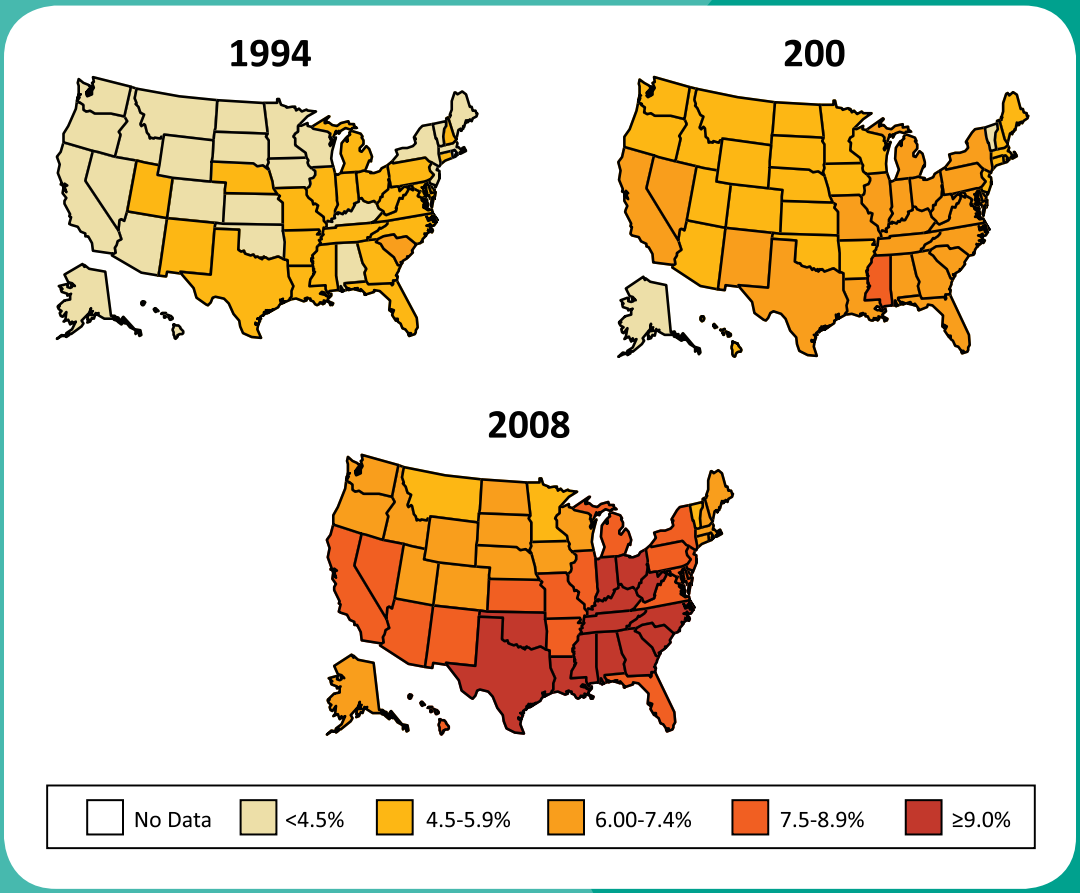



CDC statewide estimates of diagnosed diabetes in the U.S. in 1994, 2000, and 2008. The different colors represent the percent of adults 20 years of age or older with diagnosed diabetes in these years. These maps demonstrate the dramatic increase in prevalence of diabetes observed in less than two decades. (*CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at www.cdc.gov/diabetes/statistics*)

# INTRODUCTION

## contents:

# OVERVIEW

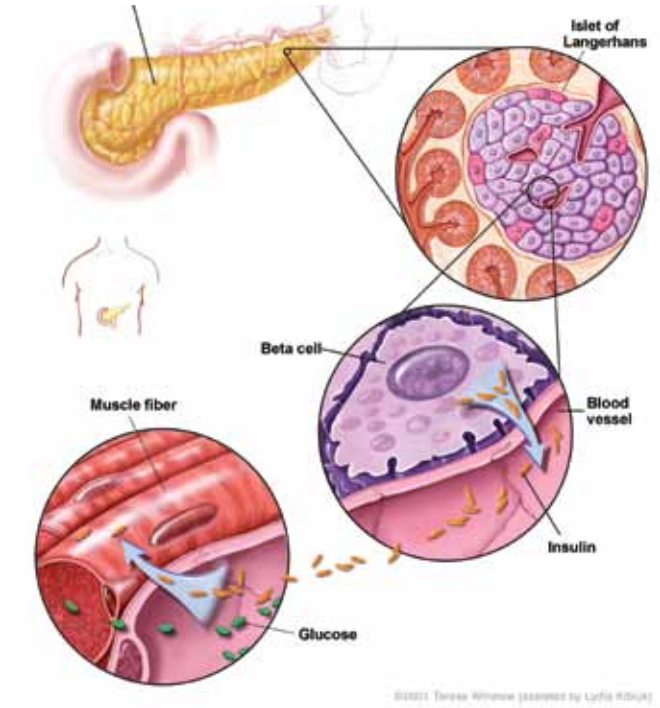
Diabetes affects an estimated 25.8 million people in the United States and is the seventh leading cause of death (1). Diabetes lowers average life expectancy by up to 15 years, increases cardiovascular disease risk two- to four-fold, and is the leading cause of kidney failure, lower limb amputations, and blindness in working-age adult Americans (1,2). In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2007—including costs of medical care, disability, and premature death—was $174 billion (1). Effective therapy can prevent or delay diabetic complications, but approximately one-quarter of Americans with diabetes are undiagnosed (1). Moreover, another 79 million Americans are estimated to be at greatly increased risk of developing diabetes in the next several years (1). One in three American children born in 2000 are predicted to develop diabetes at some point in their lives (3). Globally, diabetes will affect an estimated 285 million adults in 2010, a figure that is predicted to rise to 438 million by 2030 (4). Diabetes thus presents an immense and complex public health challenge.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of debilitating disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin; and type 2 diabetes, due to a combination of resistance to the action of insulin and insufficient insulin production. Women can develop gestational diabetes, a risk factor for type 2 diabetes, during pregnancy. Many rarer forms of diabetes also exist.

## Type 1 Diabetes

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of adults and the majority of children and youth with diagnosed diabetes (1). While it most often develops during childhood, the disease may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the beta cells of the pancreas. These beta cells are found within tiny cell clusters called islets and produce the hormone insulin. If left untreated, type 1 diabetes results in death as muscle and other tissues are starved for glucose despite high levels of glucose in the bloodstream. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—in order to regulate their blood glucose levels.

Despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for people with type 1 diabetes to achieve the precise level of regulation obtained by a healthy pancreas, which exquisitely senses and responds to insulin needs. Therefore, people with type 1 diabetes are susceptible to dangerous variations in their blood glucose levels, called hyperglycemia (high blood glucose) or hypoglycemia (low blood glucose). Both of these conditions can be life-threatening in extreme cases. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working on new beta cell replacement therapies meant to cure type 1 diabetes. Continued research to prevent type 1 diabetes in those at risk, restore insulin independence in people who are already diagnosed, and prevent the development




The pancreas is located in the abdomen, adjacent to the duodenum (the first portion of the small intestine). A cross-section of the pancreas shows one of the islets of Langerhans, or pancreatic islets. The islets are the functional unit of the endocrine pancreas. Encircled is a beta cell, the islet cell that synthesizes and secretes insulin. Beta cells are located adjacent to blood vessels and can easily respond to changes in blood glucose concentration by adjusting insulin production. Insulin facilitates uptake of glucose, the main fuel source, into cells of tissues such as muscle. (*© 2001 Terese Winslow (assisted by Lydia Kibiuk)*.)

of disease complications, is crucial to reducing the burden of the disease and improving patients' quality of life.

## Type 2 Diabetes

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases among adults in the United States (1). Type 2 diabetes is strongly associated with obesity: more than 80 percent of adults with type 2 diabetes are overweight or obese (5). Type 2 diabetes is also associated with aging, affecting an estimated 26.9 percent of Americans 65 years of age and older, and it occurs more frequently among racial and ethnic minority groups in the United States, including African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians and other Pacific Islanders (1). Other important risk factors include physical inactivity, a family history of diabetes, and a history of diabetes during pregnancy (gestational diabetes).

In type 2 diabetes, the body becomes resistant to insulin signaling, which can eventually result in impaired insulin production. Treatment approaches for controlling glucose levels include diet, exercise, orally administered medications that make tissues more sensitive to insulin or enhance insulin production, and, in some cases, injected insulin. There are also an estimated 79 million adults in the United States who have a condition called "pre-diabetes," in which blood glucose levels are higher than normal, but not as high as in diabetes (1). This population is at high risk of developing type 2 diabetes. Fortunately, the Diabetes Prevention Program (DPP) clinical trial, spearheaded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with support by many components of the National Institutes of Health (NIH), as well as the Centers for Disease Control and Prevention (CDC) and the Indian Health Service (IHS), has shown that people with pre-diabetes can dramatically reduce their risk of developing full-blown type 2 diabetes with improvements in lifestyle or with drug treatment.

Type 2 diabetes was previously called adult-onset diabetes because it was predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and

adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. First, the onset and severity of disease complications correlate with the duration of diabetes; thus, those with early diabetes onset are at greater risk with respect to complications. Second, maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of diabetes in offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could lead to a vicious cycle of ever-growing rates of diabetes. Third, diabetes often becomes more difficult to control over time. With longer duration of disease, health care providers may find it increasingly difficult to strictly control a patient's blood glucose level and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to drastically worsen the enormous health burden that diabetes already places on the United States.

## Gestational Diabetes

Gestational diabetes is a form of glucose intolerance diagnosed during pregnancy. Gestational diabetes affects at least 7 percent and possibly as many as 18 percent of pregnancies in the United States (1,6) and occurs more frequently among African Americans, Hispanic/Latino Americans, and American Indians (1). It is also more common among obese women and women with a family history of diabetes. During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in the infant. Immediately after pregnancy, 5 to 10 percent of women with gestational diabetes are found to have diabetes, usually type 2 diabetes (1). Women who have had gestational diabetes have a 35 to 60 percent chance of developing diabetes in the next 10 to 20 years (1).

## Other Forms of Diabetes

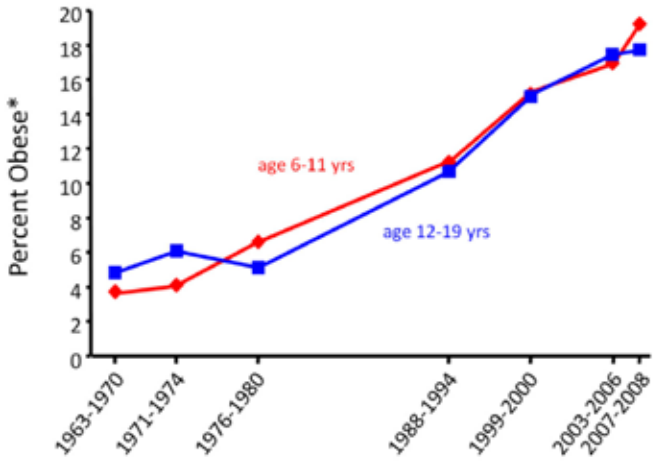
Other types of diabetes result from specific genetic conditions, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus; surgery; medications; infections; pancreatic disease; and other illnesses. Such types of diabetes account for 1 to 5 percent of all diagnosed cases (1).

## Complications of Diabetes

Persistent elevations of blood glucose levels, despite therapy, eventually damage nearly every organ in the body, including the eyes, kidneys, and cardiovascular system. Diabetes increases the risk of heart disease and heart attacks, stroke, high blood pressure, kidney failure, blindness, nerve pain and other neurological problems, limb amputation, chronic wounds and skin ulcers, gum disease, and pregnancy-related problems. Overall, diabetes is estimated to lower average life expectancy by 15 years, due to these devastating disease complications (2). The good news is that NIH-supported research has demonstrated that life expectancy for people with type 1 diabetes is increasing, type 2 diabetes can be prevented or delayed in those at risk, and intensive control of blood glucose levels dramatically prevents or delays the development of diabetes complications.

## Costs of Diabetes

In addition to the toll diabetes takes on health, it places an immense cost burden on individuals and the health care system. The estimated total financial cost for diabetes in the U.S. in 2007—including costs of medical care, disability, and premature death—was $174 billion: $116 billion for direct medical costs and $58 billion for indirect costs such as lost work productivity (1). After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes (1). One in 3 Medicare dollars is spent on people with diabetes (7). In addition to the eye, nerve, and kidney problems specific to diabetes, people with diabetes have worse outcomes after diagnosis of cancer and heart disease, require longer hospitalizations on average even for conditions unrelated to diabetes, are at increased risk of depression, and endure reduced quality of life and substantially increased personal medical expenses.




Trends in childhood overweight and obesity. The prevalence of obesity (see definition below) has increased steadily since the 1970s among 6-11 year old children. In older children (12-19 years), the rise in overweight prevalence was less gradual, with a sharp increase during the 1980s. These increases in weight have been accompanied by an observed rise in diabetes in youth. *(*Obesity is defined as equal to or greater than the 95th percentile of BMI-for-age and gender, based on 2000 Growth Charts from the Centers for Disease Control and Prevention. Sources for overweight/obesity data: NHES II & III, NHANES I, II, & III, NHANES 1999-2004; Ogden et al. JAMA 2002, JAMA 2006, JAMA 2008, JAMA 2010)*

# HIGHLIGHTS OF DIABETES RESEARCH ACCOMPLISHMENTS

Over the past decade, research has led to major discoveries benefiting people with or at risk for diabetes. Examples include:

- **Diabetes complications can be reduced by over half with intensive glycemic control early in the course of the disease.**
- **Weight loss in people with type 2 diabetes results in improved control of glucose, blood pressure, and cholesterol with less use of medications.**
- **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.**
- **Continuous glucose monitors improve glycemic control and reduce hypoglycemia in adults with type 1 diabetes.**
- **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.**
- **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.**
- **Many new susceptibility genes for type 1 and type 2 diabetes have been identified.**
- **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.**
- **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.**
- **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.**

- **Benefits of intensive control of glucose endure with reduced complications long after the period of good control. Good control of blood glucose, blood pressure, and lipids can reduce by half cardiovascular death in diabetes.**
- **Diabetes self-management training and improved health care delivery practices can improve diabetes outcomes.**
- **Affordable community-based approaches to lifestyle change for type 2 diabetes prevention have been developed.**

## GOALS OF DIABETES RESEARCH

The promise of prevention, treatment, and cure for diabetes can only be realized through the vigorous support of scientific research. This research must be conducted through a multi-pronged effort that addresses the complex challenges posed by diabetes, from dysfunctions in the most fundamental molecular and cellular processes, to the need for new approaches to translate scientific findings into improved health for people affected by the disease. This Plan addresses important opportunities in 10 major diabetes research areas.

- **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**

None of this research can be pursued without trained investigators and research facilities, and this Plan also addresses the issues surrounding the technological and human resources needed to accelerate discovery in diabetes.

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

Diabetes has a strong genetic basis that is modified by environmental factors. Powerful new tools, such as genome-wide association (GWA) studies, are accelerating gene discovery. Identification of key genes influencing risk for diabetes and its complications will not only help to predict who will develop the disease and aid in the development of new prevention strategies, but also identify key targets for the development of new molecular therapies and aid in individualization of therapy.

### Type 1 Diabetes and Autoimmunity

One way to attack type 1 diabetes is to stop it before it ever starts. Therapies based on modulating the immune system are already showing promise to slow loss of insulin-producing beta cells in the newly-diagnosed.

Increasing knowledge of what goes wrong with the immune system and identification of environmental factors that trigger the disease in those at risk will facilitate the discovery of novel ways to prevent autoimmunity, and thus prevent disease onset.

### The Beta Cell

All major forms of diabetes share a common basis in the loss of insulin-producing pancreatic beta cells. Thus, approaches to protect and/or increase the number of existing beta cells and to replace lost beta cell function are of critical importance. Understanding the steps in the normal development of beta cells coupled with advances in stem cell biology will yield approaches to replicate, regenerate, or replace beta cells and thus restore normal insulin production.

### Type 2 Diabetes As a Multi-Dimensional Disease

Systems biology may help to unlock the genetic and molecular complexity of diabetes. This new science attempts to integrate large data sets obtained by application of "omics" technologies—genomics, transcriptomics, proteomics, and metabolomics—to provide unprecedented depth of understanding of phenotypic variability and to identify novel pathways of disease development and progression.

### Obesity

Obesity is a major risk factor for type 2 diabetes and is also a problem in people with type 1 diabetes receiving intensive insulin therapy. Important new knowledge has emerged about the mechanisms by which fat tissue promotes harmful inflammation and insulin resistance, yielding new avenues for therapy. New therapeutic targets are also emerging from understanding of the powerful brain and body signals regulating appetite and energy balance. Successful approaches to sustained weight loss have demonstrated major benefits for those with or at risk of type 2 diabetes. However, to stem the rising tide of type 2 diabetes, new approaches to prevention of overweight and obesity require research on many fronts, from fundamental studies to large clinical trials.

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

Because it is proven to prevent complications, restoring glycemic control is a key goal in diabetes treatment. Devices for continuous glucose sensing and insulin delivery already provide valued treatment options for people who require insulin treatment, as well as the tantalizing near-term potential to link these technologies to create an artificial mechanical pancreas. Bioengineered insulin-releasing cells or molecules are other approaches to management of glycemia that could greatly reduce the treatment burden for people with diabetes.

### Clinical Research and Clinical Trials

Landmark NIH-supported clinical trials have provided proof that control of glucose, blood pressure, and cholesterol can dramatically reduce diabetes complications, and that the course of both type 1 and type 2 diabetes can be slowed. Yet, there is much to learn about the risks and benefits of diabetes therapies and about their comparative effectiveness. Combating the burden of diabetes requires a robust program of clinical research and clinical trials that can identify, test, and compare approaches to the treatment or prevention of diabetes and translate fundamental research advances into effective therapies for people living with or at risk for the disease.

## Special Needs for Special Populations

Increasingly, diabetes research has shown that one size doesn't fit all and that therapy and prevention approaches must be tailored for groups such as children and older adults, pregnant women, and people already battling other serious diseases and conditions. The disproportionate burden of diabetes in minority populations presents special challenges that need to be addressed by research.

## Diabetes Complications

Preventing diabetes-induced damage to eyes, kidneys, nerves, the heart, and other body tissues would go a long way to reducing the tremendous morbidity and mortality of this disease. Recognition of the phenomenon of "metabolic memory," with early aggressive glucose control yielding sustained benefits over the ensuing decades, highlights the importance of understanding the molecular mechanisms by which glucose damages blood vessels. Further research on the fundamental aspects of tissue and organ damage in diabetes will help pave the way to preventive and therapeutic strategies.

## Clinical Research to Practice: Translational Research

A huge gap exists between the levels of control of glucose, blood pressure, and cholesterol proven to reduce complications (and thus recommended in clinical practice guidelines) and the levels of control of these factors achieved in actual medical practice. Further research to translate effective practices from the research setting to the population at large will help close the gap between the ideal and current real-world practice to improve health outcomes for people with or at risk of diabetes.

## Resource and Infrastructure Needs for Diabetes Research

Addressing the complexity of diabetes and its complications, and harnessing the new and emerging technologies that offer opportunities to understand, prevent, and treat diabetes, requires the collaborative efforts of fundamental and clinical scientists in a wide spectrum of disciplines, as well as the establishment of and broad access to shared resources and state-of-the-art technologies. Finding ways to leverage and further support resource and infrastructure development and promote multidisciplinary team efforts is critical to the successful implementation of plans for diabetes and obesity research.

# NIH DIABETES RESEARCH PORTFOLIO

The NIH is the primary source of Federal support for diabetes research. Diabetes research at the NIH is supported by regularly appropriated funds that the U.S. Department of Health and Human Services (HHS) receives for diabetes research 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. The NIDDK, on behalf of the Secretary, has a leadership role in planning, implementing, and evaluating the allocation and use of these funds.

While the NIDDK is the lead institute at the NIH for pursuing diabetes research and research training, diabetes research involves nearly every Institute and Center of the NIH, including the Fogarty International Center (FIC), National Center for Complementary and Alternative Medicine (NCCAM), National Cancer Institute (NCI), National Center for Research Resources (NCRR), National Institute on Minority Health and Health Disparities (NIMHD), National Eye Institute (NEI), National Human Genome Research Institute (NHGRI), National Heart, Lung, and Blood Institute (NHLBI), National Institute on Aging (NIA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Biomedical Imaging and Bioengineering (NIBIB), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute on Drug Abuse (NIDA), National Institute of Environmental Health Sciences (NIEHS), National Institute of General Medical Sciences (NIGMS), National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), and the National Library of Medicine (NLM), as well as the Center for Scientific Review (CSR), the NIH Office of Research on Women's Health (ORWH), and the NIH Office of Behavioral and Social Sciences Research (OBSSR). In addition to the NIH, the CDC, Centers for Medicare & Medicaid Services (CMS), Food and Drug Administration (FDA), IHS, Veterans Health Administration (VHA), Department of Defense (DOD), Agency for Healthcare Research and Quality (AHRQ), Health Resources and Services Administration (HRSA), U.S. Department of Agriculture (USDA), and other governmental agencies conduct, support, or participate in diabetes research.

Also contributing to support of diabetes research are the two major diabetes voluntary organizations, the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA), as well as the pharmaceutical industry and some private foundations.

NIH funding for diabetes research in fiscal year (FY) 2009, including support from the *Special Statutory Funding Program for Type 1 Diabetes Research*, was $1.03 billion (source: *http://report.nih.gov/rcdc/categories/*).*

## Collaborative Planning Process

The statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC) provides a forum for

communication and collaboration to promote diabetes research. Its broad membership includes components of the NIH and other government agencies that support diabetes-related activities (see Appendix A). Through the DMICC, government agencies identify ways in which they can work together and build upon each other's expertise and resources. This approach helps ensure that Federal diabetes activities are coordinated and not duplicated, as well as stimulates collaborations where appropriate.

The collaborative planning process for diabetes research also involves the voluntary agencies, including the ADA and the JDRF, 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 processes

## Examples of Major Current Diabetes Research Efforts

The NIH vigorously pursues and supports research on the understanding, prevention, and cure of diabetes. Because diabetes research spans such a broad range of disciplines, research efforts are under way in diverse areas, such as genetics, genomics, proteomics, immunology, developmental biology, obesity, cell biology, imaging, stem cell research, bioengineering, glucose sensing, and insulin delivery. Most fundamental research is accomplished through investigator-initiated regular research grants. To foster bench-to-bedside translational research, the NIH has developed consortia focused on specific goals such as understanding the development of the insulin-producing beta cell or the molecular events underlying pathogenesis of diabetes complications. Clinical trials test promising agents and approaches for diabetes and its complications, as well as interventions to prevent diabetes onset. This section highlights a variety of major efforts the NIH has made to support and extend the investigator-initiated research portfolio and foster innovative approaches. Many of these efforts were undertaken in response to research priorities described in the 1999 strategic plan, "*Conquering Diabetes: A Strategic Plan for the 21st Century";* strategic planning processes for the *Special Statutory Funding Program for Type 1 Diabetes Research;* and the 2006 *"Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*." However, these examples—mostly major research consortia—are not a comprehensive list of the entire NIH diabetes research portfolio. The NIH supports investigator-initiated research projects and fosters development of research efforts in areas of particular importance and opportunity through solicitations for grant applications and research contract proposals, and the NIH will continue to strongly support these efforts.

### *Animal Models*

**Animal Models of Diabetic Complications Consortium (AMDCC)**: The AMDCC is an inter-disciplinary consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The Consortium has already developed a number of promising models for complications involving the heart, kidney, and nervous system. Development of animal models is essential for pre-clinical drug development.

**Cooperative Study Group for Autoimmune Disease Prevention:** This research network is

*In addition to these funds, in FY 2009, funding from the American Recovery and Reinvestment Act enabled NIH to spend an additional $121 million in support of diabetes research.

focused on finding ways to prevent type 1 diabetes and other autoimmune diseases by means other than broadly suppressing the entire immune system. The group's goals are to create improved models of disease pathogenesis and therapy to better understand immune mechanisms involved; to use these models to test and validate new tools that may be applicable to human studies; and to encourage research that can be quickly translated from animal to human studies, emphasizing the development of surrogate markers for disease progression and/or regulation that can be utilized in the context of clinical trials.

**Mouse Metabolic Phenotyping Centers (MMPC):** The MMPC provides the scientific community with standardized, high-quality metabolic and physiologic phenotyping services for mouse models of diabetes, diabetic complications, obesity and related disorders. Using state-of-the-art technology and on a fee-for-service basis, the MMPC provides a range of complex exams used to characterize mouse metabolism, blood composition including hormones, energy balance and physical activity, eating and exercise, insulin resistance, organ function, metabolic fluxes and morphology, physiology, histology, and measures of diabetic complications in heart, kidney, vasculature, eye, and other tissues and organs. Many tests are designed to elucidate subtle to complex traits that would define models of metabolic disease.

**Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG):** This multi-institution study group was established to evaluate the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of kidney and islet transplantation. The program also supports research to understand the underlying molecular mechanisms of immune tolerance. Pre-clinical research conducted by this group will help scientists move promising therapeutic agents from the laboratory into human clinical trials.

## *Genetics*

**Family Investigation of Nephropathy and Diabetes (FIND):** The FIND consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease in people with diabetes, as well as their genetic susceptibility to retinopathy. These studies will help researchers understand the genetic underpinnings of kidney and eye complications of diabetes, which can, in turn, inform prevention and treatment strategies.

**Genetics of Kidneys in Diabetes Study (GoKinD):** GoKinD was established to study the genetics of kidney disease in people with type 1 diabetes. The study group has collected DNA and other biological samples from over 1,700 adults with type 1 diabetes in the U.S. and Canada. Scientists will use these samples to identify genes that are important in the development of, or resistance to, diabetic kidney disease.

**Multi-ethnic Study of Type 2 Diabetes Genes:** This research consortium was established to identify the causative variants for diabetes genes in multiple populations to allow for further research on their function and role in the development of diabetes. It will serve as a research pipeline to confirm and characterize the genetic associations for type 2 diabetes already identified from GWA studies, accelerating the analysis of this wealth of genetic information.

**Type 1 Diabetes Genetics Consortium (T1DGC):** T1DGC is organizing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. The success of the T1DGC has led to an increase in the number of genetic elements identified

in association with this complex disease. With these exciting new insights, researchers may be able to identify individuals at risk for the disease, develop and test prevention-oriented strategies, and design more specific clinical trials to test interventions specifically tailored to people with similar risk profiles.

## *Epidemiology*

**Epidemiology of Diabetes Interventions and Complications (EDIC):** The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of the Diabetes Control and Complications Trial (DCCT). The DCCT/EDIC research group has observed dramatic long-term benefits of intensive glucose control in preventing and delaying complications of the eyes, kidneys, nerves, and heart. These results have had a major impact on the clinical care of people with diabetes.

**SEARCH for Diabetes in Youth (SEARCH):** There are no comprehensive population-based estimates of diabetes burden among American youth. SEARCH is defining the prevalence and incidence of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. This study will help increase understanding of how diabetes strikes and unfolds.

**The Environmental Determinants of Diabetes in the Young (TEDDY):** The goal of TEDDY is to identify environmental causes of type 1 diabetes in genetically susceptible individuals. The study completed enrollment of at-risk newborns and is following them until they are 15 years of age. This long-term study is crucial to helping researchers understand the environment triggers that play a role in type 1 diabetes disease development.

## *Clinical Research and Trials*

**Action to Control Cardiovascular Risk in Diabetes (ACCORD):** ACCORD was designed to test three treatment approaches—intensive glucose, blood pressure, and lipid management—for decreasing the high rate of cardiovascular disease among adults with type 2 diabetes who are at especially high risk for heart attacks and strokes. ACCORD found that intensive metabolic control—aiming for near-normal hemoglobin A1c (HbA1c) values, goals below the ADA guidelines—could increase risk of death. Results from ACCORD and other clinical trials suggest that there is not a "one size fits all" approach for diabetes treatment, so patients may need individualized treatment strategies. In addition to cardiovascular disease, ACCORD is studying the effects of these therapies on diabetic eye, nerve, and kidney disease, as well as on rates of cognitive decline and structural brain damage.

**Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D):** BARI 2D was designed to compare various treatment strategies for diabetes and heart disease to prevent early death, heart attack, and stroke. BARI 2D found that optimal medical therapy is as beneficial as elective revascularization procedures in patients with type 2 diabetes and stable coronary heart disease. Because heart disease is the leading cause of death in people with diabetes, findings such as these are important to help inform treatment choices by patients and health care providers.

**Clinical Islet Transplantation Consortium (CITC):** The consortium is developing and implementing a program of single- and/or multi-center clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this consortium aims to

make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

**Diabetes Prevention Program Outcomes Study (DPPOS):** The landmark DPP clinical trial showed that type 2 diabetes could be prevented or delayed in people at high risk through a lifestyle intervention (diet and exercise) or treatment with the drug metformin. While both interventions were effective in all racial and ethnic groups, lifestyle was more effective in older adults and metformin was more effective in younger participants. The DPPOS is examining longer-term effects of the trial interventions on prevention of type 2 diabetes and its cardiovascular complications in DPP participants.

**Diabetes Research in Children Network (DirecNet):** The focus of DirecNet is to investigate the use of technologic advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia that attends intensive insulin therapy. Goals of the network include assessing the accuracy, efficacy, and effectiveness of continuous glucose monitoring in children with type 1 diabetes, and determining the extent to which exercise contributes to the risk of hypoglycemia. Until cell replacement therapy is a viable treatment option for children with type 1 diabetes, research on glucose sensing and insulin delivery is crucial to improving quality of life and decreasing the number of hypoglycemic episodes.

**Diabetic Retinopathy Clinical Research Network (DRCR.net):** Diabetes causes damage to the eyes and may lead to blindness. The DRCR.net conducts multi-center clinical research studies to test promising therapeutic agents for the treatment of diabetic retinopathy (eye disease), diabetic macular edema, and associated conditions. Because blindness is such a severe and debilitating disease complication, research pursued through this network could dramatically improve quality of life for people with diabetes.

**HEALTHY**: This study was designed to target food service and physical education changes in schools and to promote healthy habits, in hopes of lowering risk factors for type 2 diabetes in middle school students. Identifying new strategies to prevent risk factors for diabetes is extremely important because recent data estimate that 1 in 14 children in the U.S. between 12 and 19 years of age has pre-diabetes (18)—and many of the children with pre-diabetes have risk factors for cardiovascular disease.

**Immune Tolerance Network (ITN):** This research network is evaluating new therapies that can selectively prevent or diminish specific harmful immune responses in type 1 diabetes, other diseases, and organ transplants, without disabling the immune system as a whole. ITN is currently conducting and developing several clinical trials related to type 1 diabetes and islet transplantation. This type of research is critical to developing promising new strategies to cure type 1 diabetes by islet transplantation or reverse disease in new-onset patients.

**Look AHEAD (Action for Health in Diabetes):** This long-term multi-center trial in over 5,100 participants is under way to determine if lifestyle intervention can improve cardiovascular outcomes in people who are obese and have type 2 diabetes. Encouragingly, first-year results of the trial have shown that while HbA1c, blood pressure, and LDL cholesterol improved in both the lifestyle intervention and control groups, participants in the lifestyle intervention group saw greater improvement.

**Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY):** Previously

considered a disease of adults, type 2 diabetes is now increasingly observed in children, particularly minority youth. Because type 2 diabetes is so new to children, physicians do not know how best to treat it in this young population. To address this gap in knowledge, the TODAY clinical study is comparing three different treatments for type 2 diabetes in youth.

**Trial to Reduce IDDM in the Genetically at Risk (TRIGR):** This multi-center, international study completed recruitment and is comparing the development of type 1 diabetes in genetically-susceptible infants who are weaned onto a hydrolysate of cow's milk formula, in which many of the cow proteins have been broken down, versus standard cow's milk formula. TRIGR could have a major impact on disease prevention if differences are observed between the two types of formulas.

**Type 1 Diabetes TrialNet:** TrialNet is an international network of investigators, clinical centers, and core support facilities. It supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new-onset patients and to prevent the disease in people at risk. TrialNet has launched several studies that are recruiting, and is in the process of evaluating several other therapeutic agents to test in the network. This type of collaborative network infrastructure is critical for facilitating clinical trials in type 1 diabetes, as well as for making real improvements in the health of people with the disease by identifying new therapeutic agents.

## *Translational Research*

**Beta Cell Biology Consortium (BCBC):** The mission of this consortium is to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet cell development and function. The long-term scientific goal is to develop a cell-based therapy to restore normal insulin production and action to people with diabetes. Towards this goal, the BCBC has created and distributed important reagents that will serve the scientific community at large.

**Translating Research Into Action for Diabetes (TRIAD):** TRIAD is a 10-year, six-center prospective study of managed care and diabetes quality of care, costs, and outcomes in the United States. TRIAD is the first and largest multi-center study of diabetes quality of care, quality of life, and factors affecting them. The overall goal of the study is to examine the influence of managed care structure on processes and outcomes of diabetes care.

**Translational Research for the Prevention and Control of Diabetes and Obesity:** This research program aims to translate recent advances in the prevention and treatment of diabetes and obesity into clinical practice for individuals and communities at risk. For example, one research study is building on the results of the DPP clinical trial to determine if a lifestyle intervention could be cost-effectively administered through the YMCA. Several other studies supported under this initiative involve communities with large minority populations disproportionately burdened by type 2 diabetes and obesity.

**Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID):** This cooperative program is designed to facilitate translation to the clinic of novel, scientifically meritorious therapeutic interventions. It does this by making available, on a competitive basis, resources for the pre-clinical development of drugs, natural products, and biologics. A partial listing of those services includes: high-throughput screening, studies in animal models, formulation, pharmacology and toxicology studies, and bulk substances acquisition.

### *Shared Research Resources*

**Diabetes Centers Program:** The Diabetes Centers Program administers two types of center awards, the Diabetes Endocrinology Research Centers (DERC) and the Diabetes Research and Training Centers (DRTC). While not directly funding major research projects, both types of center grants provide core resources to integrate, coordinate, and foster the interdisciplinary cooperation of a group of established investigators conducting research in diabetes and related areas of endocrinology and metabolism.

**Integrated Islet Distribution Program (IIDP):** Because of the substantial differences between human and rodent islets, it is essential that researchers studying the insulin-producing beta cells and other components of the pancreatic islets have access to human tissue. The major source of human islets is from organs that are donated for islet transplantation but subsequently found to be unsuitable for transplantation. This contract-supported resource acquires these human islets from subcontracted islet isolation centers and distributes them to approved investigators to facilitate basic research on human islets. In addition, the program is focused on enhancing the quality of isolated islets and establishing appropriate viability test standards.

**NIDDK Central Repositories:** These three separate contract-funded components work together to store data and biological samples (including samples for genetic analyses) from significant, NIDDK-funded clinical studies, including landmark clinical trials in type 1 and type 2 diabetes. The purpose of the Central Repositories is to expand the usefulness of these studies by providing access to the biosamples and data to a wider research community beyond the end of the study.

## DEVELOPMENT OF THE STRATEGIC PLAN

### Origin and Purpose of Plan

It has been over 10 years since the last comprehensive diabetes research plan was released. That plan, "*Conquering Diabetes: A Strategic Plan for the 21st Century*," was developed by the congressionally-established Diabetes Research Working Group and published in 1999. Opportunities described in that plan have led to many research advances described in this document. In the intervening time, however, major changes have taken place in the understanding of diabetes, new tools and technologies have been developed, and information on how to treat and prevent diabetes has grown rapidly. In addition, significant data have emerged on the burden of pre-diabetes and on diabetes in special populations, such as type 2 diabetes in children. In 2006, the NIH published "*Advances and Emerging Opportunities in Type 1 Diabetes Research*." Developed under the guidance of the DMICC, many of the opportunities described in that plan would inform all diabetes research—especially research on diabetes complications, which are common to type 1 and type 2 diabetes, as well as studies of the insulin-producing beta cell. However, the plan focused on opportunities most germane to type 1 diabetes. In light of all these

facts, the DMICC determined that the time was right to identify high-priority opportunities for all diabetes research that can be accomplished in the next 5 to 10 years. In many areas, the efforts undertaken to develop the current plan complement and extend opportunities described in the 2006 plan.

The purpose of this Strategic Plan is to serve as a scientific guidepost to the 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.

## 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 (please see Appendix A). Participants included representatives from the NIH and other Federal agencies represented on the DMICC, scientists external to the NIH, and representatives from diabetes voluntary organizations.

The Strategic Plan was organized around the important opportunities in diabetes research as described previously. To formulate the Plan, working groups were convened to address each of 10 scientific areas of important opportunity. An additional working group composed of representatives from each of the other 10 groups addressed overarching needs for scientific expertise, tools, technologies, and shared 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. The working group members were asked to survey the state of the science and develop a summary of progress and opportunities relevant to each goal. Through conference calls and electronic exchanges, they assessed the advances and emerging opportunities relevant to their scientific areas.

In addition to the focused working groups, the Strategic Plan was informed by insights provided by an overarching Diabetes Research Strategic Plan Leadership Group comprised of the chairs of the 11 working groups and representatives from the government and from diabetes voluntary organizations. The overarching Leadership Group met in person on July 7, 2009, to assure that in aggregate the components developed by the focused working groups were comprehensive and addressed the most compelling opportunities for prevention, therapy, and cure of diabetes and its complications. They provided guidance on development and integration of the products of each working group into a final Strategic Plan that will serve the purpose of informing future priority-setting in diabetes research.

## Public Input To Inform the Planning Process

To solicit broad public input into the strategic planning process, the draft Strategic Plan was posted on the NIDDK Web site for comment prior to publication (*http://diabetesplan.niddk.nih.gov*).

## Organization of the Plan

Chapters focused on each area of important research opportunity include these key sections:

- **Introduction:** A brief description of the current state-of-the-science, and an overview of the importance of the chapter subject in propelling research progress in diabetes research.
- **Recent Research Advances:** Examples of major breakthroughs in diabetes research and related efforts that have made a significant impact on the

research field or people's health, particularly in the last 5 to 7 years.

- **Key Questions and Future Directions for Research:** Specific research questions and directions are described that can be pursued to advance research in the area described by the chapter. The future directions were identified by working group members 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. This section also describes some immediate steps that can be taken to implement these research directions.
- **Importance of Research Goals and Strategies:** This closing section envisions how the research proposed in the chapter may transform the health of people with or at risk of diabetes.

## LOOKING FORWARD: FUTURE OF DIABETES RESEARCH

Successful implementation of the research directions outlined in this Plan requires the collaboration of the multiple institutes and centers of the NIH, other government agencies represented on the DMICC, industry, and the diabetes research and voluntary community. It is only through the involvement and collaboration of these different entities that research progress will be realized.

Although this document, representing current research advances and future directions, is necessarily static, the strategic planning process is dynamic. Novel findings and new technologies can dramatically and positively change the course of planned research. Therefore, for this Plan to be successful, it must periodically be assessed by scientific experts in the diabetes research field so that new and emerging opportunities can be identified. The DMICC will serve an important role by assessing progress toward attaining the objectives described in the Plan. The NIH will also continue to solicit the input of the broad scientific community through forums such as scientific workshops, conferences, and planning and evaluation meetings. This input will continue to be a valuable and necessary component of the NIH's strategic planning process for diabetes research.