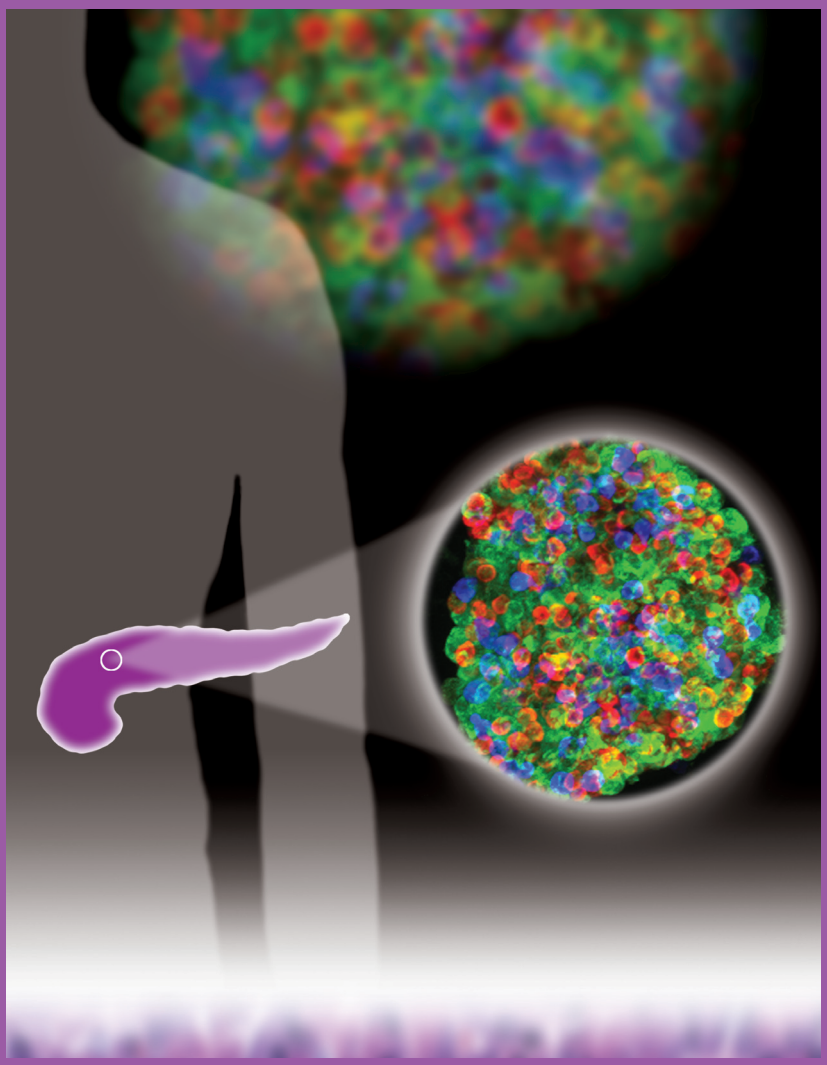

The ability to see insulin-producing beta cells within the body may prove invaluable in terms of diagnosing and managing diabetes, and could help researchers better understand the life cycle of these cells and how they are damaged in this disease. The problem is complex, because beta cells are one of several cell types in the islet, and represent only a small fraction of the total cells in the pancreas. In this image of a human islet, the insulin-producing cells are stained green, whereas two other cell types are stained blue or red. (Other colors result when these three basic colors overlap in the three-dimensional image.) A recent NIDDK-sponsored research advance toward imaging beta cells is described in this chapter.

Islet image courtesy of Drs. Marcela Brissova and Alvin Powers, Vanderbilt University.

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, they affect many millions of Americans and profoundly decrease their quality of life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 20.8 million people in the U.S.—over 7 percent of the total population—and is the sixth leading cause of death. 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 adult onset blindness. In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2002—including costs of medical care, disability, and premature death—was $132 billion. Effective therapy can prevent or delay these complications, but approximately one-third of Americans with diabetes are undiagnosed.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone which 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 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, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production.

Type 1 diabetes affects approximately 5 to 10 percent of individuals with diagnosed diabetes. It most often develops during childhood, but 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, which are found within tiny cell clusters called islets, produce the hormone insulin. If left untreated, type 1 diabetes results in death from starvation despite high levels of glucose in the bloodstream. Thus, patients 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 patients to control blood glucose levels as well as they could if they had functional beta cells. 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.

Type 2 diabetes is the most common form of the disease, accounting for about 95 percent of diabetes cases in the U.S. Type 2 diabetes is associated with several factors, including older age and a family history of diabetes. It is also strongly associated with obesity: more than 80 percent of adults with type 2 diabetes are overweight or obese. Type 2 diabetes occurs more frequently among minority groups, including African Americans, Hispanic Americans, American Indians, and Native Hawaiians.

In patients with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. Gradually, the pancreatic beta cells secrete less and less insulin, and the timing of insulin secretion becomes abnormal. To control glucose levels,

treatment approaches include diet, exercise, and orally administered medications; some patients also need to take insulin. There are also an estimated 54 million adults in the U.S. who have a condition called "pre-diabetes," in which blood glucose levels are higher than normal, but not as high as in diabetes. This population is at high risk of developing diabetes. Fortunately, the Diabetes Prevention Program (DPP) clinical trial has shown that patients with pre-diabetes can dramatically reduce their risk of developing full-blown 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 disease 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 U.S.

The NIDDK is supporting research to better understand the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the Institute's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the Institute is vigorously pursuing studies of prevention and treatment approaches for these diseases.

Genetic Mutation Linked to Some Forms of Neonatal Diabetes Mellitus: Novel mutations in a component of an ion channel in insulin-producing beta cells have been found to contribute to the development of neonatal diabetes. This form of diabetes appears in the first months of life, and may either be permanent, or transient—with the possibility of relapse later in life. Researchers studying families with neonatal diabetes screened their DNA for mutations in a gene (*ABCC8*), which encodes one subunit of a transmembrane ion channel in the pancreatic beta cells. Mutations in the gene for the other subunit of this channel (*KCNJ11*) have also been shown to cause neonatal diabetes. Investigators found mutations in the *ABCC8* gene in 9 of 34 patients with neonatal diabetes—in whom no other genetic defect had been previously identified. The mutations are thought to upset the careful regulation of potassium and calcium ions inside and outside of the beta cells. Disrupting this balance inhibits the release of insulin from the beta cells, leading to a dangerous rise in overall blood glucose levels. Fortunately, patients with mutations in either *ABCC8* or *KCNJ11* responded favorably to treatment with a class of orally-administered drugs known as sulfonylureas, simplifying their treatment. These drugs act by binding to the complex of proteins that make up the ion channel, increasing their surface expression, and inhibiting the release of potassium ions from the beta cell. These actions allow insulin release in response to elevated blood glucose. These studies identify a novel mechanism for the development of a significant fraction of permanent and transient neonatal diabetes in a particularly vulnerable group of individuals, and shed light on the biochemical mechanism of action of the drugs used to treat it.

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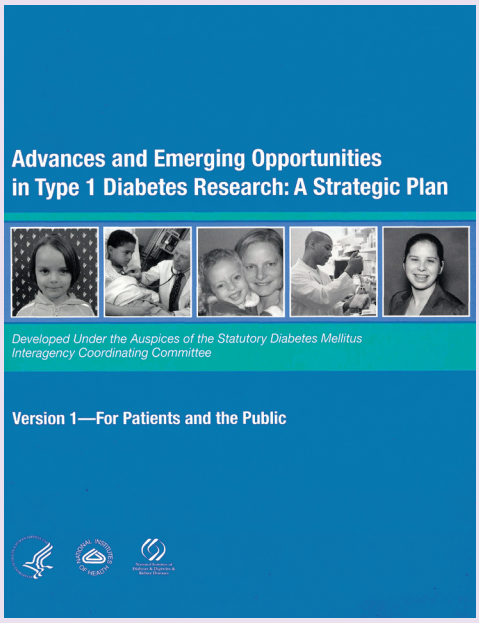
Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan

Type 1 diabetes is a devastating disease that results when the immune system destroys the insulin-producing beta cells of the pancreas. Individuals with type 1 diabetes must check their blood glucose levels many times a day with finger sticks, carefully monitor their food intake and physical activity, and administer insulin with injections or a pump. Type 1 diabetes can cause life-threatening complications, such as heart disease, blindness, and kidney failure. Continued research is critically important to reduce the toll of type 1 diabetes and its complications on human health.

To accelerate research progress, a Type 1 Diabetes Research Strategic Plan has been developed by the statutory Diabetes Mellitus Interagency Coordinating Committee, chaired by the NIDDK, with broad input from external scientific and lay experts and patient advocacy groups. The Strategic Plan is expected to serve as a scientific guidepost to inform future type 1 diabetes research efforts and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. In the news release announcing the Plan's completion, the NIH Director, Elias A. Zerhouni, M.D., noted that: "Research has greatly improved the length and quality of life of people with type 1 diabetes, and it has lowered the risk of developing certain serious complications, such as retinopathy and kidney failure. However, many challenges remain in combating this complex autoimmune disease. The Strategic Plan sets forth a cogent, multifaceted approach to future research that soundly addresses these challenges." The Plan is focused around six overarching goals of type 1 diabetes research: identify the genetic and environmental causes; prevent or reverse the disease; develop cell replacement therapy; prevent or reduce hypoglycemia; prevent or reduce complications; and attract new talent and apply new technologies to research. Based on the same general content, two versions of the Plan were developed for: (1) patients and the public, and (2) the scientific research community. The Strategic Plan was released in August 2006, and can be accessed on the NIDDK's website at: *www.T1Diabetes.nih.gov/plan*



Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan, released in August 2006, describes a comprehensive, long-range approach to guiding type 1 diabetes research toward improved care, prevention, and cure for this devastating disease. Two distributed versions—one for patients and their families, and one for the scientific community—differ primarily in level of detail. Both were developed with broad input from stakeholders, including the scientific community, patients, and patient advocacy groups.

"Seeing" New Progress in Type 1 Diabetes—Imaging Beta Cells: The goal of visualizing insulin-producing beta cells in the pancreas is closer to realization than ever before. Why is it important to "see" beta cells? Type 1 diabetes is usually diagnosed late in disease progression, when most of the beta cells have been destroyed by an autoimmune attack. Currently, there is no way to detect the first signs of beta cell destruction or to monitor beta cell loss as the disease progresses. The ability to visualize beta cells could enable earlier intervention to stop or slow disease progression, as well as permit scientists to monitor response to therapy. Toward this goal, researchers used imaging technology (positron emission tomography or PET) to visualize beta cells *in vivo* in a rat model of type 1 diabetes. They used a labeled form of a compound (DTBZ), which binds to a protein found in some cells of the body, including beta cells. Thus, when the labeled compound bound to the beta cell protein, the beta cells could be visualized by sophisticated imaging. As the beta cells were destroyed during progression to type 1 diabetes, the researchers observed a decrease in the uptake of the labeled compound in the pancreas that foreshadowed the loss of blood glucose control. This approach permitted them to noninvasively monitor beta cell destruction as the laboratory animals transitioned from a healthy to a disease state. This labeled compound is already used in humans for clinical imaging of the brain. Therefore, this approach has high potential to be translated to humans and could be enormously helpful in monitoring disease progression and response to therapy in type 1 diabetes.

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Type 2 Diabetes and Obesity—the RBP4 Protein and Implications for Medical Care: A potential new diagnostic marker and therapeutic target is emerging for type 2 diabetes, a devastating and increasingly prevalent disease. Building on their earlier research in mice, scientists tested levels of a protein called retinol binding protein 4 (RBP4) in blood samples from patients with type 2 diabetes or people with such risk factors as obesity, a family history of the disease, or levels of blood glucose that were elevated but not yet diabetic. The high blood glucose levels seen in type 2 diabetes reflect the impaired response, or "resistance," of multiple body tissues to the hormone insulin, and the eventual inability of the body to produce sufficient insulin to overcome this resistance. Levels of the RBP4 protein correlated with insulin resistance in people who were obese, either with or without type 2 diabetes. The scientists also studied another group of individuals who underwent exercise training after having been newly diagnosed with type 2 diabetes or abnormal glucose levels. In this group, those whose body's responsiveness to insulin improved the most from the exercise also had the greatest change in their RBP4 levels. Interestingly, RBP4 levels also correlated with measures of insulin resistance in people who were not obese or diabetic, but who had a close relative with type 2 diabetes, and thus a potential genetic predisposition to the disease. Additionally, the researchers found that elevated RBP4 levels occurred together with cardiovascular risk factors often associated with insulin resistance, such as high triglyceride levels and blood pressure, and abdominal obesity. The results of these studies not only suggest that a blood test for RBP4 levels may be a convenient way to assess risk for type 2 diabetes, but also illuminate a potential new strategy for combating this disease, namely, the development of drugs that could lower RBP4 levels. (For more information about RBP4, please see the Scientific Presentation by Dr. Barbara Kahn in the Obesity section.)

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Unraveling the Complexities of Childhood Diabetes: Previously known primarily as a disease of adults, type 2 diabetes is now increasingly observed in children, particularly minority youth. Little is known about the prevalence of risk factors for diabetes or cardiovascular disease (CVD) in children and youth; however, recent research has begun to shed some light on this issue. Researchers who are conducting a pilot study for a larger prevention trial (called HEALTHY) studied over 1,700 eighth grade students in 12 U.S. middle schools with predominantly minority students. They found a high prevalence of three major risk factors for diabetes—impaired fasting glucose (i.e., pre-diabetes), high levels of fasting insulin (suggestive of insulin resistance), and overweight. A surprisingly high 15 percent of the students had all three risk factors. The researchers also observed significant differences across racial and ethnic groups; for example, American Indians had the highest prevalence of overweight. Overall, nearly half of the students were overweight or at risk for overweight. Many children also had CVD risk factors, such as high blood pressure and elevated lipid levels, which were associated with overweight.

The data collected during the pilot study suggested that middle schools are appropriate targets for population-based efforts to decrease risk for overweight and diabetes. In August 2006, the NIDDK launched the full-scale HEALTHY trial, which is directed at reducing risk factors for type 2 diabetes in middle-school age children. Half of the 42 enrolled schools are receiving the intervention, which consists of: environmental changes to school food service and physical education class activities; behavior change activities; and communications and promotional campaigns. 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 have pre-diabetes—and many of the children with pre-diabetes have CVD risk factors.

What about children who already have type 1 or type 2 diabetes, who are not addressed by the HEALTHY pilot study? New insights are beginning to emerge from the Search for Diabetes in Youth (SEARCH) study, which is identifying cases of diabetes in children and youth under 20 years of age in six geographically dispersed populations encompassing the ethnic diversity of the U.S. SEARCH researchers have estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001, making diabetes one of the leading chronic diseases in children and adolescents. SEARCH researchers have also demonstrated that the prevalence of multiple CVD risk factors is high in children and adolescents with diabetes. CVD risk factors were present in youth with both type 1 and type 2 diabetes, but were more common in adolescents with type 2 diabetes. SEARCH has also demonstrated that about nine percent of adolescents with diabetes have moderate or severely depressed mood. This is similar to findings in youth without diabetes, but importantly, in young diabetes patients depressed mood was associated with poor diabetes control and a higher likelihood of emergency room visits. Another important observation was that higher body mass index (a measure of weight relative to height) was associated with younger age at diagnosis of type 1 diabetes, but only in children with substantially reduced beta cell function. These data suggest that, only among individuals with already compromised beta cell function and/or high rate of beta cell loss, overweight accelerates type 1 diabetes onset. The same study found that lower birth weight was associated with earlier age at onset of type 1 diabetes. These key observations are helping to inform treatment strategies for children with diabetes. As data continue to emerge, the knowledge gained from these studies will contribute to identifying the best ways to diagnose, treat, and manage diabetes in children, and ultimately help to reverse the trend of increasing rates of type 2 diabetes in this population.

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Genetic Variant Raises Risk for Type 2 Diabetes Development: Researchers have confirmed that a variant in a specific gene (*TCF7L2*) confers susceptibility to type 2 diabetes in individuals who participated in the landmark Diabetes Prevention Program (DPP). The DPP was the first major clinical trial to show that diet and exercise can effectively reduce the risk of developing diabetes in overweight people with pre-diabetes. In their analysis of 3,548 DPP participants, researchers found that 40 percent of the people had one copy of the gene variant, while 10 percent of participants had two copies. When people had two copies, their risk of developing diabetes was about 80 percent higher compared to people without the variant. The DPP population included people from minority groups who are disproportionately affected by type 2 diabetes. Encouragingly, even the DPP participants at highest genetic risk benefited from healthy lifestyle changes as much or perhaps more than those who did not inherit the variant. This finding emphasizes that people at risk for developing type 2 diabetes can benefit greatly by implementing a healthy lifestyle—whether they are overweight, have elevated blood glucose levels, or have the gene variant. The researchers further showed that the gene variant affected only one of the two major hallmarks of type 2 diabetes. It impaired the ability of pancreatic beta cells to secrete insulin, but it did not affect the ability of target tissues to respond to insulin (insulin resistance). Additional research to understand how the gene variant plays a role in disease could provide novel insights into the molecular basis of diabetes and lead to targeted strategies for prevention and therapy.

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STORY OF DISCOVERY

New Technology for Diabetes—Continuous Glucose Monitors

Sometimes, what you don't know *can* hurt you. For people with type 1 diabetes, undetected high or low blood glucose levels can have severe health consequences—including heart disease, blindness, and coma. With advanced technology, however, patients now have the opportunity to monitor their blood glucose (sugar) levels continuously, rather than just a few times a day. Developed with NIDDK, industry, and other support, these new, wearable continuous glucose monitors sound an alarm when glucose levels soar or plunge to dangerous levels—especially important during sleep. They also generate important data, in real time, on trends in glucose levels as they fluctuate throughout the day and night. With this new wealth of knowledge, people with type 1 diabetes may greatly improve their daily disease management by better adjusting the timing and dosages of insulin, the hormone required to prevent excessive high blood glucose, and by eating or taking other action to raise low blood glucose. The monitors also have potential to help some type 2 diabetes patients control their blood glucose levels. Finally, the realization of continuous glucose monitoring technology is a key step toward developing a mechanical replacement for disease-ravaged pancreatic beta cells, the cells that normally monitor glucose levels and produce insulin, but are destroyed in type 1 diabetes.

Decades ago, reliable and practical methods for glucose monitoring were not available, yet control of glucose levels in the body is crucial. Glucose is obtained from food and is also made by the liver. In healthy people, insulin from pancreatic beta cells directs cells throughout the body to absorb glucose from the blood for use as energy. Without beta cells, however, type 1 diabetes patients face daily the arduous tasks of glucose monitoring, insulin administration, rigorous meal planning, and other efforts to control blood glucose. Without sufficient insulin, cells are deprived of energy, and, over time, high blood glucose levels greatly increase risks for heart disease, blindness, kidney failure, nerve damage, and other severe complications. Administering too much insulin, however, can lead to dangerously low glucose levels, or hypoglycemia, which can result in coma or death if untreated, and is especially feared during sleep. Thus, researchers have long sought to develop improved glucose-monitoring methods.

For years, people with type 1 diabetes could only check their glucose levels by testing urine, a method that was not very accurate or useful. In the 1960s, scientists invented the first meter to measure glucose in the blood. By the 1980s, blood glucose meters were widely used, and, with further improvements, remain so today. Important to any developing technology is a way to evaluate it, and in the 1980s, NIDDK-supported scientists devised a method (error grid analysis) to assess the accuracy of glucose-measuring devices in diabetes management.

The tremendous health benefits of intensive blood glucose control were demonstrated in the early 1990s by a landmark, NIDDK-supported clinical trial, the Diabetes Control and Complications Trial (DCCT). This trial, which was possible because of the availability of glucose-monitoring devices, showed that intensive control greatly reduced development of diabetic eye disease, kidney disease, and nerve damage in people with type 1 diabetes, and the

STORY OF DISCOVERY

ongoing follow-up study recently demonstrated reduced risk for heart disease and stroke. The intensive control regimen is difficult, however, because it requires multiple painful finger sticks each day to draw blood for testing, as well as more frequent insulin administration than was the standard practice prior to the DCCT. The DCCT also revealed that intensive control to avoid high blood glucose levels and future complications had a serious trade-off: an increased immediate risk for hypoglycemia. With the difficulties of intensive glucose control and the threat of hypoglycemia, type 1 diabetes patients still rarely achieve recommended glucose levels. The DCCT thus also underscored the critical importance of research to improve methods for blood glucose control.

By the late 1990s, measurement of glucose in the blood had proven useful for several checks per day, but it was not readily amenable to continuous monitoring. By way of analogy, patients can see a few "snapshots" of their glucose levels per day with blood glucose meters, but miss what happens in between; with continuous monitors, patients would see an entire movie that captured glucose highs, lows, and trends throughout the day and night. Thus, scientists were actively investigating another route to assess glucose that would be both safe and practical for continuous monitoring—the interstitial fluid in tissues under the skin. A critical research question was whether glucose levels measured by a sensor in the interstitial fluid would reflect glucose levels in the blood. The answer was "yes," as shown in studies in animals and humans, by several research groups supported by the NIDDK and industry. A continuous monitor was first approved by the FDA in 1999. The glucose values obtained from this device were not as accurate as direct blood glucose measures, and could only be assessed retrospectively, not in real time. But the continuous monitor could amass hundreds of glucose readings per day for subsequent analysis by health care providers and patients.

Further research culminated in the FDA approval, in 2006, of new continuous glucose monitors for people with diabetes. These monitors provide glucose readings in real time, every 5 minutes; display trend data so patients know whether their glucose levels are rising or falling; and sound alarms when levels are too high or low—including at night, during sleep. Before taking action to adjust high or low glucose, patients will still need to confirm readings from these new monitors with a traditional finger stick and blood glucose meter. Additionally, the scientists found that, when blood glucose levels change, there is a time lag of a few minutes before a change is detected in the interstitial fluid. Patients will thus need to consider this small lag time in daily disease management. Importantly, however, researchers have demonstrated that, with the use of continuous glucose monitoring devices, patients spend less time in high and low blood glucose ranges, and more time in the recommended range. This achievement resulted from research investments by both NIDDK and industry.

Continuous glucose monitoring technology will enable people with diabetes and their doctors to better predict how meals and daily activities will affect blood glucose, and to adjust and personalize their disease management accordingly to help preempt long-term diabetic complications and acute episodes of hypoglycemia. An ongoing and critical area of NIH-funded research is the evaluation of these monitors for use in children, because they are currently approved only for adults. Finally, a key feature of one of the approved

monitors is that it transmits its data to an insulin pump. Insulin pumps are small, pager-sized machines that can deliver insulin to patients continuously in a small basal amount and provide larger boluses when needed, for example at mealtime. Although patients still must be actively involved in determining their insulin doses, based on glucose readings and other factors, this first pairing of a continuous monitor and pump has major implications. With NIDDK funding, scientists are now developing algorithms that will one day "close the loop" between the glucose monitor and insulin pump, creating an "artificial pancreas" to automate insulin delivery in response to the body's needs. In September 2006, the NIDDK Acting Director, Dr. Griffin Rodgers, presented testimony on artificial pancreas development efforts before the Senate Homeland Security and Governmental Affairs Committee. This testimony is available on the NIDDK Website (*http://www.niddk.nih.gov/federal/planning/Rodgers092706ArtificialPancreasTestimonyHSGAC.pdf*). Even before an artificial pancreas is developed, patients can improve their health now, with the unprecedented knowledge gained from continuous glucose monitors.

National Diabetes Education Program: Type 2 Diabetes Often Goes Unnoticed

One-third of adults with diabetes do not know they have it. Scientists from the NIH and the Centers for Disease Control and Prevention (CDC) analyzed data on U.S. adults aged 20 years and older from the CDC's National Health and Nutrition Examination Survey (NHANES) during two time periods: 1988 to 1994 and 1999 to 2002. Comparison of data from these two time periods revealed that the prevalence of diagnosed diabetes rose from about 5.1 percent to 6.5 percent. However, the percentage of adults with undiagnosed diabetes did not change significantly. About 2.8 percent of U.S. adults—or one-third of those with diabetes—still do not know they have it. The study noted that type 2 diabetes accounts for about 95 percent of all diabetes cases and virtually all undiagnosed diabetes cases.

The study also found that another 26 percent of adults have a form of pre-diabetes, a condition in which a person's blood glucose is high but not yet diagnostic of diabetes. Pre-diabetes usually causes no symptoms. However, many people with the condition develop type 2 diabetes within the next 10 years. Also, pre-diabetes substantially raises the risk of a heart attack or stroke even if type 2 diabetes does not develop.

Who is at risk? Risk factors for developing pre-diabetes and type 2 diabetes include being age 45 or over, having a family history of diabetes, being overweight, or having a history of gestational diabetes during pregnancy. Certain ethnic populations are also at high risk (e.g., African American, Hispanic/Latino American, American Indian and Alaska Native, Asian American, and Pacific Islander). For more information on type 2 diabetes and its risk factors, please see: *http://diabetes.niddk.nih.gov/*

The good news is that NIDDK-supported research has shown that people with pre-diabetes can prevent or delay the development of type 2 diabetes by losing a modest amount of weight by reducing the number of calories in their diet and increasing physical activity. The National Diabetes Education Program (NDEP), sponsored by the NIH, CDC, and over 200 partner organizations, is disseminating this important message to people at risk for type 2 diabetes with the *Small Steps. Big Rewards. Prevent Type 2 Diabetes.* campaign. The NDEP also spearheads the *Control Your Diabetes for Life* campaign, which encourages people with diabetes to control their blood glucose levels, as well as their blood pressure and cholesterol levels. Information about these campaigns and other diabetes education programs can be found at: *www.ndep.nih.gov/*

Diabetes Prevention Program: Continuing Benefits from Research

Type 2 diabetes is a devastating and chronic disease. But, as the NIDDK-led Diabetes Prevention Program (DPP) clinical trial demonstrated, those at high risk for this disease can prevent or delay its onset. In the years since this landmark result was reported, the Institute has brought its important prevention message to health care professionals and the public through the educational campaign: *Small Steps. Big Rewards. Prevent Type 2 Diabetes*. The NIDDK is also vigorously supporting further research on type 2 diabetes to improve people's lives.

TYPE 2 DIABETES AND THE DPP CLINICAL TRIAL

Type 2 diabetes increases risk for cardiovascular disease, kidney failure, blindness, and other debilitating conditions. It can strike anyone, but disproportionately affects certain minority groups, including African Americans, Hispanic Americans, American Indians, Alaska Natives, and Native Hawaiians. Risk increases with a family history of the disease and with older age, but, alarmingly, type 2 diabetes is increasingly being seen in children. Overweight and obesity are major risk factors for type 2 diabetes and are likely driving the rise in this disease in children. Gestational diabetes, or diabetes diagnosed during pregnancy, occurs in about seven percent of U.S. pregnancies, and puts both mother and child at heightened risk for type 2 diabetes for the rest of their lives.

The DPP clinical trial was conducted at 27 centers throughout the U.S. The volunteers were adults at high risk for type 2 diabetes: they had "pre-diabetes"—blood glucose levels higher than normal but not yet diabetic—and they were also overweight. They were randomly assigned to different groups. The "lifestyle intervention" group received an intensive program to reduce their body weight by a relatively modest 5 to 7 percent, through moderate exercise and reducing dietary fat and calories. The two other groups were given standard lifestyle recommendations along with either the diabetes drug metformin or a placebo. The DPP demonstrated that the lifestyle intervention reduced risk for type 2 diabetes by a dramatic 58 percent. The metformin intervention reduced risk by 31 percent. These interventions worked in all ethnic and racial minorities studied and in men and women, including women with a history of gestational diabetes. Participants over 60 years of age responded particularly well to the lifestyle intervention, whereas both metformin and the lifestyle intervention were similarly effective for the younger participants (ages 25 to 44) and for participants who were very obese.

At the conclusion of the DPP trial, all of the volunteers were given the opportunity to participate in the lifestyle sessions that the intensive lifestyle intervention group had received because this intervention was proven to be so successful.

SMALL STEPS. BIG REWARDS. PREVENT TYPE 2 DIABETES.

This multicultural educational campaign, based on the results of the DPP, brings the message that modest weight loss through dietary change and moderate exercise (small steps) can prevent or delay type 2 diabetes (big rewards). It was developed by the National Diabetes Education Program (NDEP), which is jointly sponsored by the NIDDK and the Centers for Disease Control and Prevention and involves many partner organizations. Campaign materials are tailored for different audiences, including older adults and minority groups at high risk for type 2 diabetes. In 2006, the NDEP launched a new component of this campaign, a prevention message focused on women with a history of gestational diabetes (GDM) and their children.

FURTHER RESEARCH PROGRESS

Now, over 5 years since the report of the Diabetes Prevention Program's key finding—that type 2 diabetes prevention is possible—the DPP continues to provide valuable results. As one example, scientists recently found that the lifestyle intervention reduced the occurrence of urinary incontinence in women with pre-diabetes. In another study, scientists found that a gene variant confers susceptibility to type 2 diabetes in the DPP participants, and that the lifestyle intervention greatly reduced risk for diabetes even in those who had this genetic variation. This study thus builds on a previous report associating this gene with type 2 diabetes—an important result given the complexity of diabetes genetics—and emphasizes that, with healthy lifestyle changes, genetics is not necessarily destiny.

Building on the success of the DPP, the NIDDK is now supporting a follow-up study of the DPP participants, the DPP Outcomes Study (DPPOS). The DPPOS is assessing the durability of the effect of the interventions on the development of diabetes and on maintenance of weight loss, and whether the interventions impact the development of cardiovascular disease. The NIDDK is also encouraging demonstration and dissemination research projects to explore various strategies for translating the DPP results from the clinical trial setting to communities.

The DPP and DPPOS are part of the NIDDK's broad spectrum of basic, clinical, and translational research on type 2 diabetes. This research is strengthening our understanding of this disease and accelerating the development and testing of prevention and treatment strategies.

RESEARCH VOLUNTEERS – ADVANCING PROGRESS AND PROVIDING HOPE FOR MILLIONS OF AMERICANS

The success of the DPP simply could not have happened without the over 3,000 volunteers who participated in this clinical trial. On the following pages, two of the DPP participants share their stories of why they volunteered for this trial, and how they continue to prevent type 2 diabetes.

PATIENT PROFILE

Carol Baker

Gestational Diabetes and the Diabetes Prevention Program

Carol Baker always knew she was at high risk for diabetes. All four of her grandparents, as well as her mother and father, had developed the type 2 form of the disease. "Throughout my entire life my parents kept telling me that I was going to get diabetes. They told me 'be careful…watch out for it,'" says the now 45-year-old substitute teacher and mother of five daughters.

But the disease manifested itself in a way Carol had not anticipated. During her second pregnancy, at age 27, she was diagnosed with gestational diabetes mellitus (GDM), and received the same diagnosis in each pregnancy, thereafter.

GESTATIONAL DIABETES MELLITUS, OR GDM

GDM is a form of diabetes that occurs during pregnancy. Like other forms of diabetes, it's characterized by high blood glucose levels and can have serious consequences. Left untreated or uncontrolled, gestational diabetes can result in babies being born very large and with extra fat, which can make delivery difficult and more dangerous for both mother and child. It also can lead to babies with breathing problems and low blood glucose right after birth.

For most women, gestational diabetes goes away after the baby is born, but leaves them at greater risk for the disease during subsequent pregnancies. Gestational diabetes also leaves both mother and child at increased risk for type 2 diabetes for the rest of their lives.

Carol Baker (on left) with her family (from second left to right): Allie, Jennifer, Molly, Katie, Natalie, and Bryce.

Despite her family history of type 2 diabetes, Carol remains free of this devastating and chronic disease—18 years after her first GDM diagnosis. "I firmly believe the reason I do not have type 2 diabetes is because of the Diabetes Prevention Program (DPP) I participated in," says Carol.

TAKING CONTROL

Carol's five daughters range in age from 12 to 22. Allie, her oldest daughter, was adopted by Carol and her husband. Carol had no problems during her first pregnancy, with daughter Katie, now 20. But she had gestational diabetes during each of her next three pregnancies, with Natalie, 18, Jenne, 15, and Molly, 12. "All of my babies were very large, each over nine pounds." says Carol. "But fortunately," she adds, "everything else was normal." Having always known of her risk for type 2 diabetes, in the mid 1990s, Carol responded to an ad in the health section of a local newspaper asking for volunteers to take part in something called the Diabetes Prevention Program, or DPP.

PATIENT PROFILE

BENEFITS OF PREVENTION

The DPP volunteers were randomly assigned to one of three groups, to test whether different interventions could prevent type 2 diabetes in people at high risk, including those from minority populations and others who had excess weight and blood glucose levels that were higher than normal, but not yet diabetic. Carol's group received a drug called metformin along with standard lifestyle recommendations. Another group received the standard lifestyle recommendations and a placebo. The third group received a more intensive lifestyle intervention program aimed at modest weight loss through improved diet and moderate exercise. The DPP trial showed that this lifestyle intervention dramatically reduced risk for type 2 diabetes. The metformin intervention also reduced risk, although not by as much overall.

The DPP study ended in 2001, but Carol remains vigilant. "I'm very successful at eating properly and taking my medication," says Carol. "I watch my portion sizes, eat whole grains, lean meats, and fruits and vegetables, and I encourage my daughters and husband to do the same." She also strives to keep exercising. "I know I should try to get 30 minutes of physical activity, 5 days a week. Some months I do better than others." Her exercise usually entails walking outdoors or on her treadmill at home, or working out in the basement gym of a friend. She also gets her blood glucose checked every 6 months. "I'm very faithful about these check-ups," she says. "I never miss them."

Fortunately, Carol says, "I have always encouraged my children to lead healthy lifestyles because of their family history of diabetes." And it has paid off—even for the daughters from pregnancies affected by gestational diabetes. These daughters are not overweight, "and so far, no diabetes," she adds, thankfully.

Based on results of the DPP, the National Diabetes Education Program (NDEP), led by the NIDDK and the Centers for Disease Control and Prevention, along with many partner organizations, developed the educational campaign: *Small Steps. Big Rewards. Prevent Type 2 Diabetes*. Recently, the campaign added a new prevention message: "*It's Never Too Early To Prevent Diabetes. A Lifetime of Small Steps for a Healthy Family*." This message raises awareness that women with a history of gestational diabetes and their children have an increased risk for type 2 diabetes. It also emphasizes that lifestyle changes can reduce this risk.

"I have always encouraged my children to lead healthy lifestyles because of their family history of diabetes." And it has paid off—even for the daughters from pregnancies affected by gestational diabetes. These daughters are not overweight, "and so far, no diabetes," says Carol.

Carol Baker understands this very well. In April 2006, at the launch of this new prevention message, Carol was invited to speak, and her words were loud and clear: "I am proof that diabetes prevention is proven, possible and powerful, and I am going to continue taking these 'Small Steps' in an effort to prevent type 2 diabetes from affecting my life or the lives of my children."

NIDDK RESEARCH

The NIDDK's extensive portfolio of research on diabetes and its risk factors includes research related to pregnancy, to benefit mother and child. For example, an NIDDK-led initiative has fostered new studies addressing maternal diabetes or obesity during pregnancy and the long-term metabolic effects on the offspring. These studies complement the NIDDK's research on aspects of pregnancy that affect a mother's risk for diabetes.

For more information:

"What I need to know about gestational diabetes" – http://diabetes.niddk.nih.gov/dm/pubs/gestational/index.htm

"It's Never Too Early To Prevent Diabetes. A Lifetime of Small Steps for a Healthy Family" – http://www.ndep.nih.gov/campaigns/SmallSteps/SmallSteps_nevertooearly.htm

PATIENT PROFILE

Irish Stovall

Diabetes Prevention Program (DPP) Helps Ward Off Type 2 Diabetes

When a card arrived in her mailbox asking Irish Stovall if she would be interested in participating in something called the Diabetes Prevention Program (DPP), Irish, whose family has a long history of type 2 diabetes, had no hesitation responding, "yes."

Irish's mother had diabetes, as well as five out of 10 of her siblings, at least one of whom died from the disease. Several others have suffered serious complications, including a stroke and heart attack. "That's why I was so interested in taking part in this program," says 74-year-old Irish, whose lively and engaged personality resonates in her voice.

The year was 1998 and the mailing said the program was being sponsored by the NIDDK and others. It also listed many research centers across the country that were involved, including those in her hometown of Washington, D.C., Howard University Hospital and MedStar Research Institute. Irish was selected to participate because, in addition to her family history, tests showed she had high glucose levels, a risk factor for type 2 diabetes. "I didn't have diabetes at that time and, thanks to the study, I still don't," she says.

In the DPP, participants were randomly assigned to different groups, to test whether different interventions could reduce the risk of type 2 diabetes. Irish was in the lifestyle intervention group. This intervention aimed for relatively modest weight loss through reduced caloric intake, eating less fatty foods and exercising moderately. Irish turned out to be the perfect candidate.

Irish Stovall

"I weighed 229 pounds when I went into the program," she says. "Because of the way I changed my eating habits, I'm down to 178 pounds and feel great," she adds as she proudly rattles off her daily dietary routine. "I no longer eat fried foods. Breakfast usually consists of a bowl of oatmeal and orange juice. Around mid-morning, I eat a piece of fruit. I also drink six to eight glasses of water a day, which helps to hydrate me and curbs my appetite. I try to eat a green vegetable every day and no more than three ounces of meat. For snacks I have a salad, fruit or yogurt, and I try not to eat anything after 7:30 at night." As for exercise, Irish says she walks three to four miles outdoors 5 days a week. During inclement weather when she can't get out, she exercises on the treadmill in her basement. She also has a supportive

spouse. "My husband is 77 years old," says Irish. "His mother and sisters had diabetes, but he doesn't. We encourage each other to eat well and exercise. Like me, he exercises every day."

"I weighed 229 pounds when I went into the program," she says. "Because of the way I changed my eating habits, I'm down to 178 pounds and feel great."

The DPP ended in 2001, but Irish is currently taking part in the ongoing DPP Outcomes Study (DPPOS). She says she would advise anyone with an interest in his or her health to take part in studies like these. As part of the DPPOS study, Irish goes twice a year for a "very thorough" checkup. "They take my blood pressure not only from my arm, but my leg, as well. They weigh me, give me an electrocardiogram, check my skin and ask me about my diet and exercise routine. I also have a coordinator who monitors and advises me."

Her message to others: "Try to eat more healthy types of foods—and exercise."

For more information:

"Am I at Risk for Type 2 Diabetes?" – http://diabetes.niddk.nih.gov/dm/pubs/riskfortype2/index.htm

"Small Steps. Big Rewards. Prevent Type 2 Diabetes" – http://www.ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm

PATIENT PROFILE

Berg Family

What It's Like When Two of Your Children Have Type 1 Diabetes

Aiden Berg was a 14-month-old toddler when he was diagnosed with type 1 diabetes. Two years later his older sister, Heather, was diagnosed with the disease at age 10. If you ask their parents, Toni and Rob Berg, what is the most difficult thing about raising a family when more than one child has diabetes, without hesitation, the answer comes back: scheduling!

"I think of myself as a pretty organized person," says 38-year-old Toni, who works as an airline customer service agent, "but with this disease, we have to stay on top of things all the time." Even then, things can go wrong.

About a month after Heather was diagnosed, the Bergs inadvertently mixed up Heather's and Aiden's doses of insulin, which resulted in a "mini crisis," says Rob. "Heather's dosage was way too much for Aiden, so we were up the entire night monitoring him. Now we always double check everything," adds the 39-year-old accountant. The Bergs have a third child, Dillon, age 8, who so far does not show any signs of the disease. "We check Dillon's blood sugar at least once a month," says Toni, "and keep our fingers crossed."

UNDERSTANDING THE GENETIC LINK

About 1 out of 5 people with type 1 diabetes has a close family member with the disease. To help scientists better understand the genetics of diabetes, the Bergs are currently taking part in a study called the Type 1 Diabetes Genetics Consortium (T1DGC). This consortium is designed to gather valuable information from 2,800 families like the Bergs, with at least two siblings who have type 1 diabetes. The study, sponsored by the NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), involves researchers from around the world—Europe, North America, Asia-Pacific, and the United Kingdom.

The Berg children

The T1DGC is expected to provide a better understanding of the genetics of diabetes, which may suggest valuable new avenues for treating the disease. Furthermore, genetic testing may one day permit very early diagnoses, thereby enabling earlier management of the disease.

The T1DGC is different from many other clinical studies in that it does not test a medical intervention, but rather, is designed to gather valuable information. Ultimately, information about the genetic basis of the disease may not only help identify new therapies but also predict which therapy might be best for a particular person. Finding the genes predisposing

to type 1 diabetes will also enable those at risk to be identified early so they can benefit from future research. The study is closely aligned with the Type 1 Diabetes TrialNet, which is investigating the development, prevention, and early treatment of type 1 diabetes. Both the T1DGC and TrialNet are supported by the *Special Statutory Funding Program for Type 1 Diabetes Research.*

DEALING WITH THE NEWS

Toni and Rob were familiar with diabetes long before Aiden and Heather were diagnosed. Toni's mother died at age 56 from complications of type 2 diabetes, which she developed after having been diagnosed with gestational diabetes during her last pregnancy. Rob's mother also has type 2 diabetes, but has avoided its complications so far.

According to the Bergs, before Aiden's diagnosis, he was manifesting many of the symptoms of diabetes. "At 12 months he had lost weight and was drinking lots of water," says Toni. "I said to our family doctor, 'My God, he has diabetes.'" Toni was told that the weight loss was probably because Aiden had started to walk, and thus, was using more energy. As for drinking lots of liquids, it was summertime and the temperature was very hot. Aiden's symptoms persisted, however, including: lethargy, constant irritability, and extreme thirst. "We were told over and over that children Aiden's age don't get diabetes," say the Bergs. Recent reports from physicians at diabetes centers suggest that type 1 diabetes may be occurring in younger children than was previously recognized. This is a problem because it is much harder to control the disease in infants and young children who cannot recognize or respond to episodes of dangerously low blood glucose (hypoglycemia).

Finally, Aiden was given a blood test and was diagnosed with type 1 diabetes. By that time, he was so sick he had to be taken immediately to the hospital where he spent 2 days in the intensive care unit. "It just sank in that this was going to be life-long," says Toni. She adds that she was overcome by it all, especially knowing the history of what her mother and others in her family had gone through because of the disease. However, things didn't end there.

Two years later, Aiden's sister, Heather, was diagnosed with the disease. According to the Bergs, Heather's blood glucose was always a bit higher than the levels of the rest of the family. One day, while at a diabetes health exposition in Seattle, where the family resides, Heather used a blood glucose tester and her reading came out well above the healthy range. The vendor for the product told the Bergs to make sure to have Heather's blood glucose checked by a doctor.
Toni hesitated. "I was in denial that two of my children could have diabetes," she says. Heather insisted on having the test because she would feel more comfortable knowing one way or the other.
Sure enough, Heather's blood glucose number came out high again. "I still didn't want to believe it—until we got the [hemoglobin] A1c test results—which confirmed for me Heather's diagnosis," says Toni.

"I felt overwhelmed," Toni recalls, "but Heather was brave and never shed a tear." "I can handle it," the precocious Heather told her parents. And handle it, she has.

USING AN INSULIN PUMP

One year after Heather was diagnosed she went on an insulin pump. "She wanted to go on the pump the day she was diagnosed, but we decided we should

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wait a while," says Rob. Heather has taken to the pump well and it has helped a lot in terms of family scheduling. "Heather is an extremely competent child and pretty much takes care of herself," says Rob.

"It's not as bad as I thought it would be," says Heather, who is now 11. "The shots don't hurt much, and because I'm on the pump, I don't have to have so many pokes. Also, Aiden had diabetes before me, so I kind of knew what to expect." Besides, she adds, "the pump is cool because people think it's a cell phone."

NO TYPICAL DAY

The Bergs say that no day is "typical" for their family, but they certainly keep diabetes-related procedures well under control.

Each morning the Bergs check Aiden's and Heather's blood glucose levels and administer insulin according to need. Then, the family goes over what they're going to have for breakfast so they know how many carbohydrates will be taken in; the same for when lunches are made. "There's no such thing as buying lunch at school anymore," says Toni. Most days the Bergs check in with the school or day care center to see how the kids are doing. After school, blood glucose levels are checked again, and Aiden and Heather have a snack—either with or without carbohydrates, depending on what their glucose levels turn out to be.

The Bergs also are big on sports. "There is always one sporting event or another that the kids play in," says Toni. Rob adds that, "We try to keep them active all year round. Whether it's baseball, swimming, soccer, cheerleading, gymnastics, riding their bikes or playing in the backyard pool, it makes a big difference in their (blood glucose) numbers." In the winter months, those numbers are a bit higher because they are not quite as active as in the summer, which, according to Rob, means more of an insulin adjustment.

In the evening, the family has dinner, and blood glucose levels are checked just before bedtime. Depending on how much Aiden's and Heather's blood glucose levels fluctuate on any given day, "Either Rob or I will get up in the middle of the night and check them again," says Toni.

TAKING PART IN RESEARCH STUDIES

Like many families with a high incidence of diabetes, the Bergs are seeking as much information as possible about the disease. They became involved with the T1DGC study when they stopped by the Benaroya Research Institute's booth at the Diabetes Expo in Seattle and were asked if they would like to participate in diabetes research. They jumped at the opportunity.

Such studies give hope to families like the Bergs. The T1DGC is expected to provide a better understanding of the genetics of diabetes, which may suggest valuable new avenues for treating the disease. Furthermore, genetic testing may one day permit very early diagnoses, thereby enabling earlier management of the disease. Early intervention could reduce or delay onset of diabetes complications, and

prevent some emergency hospital admissions, such as was necessary for Aiden when he was first diagnosed. Indeed, ongoing research studies are using genetic tests to identify some newborns at high risk for developing diabetes. The studies are indicating that, with careful monitoring of such children, it may be possible to dramatically reduce the likelihood of such hospitalizations.

The hope extends beyond early diagnosis. "Knowing the amount of research going on, we're hopeful that a cure for diabetes will be found by the time our children reach adulthood," says Toni. "We hope and pray other families will participate in this research. The larger the pool of people they have to study, the more they can learn about combating this disease," she adds.

More information on participating in the T1DGC and TrialNet can be found at:

www.t1dgc.org and *www.diabetestrialnet.org*