younger individuals, particularly in minority youth, adding to the enormous public health burden of diabetes. Research led by the National Institutes of Health (NIH) has shown that type 2 diabetes can be prevented or delayed in adults at high risk through modest weight loss with diet and exercise or through use of the diabetes medication metformin. Other forms of diabetes include gestational diabetes, which affects at least 7 percent and possibly as many

as 18 percent of pregnancies in the United States, and diabetes that results from rare genetic conditions, surgery, medications, infections, pancreatic disease, and other illnesses.

Diabetes eventually damages nearly every organ system in the body. People with diabetes are at increased risk of heart disease and heart attacks, stroke, high blood pressure, kidney failure, blindness, nerve pain and other neurologic problems, limb amputation, chronic wounds and skin ulcers, gum disease, sleep apnea, erectile dysfunction, and bladder, gastrointestinal and pregnancy-related problems. NIH-supported research has shown that intensive control of blood glucose can prevent or delay the development of many of these complications.

NIH SUPPORT FOR DIABETES RESEARCH

NIH Funding and Coordination of Diabetes Research

The NIH is the primary source of Federal support for diabetes research. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is the lead NIH component for supporting diabetes research. Because it is a systemic disease, diabetes and its complications are also addressed by many other NIH Institutes and Centers, as well as the Centers for Disease Control and Prevention (CDC), the Veterans Health Administration (VHA), and other Federal agencies.

Diabetes research funded by the NIH is supported by regularly appropriated funds that the U.S. Department of Health and Human Services (HHS) receives through the Labor-HHS-Education Appropriations Committees. It is also supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, which is a special appropriation to the Secretary of HHS to pursue research on type 1 diabetes and its complications. Total NIH funding for diabetes research in fiscal year 2009 was \$1.03 billion. Support from the American Reinvestment and Recovery Act also enabled the NIH to spend an additional \$121 million for diabetes research during that fiscal year.

The statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC) coordinates the Federal investment in diabetes programs to improve the health of Americans. Chaired by the NIDDK, the DMICC provides a forum for communication and collaboration to promote diabetes research across the Federal government. Components of the NIH and other government agencies that support diabetes-related activities are represented on the DMICC. Through the DMICC, government agencies identify ways to work together and build on each other's expertise and resources. This approach reduces duplication of Federal diabetes activities and stimulates collaboration.

NIH-led planning processes for diabetes research also involve voluntary agencies, such as the American Diabetes Association and the Juvenile Diabetes Research Foundation International, in an attempt to avoid duplication and enhance efficiency in providing resources. In addition, the NIH seeks input from the external scientific community, through venues such as scientific meetings and conferences, to inform its planning efforts.

Current Efforts and Recent Advances in NIH-Supported Diabetes Research

The NIH vigorously pursues and supports diabetes research across a broad range of disciplines and research areas, from basic to clinical to translational research, including genetics, genomics, proteomics, immunology, developmental biology, obesity, behavioral studies, cell biology, imaging, stem cell research, bioengineering, glucose sensing, and insulin delivery. Most fundamental research is accomplished through investigator-initiated regular research grants. The NIH also leads a variety of major efforts to support and extend the investigator-initiated research portfolio and foster innovative approaches. Multiple consortia,

clinical research networks, and clinical trials have been established to pursue specific goals for bench-to-bedside translational research and testing of prevention and intervention strategies. Shared research resources, including diabetes centers and central repositories, support a broad array of diabetes investigations. Many of these efforts were undertaken in response to research priorities identified in the 1999 strategic plan, *Conquering Diabetes: A Strategic Plan for the 21st Century*, the strategic planning processes for the *Special Statutory Funding Program for Type 1 Diabetes Research*, and the 2006 report, *Advances and Emerging Opportunities for Type 1 Diabetes Research: A Strategic Plan*.

Over the past decade, NIH support for biomedical research has led to major discoveries benefiting people with or at risk for diabetes. Progress has been made on multiple fronts, including better understanding the causes of diabetes and the molecular pathways that are affected by the disease, as well as developing new approaches to prevent or treat diabetes in individuals and within communities. Examples of diabetes research advances include:

Reducing Diabetes Complications

- ▶ **Diabetes complications can be reduced by over half with intensive glycemic control early in the course of the disease.**
- ▶ **Benefits of intensive control of glucose endure with reduced complications long after the period of good control. Continuous glucose monitors have been developed that improve glycemic control and reduce hypoglycemia in adults with type 1 diabetes.**

- Weight loss in people with type 2 diabetes results in improved control of glucose, blood pressure, and cholesterol with less use of medications.
- Good control of blood glucose, blood pressure, and lipids can reduce by half cardiovascular death in diabetes.
- Some people with diabetes and cardiovascular disease can do as well with medical management as with revascularization procedures.
- Intensive control of blood glucose during pregnancy can reduce birth defects, birth injuries, and the need for Cesarean section.
- Diabetes self-management training and improved health care delivery practices can improve diabetes outcomes.

Preventing or Delaying Type 2 Diabetes

- Risk of developing type 2 diabetes can be dramatically reduced in people at high risk for developing the disease through diet and exercise to promote modest weight loss or by treatment with the diabetes drug metformin. Benefits persist for at least 10 years.
- Women with gestational diabetes can lower their substantial risk for developing type 2 diabetes postpartum either through diet and exercise to induce weight loss or with diabetes medication.

- Affordable community-based approaches to lifestyle change for type 2 diabetes prevention have been developed.

Restoring Insulin Production and Reversing Diabetes

- Insulin independence has been achieved in people receiving islet transplants as treatment for severe type 1 diabetes. Residual insulin secretion has been found in many people with type 1 diabetes at diagnosis and beyond, spurring research on ways to preserve or expand this capacity.
- Insulin-producing cells have been generated in the laboratory from non-beta-cell sources, providing proof-of-principle for regenerative approaches to beta cell replacement.

Discovering New Therapeutic Pathways

- Many new susceptibility genes for type 1 and type 2 diabetes have been identified.
- New genetic tests can identify infants with neonatal diabetes—a rare form of diabetes—who may be treatable with oral drugs (sulfonylureas) rather than insulin injections.
- New treatments for type 2 diabetes are available based on discoveries about how gastrointestinal tract hormones influence insulin secretion.

- **Gastric bypass and other bariatric surgeries to treat extreme obesity may resolve type 2 diabetes independently of weight loss, opening the door to discovery and to new therapeutic options for some individuals.**
- **Metabolically active brown fat has been detected in adults and may prove therapeutically useful in obesity prevention or treatment.**

FUTURE DIRECTIONS FOR DIABETES RESEARCH

Identification of High-Priority Research Goals

The promise of prevention, treatment, and cure for diabetes can only be realized through the vigorous support of scientific research efforts ranging from fundamental discovery research to clinical trials and translation of scientific findings into clinical practice. This Strategic Plan addresses important opportunities in 10 major diabetes research areas, as well as issues related to resource and infrastructure development for diabetes research.

The Strategic Plan was developed in a collaborative planning process led by the DMICC Chair and involving input from multiple stakeholders (see sidebar, “Process for the Development of the Strategic Planning Report of the DMICC”). Focused working groups of Federal staff, external scientists, and representatives from diabetes-related voluntary organizations identified forward-

looking, high-priority goals for research on diabetes and its complications within each research area. Broad input on Strategic Plan goals was also sought through a public comment period prior to publication. The major research areas and future directions for research, which are not listed in priority order, are summarized below*.

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

Type 1 diabetes, type 2 diabetes, obesity, and their complications have strong genetic bases that interact with environmental and behavioral factors. Identifying those factors that influence disease susceptibility is key to development of strategies for prevention and treatment of diabetes. Goals in this area span the following research needs and opportunities:

* These summaries synthesize multiple research goals/suggested strategies to achieve goals, and are organized by subheadings used in the Future Directions section of the Strategic Plan chapters.

- **Genes and Pathways** – Understanding how candidate susceptibility genes contribute to a person’s risk and elucidating the interactions among those genes at a cellular level will help researchers discover common pathways of risk.
- **Detection of Rare Variants** – Fully characterizing susceptibility genes could be accelerated by sequencing the DNA of tens of thousands of individuals with type 1 diabetes, type 2 diabetes, or obesity to uncover the entire range of variations in DNA, from common to rare, that are linked to risk.
- **Gene-Environment Interactions** – Research on how genes or variants associated with risk interact with potential environmental factors, such as viral infections, nutrition, or gut microbes, to trigger disease will provide important insights to understand the development of diabetes, obesity, and complications.
- **Genetics and Health Disparities** – It will be especially important to identify genetic and environmental risk factors in high-risk, racial and ethnic minority populations in the United States that might explain the different rates of diabetes, obesity, and complications in those groups.
- **Epigenetic Contributions to Risk** – Environmental exposures may directly influence diabetes risk in part by interacting with the genome to alter how certain genes are expressed. Studying these interactions could explain how gestational diabetes contributes to the risk of diabetes and obesity in the offspring, or how a period of good glucose control early in the course of diabetes could reduce the risk of complications even years later.
- **Translation of Genetic Research from Bench to Bedside** – Increased knowledge of the causative factors of diabetes, obesity, and their complications

will open up new avenues of translational research to inform the design of innovative clinical trials for prevention or early intervention.

- **Pharmacogenetics/Pharmacogenomics** – Identifying genes and variants that influence positive and negative responses to diabetes therapies will open up prospects for personalized medicine, in which the use of specific pharmacologic agents can be tailored to individuals or populations based on their genetic profiles.

Research goals in this area of the Strategic Plan will guide future efforts to identify the genetic and other causes of diabetes, obesity, and their complications and use that knowledge to develop more effective strategies for prediction and intervention.

Type 1 Diabetes and Autoimmunity

Preventing the onset of type 1 diabetes will require detailed knowledge of the causes and mechanisms of the autoimmune process that destroys pancreatic beta cells. Research goals in this area are aimed at understanding the immune system attack that destroys the pancreatic beta cells in people with type 1 diabetes and developing new therapeutic strategies to prevent or halt this harmful immune response. They focus on addressing gaps and opportunities in five key aspects of type 1 diabetes research:

- **Human Type 1 Diabetes Trials (Prevention/ Reversal/Transplantation)** – Expanded clinical trials to test therapies to prevent or reverse type 1 diabetes would require recruitment of adequate numbers of well-characterized individuals who are at risk of or newly-diagnosed with the disease. Trials should capitalize on advances in new biomarkers of disease and improved models to

predict who is most likely to develop type 1 diabetes, in order to test promising prevention strategies.

- **Natural History and Pathogenesis of Human Type 1 Diabetes** – The development of prediction models and prevention strategies would be advanced by research to identify environmental factors that trigger autoimmunity in genetically susceptible individuals and that affect the rate of disease progression. Defining the natural history of type 1 diabetes would help researchers design intervention therapies that target specific stages in the progression of islet destruction.
- **Animal Models/Translational Efforts from Pathogenesis to Therapy** – New animal models of type 1 diabetes have opened up new research opportunities for therapeutic development and biomarker identification. The development of a mouse model with higher fidelity to human disease or computer-based models of type 1 diabetes would provide critical tools for research on disease progression and prevention.
- **Beta Cell Function in Type 1 Diabetes: Autoimmune Attack and Prospects for Recovery** – Research is needed to detect early signs of beta cell dysfunction, identify genes and mechanisms that protect beta cells from autoimmune destruction, and develop surrogate markers of beta cell recovery so that response to immune therapy can be evaluated.
- **Immune Mechanisms of Pancreatic Pathology** – Defining the roles of immune regulatory cell populations, including B cells, T cells, dendritic cells, and others, will be a key step in understanding the autoimmune destruction processes. Research to distinguish molecular pathways that are important in other autoimmune diseases from those that are unique to type 1 diabetes would inform decisions about whether to

test immune therapies that are in development for other autoimmune diseases in people with type 1 diabetes as well.

Pursuing opportunities outlined in this area of the Strategic Plan, ranging from basic studies to clinical trials, will advance knowledge of autoimmunity in type 1 diabetes and lead to new approaches for disease prevention and treatment.

The Beta Cell

All major forms of diabetes share a common basis in loss of the insulin-producing pancreatic beta cells. Research on the normal development and function of beta cells will inform efforts to replicate, regenerate, or replace beta cells and restore normal insulin production. Goals in this area are aimed at elucidating the causes of beta cell dysfunction and on strategies to restore or replace insulin production and span the following research needs and opportunities:

- **Integrated Islet Physiology** – Understanding how the human beta cell functions in the context of the pancreatic islet would help scientists design scaffolds and other systems to improve the survival and function of transplanted beta cells and to develop drugs that can restore important signaling pathways within islets in people with type 2 diabetes.
- **Beta Cell Dysfunction and Failure** – Inflammation is now recognized as a factor in beta cell loss in type 2 diabetes as well as in type 1 diabetes. Identifying the signaling pathways involved in chronic islet inflammation could aid in the development of new anti-inflammatory agents to protect beta cells. Research to identify intracellular signaling

pathways that might be manipulated to protect beta cells, including the role of the intrauterine environment on islet development and function, could reveal mechanisms to preserve and restore beta cell mass and function.

- **Prevention and Treatment of Diabetes** – The development and testing of strategies to preserve and restore beta cell mass and/or function in people with pre-diabetes or diabetes are needed. Clinical research in this field would benefit from the identification of biomarkers to detect and monitor type 2 diabetes progression and remission.
- **Cellular Replacement Therapies for Diabetes** – Several lines of research hold promise for replacing beta cells lost in type 1 diabetes, including optimization of techniques for islet transplantation; stimulation of beta cell development from stem cells; reprogramming of non-beta cells into glucose-responsive, insulin-producing cells; and regeneration of beta cells in an individual's pancreas. New animal models will be needed to test potential beta cell replacement therapies.
- **Imaging the Pancreatic Islet** – The development of more accurate and reproducible techniques to image beta cells or islets in a living person would aid research in all areas of beta cell biology.

Collectively, the pursuit of Strategic Plan research goals related to the beta cell has the potential to transform diabetes treatment by advancing understanding of the cell that plays a critical role in all forms of diabetes.

Type 2 Diabetes As a Multi-Dimensional Disease

In addition to beta cell failure, type 2 diabetes is marked by metabolic abnormalities in multiple organ systems, including muscle, liver, fat, and the brain. A systems biology approach could provide an unprecedented depth of understanding of the disease variability observed in people with type 2 diabetes and help identify pathways of disease development and progression. Research goals in this area integrate many different areas of type 2 diabetes research to achieve a comprehensive portrait of the disease, and address a variety of opportunities:

- **Insights into Gene and Environment Interactions in Type 2 Diabetes** – New tools and technologies are needed to facilitate research on these interactions, which might be mediated by factors such as microRNAs, epigenetic changes, or nutrients and xenobiotics.
- **Metabolic and Hormonal Regulation in Diabetes** – Defining the diverse molecular pathways of metabolic and hormonal regulation in diabetes could point to new therapies.
- **Inflammation and Endoplasmic Reticulum Stress—Impact on Insulin Signaling and Glucose Metabolism** – Research efforts are needed to understand the links between metabolism, chronic low-grade inflammation, and cellular stress and to identify potential targets for therapeutic intervention.
- **Mitochondrial Metabolism** – Studying the role of mitochondrial dysfunction in diabetes could clarify the relationship of obesity and overnutrition with the development of insulin resistance.

- **Nutrient Role in Glucose Homeostasis — Mechanisms of Overnutrition-Driven Tissue Dysfunction** – Identifying factors that regulate fat storage and mechanisms by which excess nutrient load damages organs would likewise help researchers understand the link between obesity and type 2 diabetes.
- **New Players in Control of Metabolism: Role of the Brain and the Gastrointestinal Tract** – A systems biology approach to research on diabetes should consider the role of the brain and the gastrointestinal tract, including the gut flora, in whole-body energy balance.
- **Defining the Subtypes of Type 2 Diabetes by Molecular Phenotyping** – A systems biology approach could be applied to characterizing in detail a large cohort of individuals across the range of normal metabolism to diabetes, to define subtypes of type 2 diabetes that might respond differently to specific prevention and intervention strategies.
- **Obesity, Inflammation, Insulin Resistance, and Macrophage Function** – Macrophages and inflammation appear to be activated by excess nutrients and subsequently play a role in eliciting insulin resistance as a consequence of obesity. Research is needed to clarify the mechanisms and outcomes of tissue-specific inflammation in obesity.
- **Mechanisms Underlying Energy Homeostasis: Impact on Obesity Pathogenesis and Treatment** – Untangling the complex networks of hormonal and neural mechanisms that control energy balance in the body could point to new therapeutic targets to prevent or treat obesity.
- **Central Nervous System Control of Thermogenesis** – New technologies are needed to facilitate study of the complex control of energy expenditure and how it contributes to weight maintenance and obesity in people.
- **Discovering Genetic and Intrauterine Determinants of Obesity Susceptibility That Predispose to Developing Diabetes** – Research on genetic factors that increase susceptibility to obesity could shed light on the molecular pathways involved in this disease. Likewise, studying the impact of the intrauterine environment on the offspring’s long-term risk of obesity, insulin resistance, and type 2 diabetes could reveal epigenetic modifications that affect the expression of obesity-related genes.
- **Adipose Tissue Biology** – Adipose tissue research is key to the development of treatments for obesity and type 2 diabetes. Understanding the mechanisms that regulate fat cell number, size, distribution, and signaling, and developing new technologies for studying adipose tissues, are urgent research goals.

Research goals identified for this area of the Strategic Plan build on and expand the perspective of diabetes as a disease that affects multiple systems in the body and that varies in both causes and outcomes among individuals.

Obesity

Obesity is a major risk factor for type 2 diabetes and insulin resistance and is also a problem in people with type 1 diabetes receiving insulin therapy. Stemming the rising tide of type 2 diabetes will require research to understand the causes of obesity and overweight and to develop prevention strategies. Goals in this area are focused on opportunities to expand the understanding of molecular pathways, as well as behavioral, social, and environmental factors, that link obesity and type 2 diabetes:

- **Obesity Prevention and Treatment** – Behavioral strategies are needed to prevent inappropriate weight gain and promote or maintain weight loss in individuals across the lifespan, as well as in communities or large populations. The development and testing of such strategies would be supported by research on the non-biological determinants of obesity and obesity prevention and the use of technologies to tailor the delivery of interventions to individuals.
- **Improving Clinical Investigative Tools** – Progress in obesity research would be facilitated by the development of improved tools for clinical investigation, including advanced instrumentation to measure body composition, energy intake, physical activity, diet composition, and other parameters in a variety of laboratory and clinical settings.

Addressing Strategic Plan goals for obesity research is a critical component of public health efforts to reverse the rising epidemic of type 2 diabetes that is largely driven by the high rates of obesity in the American population.

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

Maintaining blood glucose levels at near-normal levels has multiple long-term benefits for individuals with diabetes, but daily management of the disease is arduous for even the most diligent individuals. New technologies for glucose sensing and insulin delivery are needed that could help all people with diabetes easily and consistently manage their blood glucose at optimal levels and greatly reduce the burden of diabetes treatment. Goals in this area form a multi-pronged approach to meet complex research needs and opportunities in the quest for an artificial pancreas:

- **Glucose Sensors** – The development of a new generation of small, implantable, unobtrusive glucose sensors that report reliable and accurate data on glucose levels and warn of impending hypoglycemia could drastically reduce the number of daily finger sticks that people with diabetes who treat with insulin must endure, and could improve their metabolic control.
- **Algorithm Development-*In Silico*/Simulation Models** – To close the loop between glucose sensing and insulin delivery, glucose sensors will need to be linked to an automated insulin delivery device. Realizing this goal requires research to develop complex computer programs that account for numerous factors, including patient-to-patient variability and changes in a person’s behavior or environment.
- **Insulin—Improving Delivery and Formulation** – Research to develop novel insulin formulations or delivery methods—such as the development of a glucose-sensitive insulin molecule, or systems that integrate insulin pumps with glucose sensors into a single device—could lead to improvements in glucose control for many people with diabetes.
- **Telemedicine** – Telemedicine approaches that apply advances in information and communication technology, such as the Internet, mobile phones, and personal digital assistants, to diabetes management have the potential to improve outcomes, especially in younger age groups that are high users of telecommunication technologies and services.
- **Tissue Engineering for Replacement of Pancreatic Islets** – In addition to research on mechanical devices for diabetes management, bioengineering research to develop new

biomaterials could improve the efficiency and effectiveness of islet transplantation as a means to restore biologic regulation of glucose.

- **Impact of Closed-Loop Control on the Pathophysiology of Diabetes** – As work to close the loop between glucose sensing and insulin delivery progresses, a parallel research effort is needed to understand how these new technologies affect the pathophysiology of diabetes. Defining the impact of an artificial pancreas on brain metabolism, or determining the ability of mechanical devices to restore normal pathways for regulating glucose levels or reverse hypoglycemia unawareness, are some of the important research questions.
- **Behavioral Aspects** – Behavioral research could uncover factors that influence the adoption and effective use of new diabetes management technologies by people with diabetes and health care providers.
- **Design of Clinical Trials and Clinical Outcomes** – Clinical trials are needed to evaluate the optimal use of new technologies in populations that vary by form of diabetes, age, presence of complications, or other parameters.

Ultimately, pursuing research goals outlined in this area of the Strategic Plan could lead to the development of a fully automated, mechanical, artificial pancreas that could maintain blood glucose within a physiologic range with minimal input from the user, thus reducing the burden of disease management and improving quality of life for many people with diabetes.

Clinical Research and Clinical Trials

Combating the diabetes epidemic requires a robust program of clinical research and clinical trials to identify, test, and compare approaches to the treatment

or prevention of diabetes and to translate research findings into effective therapies. Goals in this area address needs and opportunities in four key aspects of clinical diabetes research and could improve outcomes for all persons who are at risk for or are living with diabetes:

- **Preventing Type 2 Diabetes** – Landmark clinical trials in the past decade have demonstrated that type 2 diabetes can be prevented or delayed in individuals at high risk of developing the disease. More research is needed to understand how to better prevent or treat gestational diabetes, as well as to lower the associated long-term risk of type 2 diabetes in mothers with gestational diabetes and their offspring. In addition, research to widely disseminate the results of clinical trials for type 2 diabetes prevention has the potential to have a positive impact on public health.
- **Treatment** – Research efforts aimed at determining the optimal treatment of people with type 2 diabetes, especially early in the course of disease, could help to prevent or delay the onset of devastating complications and could inform efforts to develop individualized therapy for diabetes. Similarly, research to understand and reverse hypoglycemia could improve outcomes for people with type 1 diabetes.
- **Etiology of Diabetes and Its Complications** – Diabetes is a heterogeneous disease with multiple causes and a highly variable clinical course. Clinical research to define the genetic, metabolic, and environmental factors in diabetes is needed to fully understand the disease and its progression to complications in many people with diabetes.
- **Complications** – Identifying risk factors for diabetic cardiovascular disease and understanding how those factors differ between people with type 1

and type 2 diabetes could lead to better treatment strategies for all individuals with diabetes. The identification and validation of surrogate end points and biomarkers for vascular complications would greatly accelerate clinical trials to test new diabetes therapeutics.

Strategic Plan goals for clinical research and clinical trials in diabetes represent critical steps toward increasing the effectiveness of prevention and treatment strategies for diabetes and realizing maximal public health benefits from the diabetes research enterprise.

Special Needs for Special Populations

Developing tailored approaches to diabetes treatment and prevention would reduce the burden of disease in specific populations, including children, older adults, pregnant women, people with other serious diseases and conditions, and minority populations that are disproportionately affected by diabetes. Goals in this area address the special needs and challenges related to the prevention and treatment of diabetes in these populations:

- **Ethnic and Racial Disparities** – Eliminating the disproportionate risks of diabetes and diabetes complications faced by certain ethnic and racial populations in the United States will require research to understand the genetic, behavioral, and biologic mechanisms that underlie ethnic and racial differences in diabetes susceptibility, as well as efforts to develop programs for lifestyle interventions that can target and reach large numbers of at-risk individuals.
- **Pregnancy and the Intrauterine Environment** – Research on the causes and consequences of diabetes in pregnant women and their developing fetuses could lead to new strategies

to improve long-term health outcomes in these women and their offspring.

- **Diabetes in Children and Youth** – The rates of type 1 diabetes, type 2 diabetes, and obesity or overweight are increasing in American children and youth. Research is urgently needed to understand the underlying triggers for these diseases in children, as well as to develop better diabetes management strategies that can improve long-term health outcomes and reduce the risk of diabetic ketoacidosis in the pediatric population.
- **Diabetes in Older Adults** – For older adults, research on behavioral approaches to help people make lifestyle changes that could prevent or better control diabetes could reduce the impact of diabetes in this vulnerable group, as could research that addresses age-related changes in metabolism and clearance of therapeutic drugs and therapy of diabetes in the context of multiple chronic diseases.
- **Diabetes and Psychiatric Disorders** – The mechanisms that link diabetes and psychiatric disorders and treatments are not well understood; research to uncover those mechanisms could point to novel strategies for diabetes screening and treatment in people with mental illness.
- **Secondary Diabetes** – Individuals with certain chronic conditions—such as cystic fibrosis, HIV infection, or organ replacement—often develop diabetes either as a result of their underlying disease or as a consequence of treatment. Research on secondary diabetes should focus on both understanding how these conditions or their treatment impair glucose metabolism and developing strategies to prevent diabetes and reduce the risk of cardiovascular disease and other complications.

By addressing the unique challenges posed by diabetes in different populations, Strategic Plan research goals in this area will ensure that the benefits of diabetes research are available to all individuals with diabetes.

Diabetes Complications

Diabetes-related complications of the eyes, kidneys, nerves, heart, and other organs exact a significant toll on the personal health of individuals with diabetes and contribute significantly to the costs of health care in the United States. Goals in this area are aimed at reducing the considerable health burden caused by diabetes complications by spurring discovery in a variety of disciplines:

- **Metabolic, Biochemical, and Signaling Pathways** – Many gaps remain in the understanding of the molecular and cellular pathways that are disrupted in diabetes, eventually leading to organ and tissue damage. Research on the roles of mitochondria, inflammation, protein modification, and cellular self-digestion, among other biologic processes, could provide new insights into the pathophysiology of diabetes complications.
- **Genetics and Epigenetics** – Identifying the genetic and epigenetic factors that predispose or protect individuals from complications could reveal disease pathways and uncover targets for therapeutic development.
- **Tissue and Organ System Injury** – In addition to mapping general pathways that affect the development of complications, it will be important to study tissue-specific responses to diabetes. These lines of research would benefit from the development of *in vitro* models of vascular complications and the establishment of repositories of well-characterized human cells and tissues

representing all stages in the development and progression of complications.

- **Tissue Repair and Regeneration** – Research efforts to understand how diabetes impairs the body's normal repair and regeneration processes could also point to novel therapeutic strategies.
- **Biomarkers, Imaging, and Bioinformatics** – Focused development of effective biomarkers, noninvasive imaging techniques, animal and cell models that mimic human diabetes, and bioinformatics platforms would accelerate research on diabetes complications. Such tools and technologies could dramatically shorten the time required for development and testing of new drugs or other therapeutic strategies.
- **Therapeutic and Preventive Strategies** – Research on therapies for the prevention and treatment of diabetes complications needs to take a multi-pronged approach that includes the development of pharmacologic, nutritional, and behavioral strategies, as well as efforts to tailor interventions to individuals or to specific organs or cell types.

Achieving research goals for diabetes complications outlined in the Strategic Plan has the potential to enhance the lives and health of millions of people at risk for or living with the devastating complications of diabetes.

Clinical Research to Practice: Translational Research

A key challenge in diabetes research is translating the important findings of controlled clinical trials for diabetes prevention or treatment into approaches that are effective, affordable, safe, and sustainable in real-world settings. Research goals in this area are aimed

at designing diabetes interventions to work in different populations and individuals and within discrete systems of care, and focus on needs and opportunities in five major aspects of this challenge:

- **Prevention of Type 2 Diabetes** – Translating the results of landmark clinical trials showing that type 2 diabetes could be prevented or delayed is critically important. Finding ways to accurately identify individuals who would benefit from prevention programs and developing approaches to prevent type 2 diabetes through integration of health care services or community programs could help stem the diabetes epidemic in adults and youth.
- **Diabetes Clinical Care** – The results of some clinical trials suggest that a standard approach to diabetes management might not be suitable for all people with the disease. The development of individualized approaches to diabetes clinical care would optimize the quality of life and health outcomes for all, including those in groups that have particular challenges with daily diabetes management, such as children and older adults.
- **Patient-Centered Care** – Research is needed to identify patient-specific factors that affect diabetes medical care or self-management.
- **Health Disparities** – Understanding why some populations, such as the poor, uninsured, or certain ethnic and racial minority groups, experience inferior quality of health care delivery, processes of care, and health outcomes is key to efforts to improve diabetes care. Research in this field must consider multiple factors at the level of the individual, provider, community, and health system while developing culturally appropriate interventions to improve health care and outcomes and reduce disparities.

- **Systems of Care** – Determining the optimal systems of care, both within and outside of the traditional health care system, as well as developing strategies to systematically improve the quality of diabetes care, are critical to the successful translation of diabetes research findings throughout the Nation.

Realizing Strategic Plan goals for translational research in diabetes is essential for improving public health and controlling the ever-growing costs of diabetes care.

Resource and Infrastructure Needs for Diabetes Research

Diabetes and obesity are heterogeneous conditions with complex management needs and the potential for devastating complications. Much about the causes of these disorders and the most appropriate and effective means to treat them at the level of individuals, population groups, and health care systems remains to be discovered. All areas of diabetes research would benefit from efforts to encourage collaborative, multidisciplinary research, as well as the establishment of and broad access to shared resources and state-of-the-art technologies.

An eleventh working group was formed with representatives from each of the 10 research area working groups to consider resource and infrastructure needs for diabetes research. This group identified future directions for the development of research resources and infrastructure that would enable the successful implementation of this Strategic Plan for research and promote research progress towards reducing the medical, personal, financial, and societal burdens of diabetes.

- **Research Training and Human Resource Development** – Progress in diabetes research depends on the ongoing recruitment, training, and support of new researchers in basic and clinical research related to diabetes, including transdisciplinary approaches to research. Programs are needed to encourage the application of diverse fields of study, such as computational biology, engineering, nanotechnology, social sciences, and other disciplines, to diabetes research. Educating the medical community and the general public on clinical research would facilitate the implementation of clinical trials to understand pathophysiologic mechanisms and test new therapies for diabetes.
- **Diabetes Research Resources** – Research on diabetes and obesity would benefit from the establishment of central biobanks with annotated human tissue samples from individuals representing the entire disease spectrum, from healthy metabolism to complicated diabetes. Shared resources, such as biobanks, can improve the efficiency of research and allow scientists to evaluate novel hypotheses that depend on access to tissues that might be difficult for an individual laboratory to obtain. Support for longitudinal studies of individuals with type 1 diabetes or youth with type 2 diabetes could lead to new insights on the progression, treatment, and outcomes of these diseases. Mechanisms to encourage communication and collaboration among researchers and clinicians and between NIH-supported research centers would stimulate new hypotheses and facilitate translation of research findings into clinical practice.
- **New Technologies, Methodologies, and Measurements for Research** – The development and application of state-of-the-art technologies, methodologies, and measurements would open up significant new avenues of research on diabetes and obesity. Such tools and techniques include: advanced technologies for gene discovery, methods to analyze epigenetic processes, stem cell lines and technologies, proteomic and metabolomic methods, imaging techniques and reagents, bioinformatics resources, tools for measuring energy balance, methods for studying environmental influences, standardized measurements for translational research, methods for comparative effectiveness research, and emerging information and communication technologies.
- **Animal Models for the Study of Diabetes and Obesity** – Animal model research has contributed substantially to the understanding of diabetes and obesity, but these models exhibit substantial differences when compared to these diseases in humans. New small and large animal models, as well as *in silico* models, are needed that better represent the pathology and treatment of human diabetes and obesity. The development of standardized research protocols and definitions of abnormalities in mouse models of diabetes would facilitate comparison of research findings across research laboratories. Better methods to characterize mouse models in detail, including the application of advanced imaging technologies, would also improve research on diabetes, obesity, and their complications.

- **Distribution and Sharing of Human Data and Biosamples** – Mechanisms to disseminate information on available resources are needed to maximize access to and use of biosample collections, new technologies and methodologies, intervention programs, and other resources. Efficient sharing of clinical biosamples and data will rely on the development of policies that facilitate research while maintaining individuals’ right to privacy.
- **Public-Private and International Partnerships** – Building partnerships between NIH and other governmental agencies,

the pharmaceutical industry, the health insurance industry, private foundations, foreign research agencies or investigators, and community organizations can enhance diabetes research at all levels, accelerate the validation and approval of new therapies, and promote dissemination of research results to individuals affected by diabetes.

IMPLEMENTATION: GUIDING FUTURE RESEARCH EFFORTS

This Strategic Plan reflects a dynamic planning process that involves collaboration among numerous stakeholders to ensure that research progress is regularly assessed and that new and emerging opportunities for diabetes research are identified. The statutory DMICC will continue to play a key role by assessing progress toward the research goals described in this Plan, which was developed under its auspices. The NIH will also continue to solicit broad external

input from the scientific, lay, and patient advocacy communities to inform its planning efforts. The NIH, other DMICC member organizations, and the scientific community will use the research questions and future directions described in the Strategic Plan as a scientific guidepost to enhance fundamental understanding of diabetes, improve current treatment strategies, and identify ways to prevent or cure diabetes and its complications.

PROCESS FOR THE DEVELOPMENT OF THE STRATEGIC PLANNING REPORT OF THE DMICC

Origin

In 1999, the NIH published a comprehensive plan for diabetes research, entitled *Conquering Diabetes: A Strategic Plan for the 21st Century*. In the decade since that plan was released, major advances have been made in the understanding of diabetes, new tools and technologies have been developed, and strategies for diabetes prevention and treatment have been expanded. In 2006, the NIH published *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*, a report that described opportunities that would inform research on many areas of commonality between type 1 and type 2 diabetes, but with a primary focus on type 1 diabetes research. In 2008, the DMICC determined that the time was appropriate to update these plans by identifying the most up-to-date, high-priority opportunities for all areas of diabetes research that build on recent research advances and that can be accomplished in the next 5 to 10 years.

A Collaborative Planning Process

The Strategic Plan was developed with broad input from a diverse and talented group of researchers and lay experts dedicated to advancing diabetes research. Working groups were assembled to address each of 10 scientific areas of important opportunity related to diabetes. An additional working group composed of representatives from each of the other 10 groups addressed overarching needs for scientific expertise, tools, technologies, and shared research resources. Each working group was

chaired by a scientist external to the NIH and was comprised of additional external scientific experts, as well as representatives of DMICC member organizations and diabetes voluntary organizations. Working groups met through conference calls and electronic exchanges to assess the state of the science and identify advances and emerging opportunities in their scientific areas.

An overarching Diabetes Research Strategic Plan Leadership Group was formed of the chairs of the 11 working groups and representatives from the government and diabetes voluntary organizations. This overarching working group met in person on July 7, 2009 to review progress of the scientific working groups and ensure that the Strategic Plan was comprehensive and addressed the most compelling opportunities for prevention, therapy, and cure of diabetes and its complications. A draft of the Strategic Plan was posted on the NIDDK website to provide an opportunity for broad public input prior to publication.

Organization of the Strategic Plan

The Strategic Plan was framed around 10 major scientific areas representing important opportunities in diabetes research. These areas are overlapping but complementary in scope:

- 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

Each of the 10 chapters in the Strategic Plan addressing these areas of scientific opportunity includes an introduction, summaries of recent research advances, key questions and future directions (goals) for research, and a closing section describing how the research directions outlined in the chapter may transform the health of people with or at risk of diabetes. 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 by the working groups.

