

# GOAL IV

**PREVENT OR REDUCE  
HYPOGLYCEMIA**



**H**ypoglycemia is the major obstacle to achieving the tight glucose control that has been proven to reduce the deadly complications of type 1 diabetes. To overcome this obstacle, the *Special Statutory Funding Program for Type 1 Diabetes Research* has supported multifaceted efforts ranging from fundamental research to understand how the body recognizes and defends against hypoglycemia and how diabetes impairs this defense, to applied research in partnership with industry to develop technology for continuous glucose monitoring and automated insulin delivery; and has established a clinical network to test the latest technology that can stabilize glucose levels and prevent or reduce hypoglycemia in children with diabetes. In addition to the significant research progress described in this chapter, information on the program evaluation related to Goal IV can be found in Appendix A (Allocation of Funds), Appendix B (Assessment), and Appendix C (Evaluation of Major Research Consortia, Networks, and Resources).

While the results of NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow-up effort, the Epidemiology of Diabetes Interventions and Complications (EDIC) demonstrated that intensive control of blood glucose (sugar) levels can have long-lasting effects toward reducing the onset and progression of diabetes complications involving the kidneys, eyes, nerves, and heart, obstacles remain for many people with type 1 diabetes to achieving tight blood glucose control. Although finger pricks provide "snap shots" of a person's blood glucose levels, they are painful and do not provide data about "trends" that indicate whether blood glucose levels are increasing or decreasing. Even if patients test as much as a dozen times a day to help adjust insulin, they will spend prolonged periods each day outside the target glucose levels. Moreover, excessive treatment with insulin relative to food intake and physical activity can cause blood glucose levels to fall dangerously below a minimal threshold required to fuel the body's activities, particularly brain function. The immediate effects of abnormally low blood glucose (hypoglycemia) can be severe, including changes in cardiovascular and central

nervous system function, cognitive impairment, increased risk for unintentional injury, coma, and death. Thus, in addition to the need for better tools to help people with type 1 diabetes achieve and sustain tight blood glucose control, the potential for hypoglycemic episodes has limited the use of intensive insulin therapy protocols. Research to develop and test new disease management technologies and to understand how to predict and prevent episodes of hypoglycemia is critical to helping people with type 1 diabetes prevent the deadly complications that can accompany the disease.

The *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program or Program)* has played an important role in the generation of new tools to improve patients' ability to control their blood glucose levels. As described in greater detail in this chapter, the *Program* supported the development of recently approved continuous glucose monitors (CGMs), which reveal the dynamic changes in blood glucose levels by assessing glucose levels hundreds of times per day and displaying trends. The *Program* filled an industry

*Graphic: Blood glucose test results from a glucose meter recorded in a chart format. Image credit: Steve Horrell/Photo Researchers, Inc.*

gap by first testing CGMs in children, a population that could benefit greatly from this technology, and supports research to “close the loop” by linking glucose monitoring to insulin delivery—what is often referred to as an “artificial pancreas.” Additionally, the *Program* has supported research initiatives to better understand the

causes of hypoglycemia and how to prevent this serious, life-threatening condition. Due to support from the *Program*, new technologies and research results have revolutionized the way that patients manage their disease, improved the outlook for people with type 1 diabetes, and accelerated the pace of research to close the loop.

#### HIGHLIGHTS OF RECENT RESEARCH ADVANCES RELATED TO GOAL IV

**Approval of New Glucose Monitoring Technologies:** In 2006, the U.S. Food and Drug Administration (FDA) approved a continuous glucose monitoring device displaying results on an insulin pump for use in people over age 18. Additional CGMs developed by other manufacturers with NIH support have recently been approved for use in both adults and children. This major technological advance represents the culmination of years of effort by the U.S. Department of Health and Human Services (HHS) and the *Program* in bringing together and funding collaborations of clinicians, engineers, and basic biologists from industry and academia. The new CGMs have been shown to improve control of glucose levels and reduce hypoglycemia and are a major milestone in the future development of an artificial pancreas.

**Tested CGMs in Children:** The Diabetes Research in Children Network (DirecNet) filled an industry gap by first testing the safety and efficacy of continuous glucose monitoring technology in children. DirecNet has carried out independent and scientifically rigorous studies to determine the true benefit of new monitoring technologies. Without the initial information from DirecNet, it could have been many years before the manufacturers of these devices conducted studies in the pediatric population. The DirecNet group is well positioned to assess new devices for their accuracy, as well as their clinical usefulness in the home environment.

**Practical Steps To Avoid Nocturnal Hypoglycemia:** DirecNet has examined factors that contribute to nocturnal hypoglycemia in children. Using the new CGMs, investigators found that exercising in the late afternoon caused a delayed nighttime drop in glucose levels and nearly doubled the risk for nocturnal hypoglycemia relative to exercise-free days. Additional DirecNet studies have shown that the risk of hypoglycemia can be markedly reduced in insulin pump-treated patients by suspending the basal insulin infusion during exercise. Exercise is important for these children, particularly in keeping blood glucose from rising too high, and these findings point to the importance of adjusting patients’ diabetes regimen on active days.

**Recurrent Episodes of Low Blood Glucose Do Not Impact Long-term Cognitive Function:** The landmark DCCT found that tight blood glucose control—while reducing complications—increased the risk of severe hypoglycemia three-fold. There was fear that in addition to its dangerous short-term effects, hypoglycemia might also lead to a long-term loss of cognitive ability. Twelve years after the conclusion of the DCCT, researchers in its follow-up study, EDIC, reported the absence of a link between multiple severe hypoglycemia reactions and impaired cognitive function in people with type 1 diabetes in the study.

## CONTINUOUS GLUCOSE MONITORS CHANGE MANAGEMENT OF TYPE 1 DIABETES

The results of DCCT/EDIC showed that good blood glucose control is a key factor in lowering the risk of many of the devastating long-term complications of diabetes, including blindness, kidney failure, and cardiovascular disease. For children and adults with type 1 diabetes, this has led to the use of intensified insulin therapy. However, the wide-spread application of this approach has been limited by a lack of technologies that would enable people with diabetes to easily and appropriately adjust delivery of insulin in response to minute-to-minute changes in circulating glucose. By the late 1990s, several daily measurements of glucose in the blood had proven useful, but did not provide patients with information about what happened in between readings and it was difficult to ascertain the highs, lows, and trends throughout the day and night. Scientists were actively pursuing new approaches to assess glucose continuously that were both safe and accurate (for more information about the development of CGMs, please see the accompanying Story of Discovery in this chapter). Research supported by NIH and industry led to FDA approval of the first CGM in 1999. While this device was a large step forward, measurements obtained from this CGM were not as accurate and could only be assessed retrospectively, not in real time.

**Improving CGMs:** Support from NIH and the *Program* accelerated the pace of research on glucose sensing technologies through research solicitations and investigator-initiated projects. This research culminated in FDA approval in 2006 of a continuous glucose monitoring device displaying results on an insulin pump for use in people over age 18. Additional CGMs developed by other manufacturers with NIH support

have recently been approved for use in both adults and children. Currently, CGMs used in combination with finger sticks are FDA-approved. This major technological advance represents the culmination of years of effort by HHS and the *Program* in bringing together and funding collaborations of clinicians, engineers, and basic biologists from industry and academia to develop both the technology underlying the glucose sensors and the algorithms used to assist insulin delivery decisions. The new continuous glucose monitoring devices are a major milestone in the future development of an artificial pancreas. These CGMs combine a continuous glucose sensor with a unit displaying glucose levels. The sensors are inserted under the skin for up to 3 to 7 days and transmit readings of glucose levels in tissue fluid—an approximation of blood glucose levels—every 1 to 5 minutes to a receiver carried by the individual, whether the patient is awake or asleep, and trigger an alarm if levels become too high or too low. CGMs have the potential to dramatically improve patients' ability to control glucose levels, which is key for minimizing or preventing complications. They can also improve quality of life by reducing the need for frequent monitoring and alleviating the fears that children and their parents have of nocturnal hypoglycemia.

**Testing CGMs in a Target Population:** A critical component to any new technology is evaluating how well it will work in the people who use it. Therefore, the NICHD-led and *Program*-supported Diabetes Research in Children Network (DirecNet) took on the task of filling an industry gap by testing new continuous glucose monitoring technology in children. Because no regimen of insulin replacement in type 1 diabetes will be able to completely eliminate the risk of severe hypoglycemia in the absence of feedback control of insulin delivery

based on real-time changes in blood glucose levels, DirecNet critically evaluated whether the recent advances in glucose sensor technology could be utilized to improve metabolic control and reduce the frequency of hypoglycemia without having adverse effects on health and psychosocial well-being in children and adolescents with type 1 diabetes. DirecNet developed a template inpatient protocol to test the accuracy of CGM devices and newer home glucose monitors in comparison with reference glucose determinations made at a central laboratory. Initial studies illustrated the limitations in accuracy of the first-generation CGM devices, especially for blood glucose values in the hypoglycemic range. In contrast, certain glucose meters were very accurate over the full range of glucose values. The results of these DirecNet studies have had a major impact on the analysis of CGM performance and indicated that reliability and ease of patient use are critically important factors in the clinical efficacy of CGM devices. DirecNet is continuing to study the efficacy, tolerability, safety, and effect on quality of life of CGMs in children 4 to less than 10 years of age with type 1 diabetes and has launched a pilot study to test this technology in children less than 4 years of age.

DirecNet accomplishments also include the development, modification, testing, and validation of several psychosocial and other outcome measures for use in future clinical trials. Subsequent JDRF- and industry-supported studies demonstrating improved glucose control with CGMs built upon the initial DirecNet studies. Scientists have begun to answer important clinical questions about the added value of CGM in people newly diagnosed with type 1 diabetes. Studies are also beginning in select people who have type 2 diabetes, such as those particularly prone to glucose fluctuations

due to the disabling diabetes complication gastroparesis. Not only are such trials key to identifying the population with the potential for maximum benefit from this technology, but these studies will lay the groundwork for trials to accelerate the development and evaluation of artificial pancreas technologies. DirecNet and TrialNet investigators (see Goal II) are currently collaborating on a clinical trial evaluating whether early and intensive blood glucose control can protect patients' remaining insulin-producing beta cells from the toxic effects of high blood glucose. The trial participants are placed on a closed-loop system, linking blood glucose monitoring via CGMs and insulin delivery via an insulin pump, to intensively manage their blood glucose levels shortly after disease onset. This trial will determine if near normalization of glucose levels at onset can protect beta cells from injury caused by high glucose levels and slow disease progression. For more information on the trial, see the Investigator Profile of Dr. Bruce Buckingham later in this chapter.

#### **Research To Help Patients Use New Technologies:**

To optimize the potential impact of new technologies such as CGMs, research is needed that considers clinical and behavioral factors that may enhance or constrain their sustained use. There is an implicit assumption that more information will lead to better patient managed glucose control. But for patients and providers to make optimal use of the vast amounts of information these tools provide, additional knowledge, skill, and motivation is required. Individuals need to be able and willing to make the appropriate regimen course corrections on an ongoing basis and be savvy enough about their glucose trends to avoid over-correction with insulin. The user interface requirements will also be different across the lifespan. For example, the way a technology

is used may require different behavioral approaches when it is employed in different age groups, such as young children, adolescents, and adults. Research is key to support the broad adoption of CGMs as a daily self-management tool and to identify the most effective ways to incorporate these technologies into clinical care. Behavioral research funded by the *Program* is seeking to improve outcomes of people with type 1 diabetes. Although this research is still in progress, it is expected that results will be used to enhance the usability of new technology and help patients in their decision-making regarding diabetes management. This research will identify ways to assist patients to effectively use new technologies to benefit their health and quality of life.

## **NEW KNOWLEDGE TOWARD PREVENTION OF HYPOGLYCEMIA**

Although CGMs enable people with type 1 diabetes to adjust their insulin doses to avoid extreme high and low glucose levels, this approach cannot replicate the exquisitely precise and dynamic regulation of insulin levels achieved by insulin-producing beta cells. Thus, despite a person's best efforts, glucose levels can rise excessively (hyperglycemia)—particularly after meals—and at other times can fall dangerously low (hypoglycemia), causing unconsciousness, seizures, and even death. Normally, a drop in blood glucose triggers the body's warning system to release stress hormones, including adrenaline, and to stimulate a part of the nervous system that raises glucose and results in symptoms such as shaking and sweating. However, in individuals who experience repeated episodes of hypoglycemia, these counterregulatory mechanisms are impaired so the typical signs and symptoms disappear. These affected individuals do not recognize, and therefore, cannot correct for, the low blood glucose—a

syndrome known as hypoglycemia unawareness. A vicious cycle is initiated as each hypoglycemic event makes it more likely that these compensatory signals will fail in the future, leading to another unrecognized hypoglycemic event. People with type 1 diabetes, especially children, are particularly vulnerable to hypoglycemia unawareness while they are asleep. Therefore "nocturnal hypoglycemia" is a primary concern and the source of many anxious nights for parents of children with type 1 diabetes who stay awake to check on the well-being of their children throughout each night.

Understandably, the fear of severe hypoglycemia represents the single greatest barrier to full implementation of the recommendations of the DCCT/EDIC. Therefore, in parallel to the development of better technologies to assist people with type 1 diabetes in managing the disease, it is critical to conduct research to understand the molecular mechanisms of hypoglycemia towards improvement of prevention strategies. Through DirecNet and other research, the *Special Diabetes Program* has supported a variety of efforts to improve understanding of hypoglycemia. While much still remains to be learned about this condition, studies supported by the *Program* have advanced progress in this field.

### **Practical Suggestions To Prevent Hypoglycemia:**

Data using continuous glucose monitoring have shown that low glucose levels are even more common than previously thought, but are often undetected; low levels sometimes go back up before the morning blood glucose check. DirecNet has examined factors that contribute to nocturnal hypoglycemia in children. Using the new continuous glucose sensors, investigators found that exercise in the late afternoon caused a delayed nighttime drop in glucose levels and increased the risk for nocturnal hypoglycemia relative to exercise-free days. Exercise is

important for these children, particularly in keeping blood glucose from rising too high, and these findings point to the importance of adjusting patients' diabetes regimen on active days. A DirecNet follow-up study showed that the risk of hypoglycemia can be markedly reduced in patients treated with insulin pumps by suspending the basal insulin infusion during exercise. In addition, this work generated the practical suggestion of increased bedtime snacks on days when children with diabetes are particularly physically active even if the bedtime glucose measurement is not low. DirecNet further showed that both low-fat and high-fat bedtime snacks provide similar protection against nocturnal hypoglycemia. *Program*-supported efforts by DirecNet are yielding practical suggestions for children with diabetes and their caregivers to maintain healthy blood glucose levels more safely and effectively by managing diet and exercise.

**Brain Function Not Permanently Damaged by Hypoglycemia:** The landmark DCCT found that intensive glucose control—while reducing complications—increased the risk of severe hypoglycemia three-fold. There was fear that in addition to its dangerous short-term effects—confusion, irrational behavior, convulsions, and unconsciousness—hypoglycemia might also lead to a long-term loss of cognitive ability. Twelve years after the conclusion of the DCCT, researchers reported results of a study in which DCCT participants were evaluated using the same neuropsychological tests administered during the DCCT trial. The tests analyzed problem solving, learning, immediate memory, delayed recall, spatial information, attention, psychomotor efficiency, and motor speed. The tests revealed no link between multiple severe hypoglycemic reactions and impaired cognitive function in people with type 1 diabetes in the study. The results demonstrate that while acute episodes

of hypoglycemia can impair thinking and can even be life-threatening, people with type 1 diabetes do not have to worry that such episodes will damage their mental abilities and impair their long-term abilities to perceive, reason, and remember. However, investigation regarding this issue is ongoing to assess more subtle effects, and NIH is supporting imaging studies to elucidate whether brain structure is affected by recurrent hypoglycemia and to determine any possible correlation between recurrent hypoglycemia and cognitive capability.

**Understanding Why Hypoglycemia Is Not Prevented in People with Type 1 Diabetes:** Counterregulatory hormones, like glucagon, adrenaline, norepinephrine, cortisol, and growth hormone, oppose the action of insulin by raising the level of glucose in blood in multiple ways. In healthy individuals, counterregulatory hormones act as a principal defense against hypoglycemia; levels of these hormones rise as glucose levels fall, thus promoting processes to raise the levels of glucose in the blood. It is not understood why this mechanism appears to fail in people with type 1 diabetes. In people with the disease, dangerous episodes of hypoglycemia reflect the failure of the body to trigger normal warning systems (like adrenaline and glucagon) that wake the patient and increase blood glucose in response to hypoglycemia. Progress in understanding these systems in people with type 1 diabetes has been made both by DirecNet and other research efforts through the support of the *Program*. For example, a DirecNet study demonstrated that young children (3-8 years of age) and adolescents (12-18 years of age) with well-controlled type 1 diabetes have impaired counterregulatory hormone responses to hypoglycemia. The results of this study showed that, regardless of age, these well-controlled pediatric patients failed to release the counterregulatory hormone

epinephrine until blood glucose concentrations approach values that indicate a shortage of glucose in the brain.

To further understand why exercise increased the risk for nocturnal hypoglycemia, DirecNet investigators examined the levels of counterregulatory hormones on inactive and active (exercise) days. Through hourly measurement of hormone levels on nights following days of exercise or inactivity, this study demonstrated that counterregulatory hormone responses to spontaneous nocturnal hypoglycemia are blunted throughout the nighttime period with or without antecedent exercise. Similar DirecNet studies indicated that levels of adiponectin (a protein that is directly related to insulin sensitivity and is released from fat) are stable from day-to-day and are not affected by exercise or metabolic control. Moreover, higher levels of adiponectin appear to be associated with a decrease in hypoglycemia risk. Additional efforts will be necessary to understand this relationship and whether it can be utilized to prevent hypoglycemia.

Studies of the pancreatic alpha cell are also providing insights into why protective counterregulatory hormones fail to work in people with type 1 diabetes. The pancreatic islets are composed of several cell types. The counterpart to the insulin-producing beta cell is the glucagon-producing alpha cell. Just as insulin injections control high blood glucose, glucagon injections can be used in an emergency to raise glucose levels that may fall dangerously low after insulin therapy. Glucagon is the major counterregulatory hormone that causes glucose to be released by the liver into the blood stream. Researchers have long recognized that people with type 1 diabetes do not secrete glucagon in response to hypoglycemia, despite their ability to secrete glucagon under other circumstances. Findings from research supported by the *Program* suggest

that a decrease in intra-islet insulin is necessary for glucagon secretion, explaining why the protective glucagon response is impaired in type 1 diabetes. The inflammatory process seen in type 1 diabetes may affect nervous system regulation of the islets contributing to the deficient glucagon response, as reported recently in animal models by investigators supported by the *Program*. By discovering the mechanisms involved in the body's reaction to hypoglycemia, scientists may be able to develop therapies that break the vicious cycle of recurrent hypoglycemia.

### **CLOSING THE LOOP: DEVELOPMENT OF AN ARTIFICIAL PANCREAS**

An artificial pancreas based on mechanical devices requires, at a minimum, three basic components: a continuous blood glucose sensor, an insulin delivery system, and a way to link the two in a loop. Such a system would automatically turn the measurement of blood glucose levels into a practical, precise, and “real-time” insulin-dosing system. Importantly, artificial pancreas technology could help people safely achieve the tight blood glucose control associated with preventing or delaying life-threatening disease complications. Thus, this technology has high potential to have a positive impact on patients’ health and quality of life, alleviate an enormous amount of patient burden, and improve long-term health outcomes. There are numerous research opportunities to promote the development of the artificial pancreas. These include the development of more accurate and robust glucose sensing devices; improved methods of insulin delivery and faster acting insulin; and the development of improved computer algorithms that appropriately translate glucose measurements into changes in the delivery of insulin, including its interruption—*i.e.*,

methods that can “close the loop” between glucose measurements and insulin delivery.

A key aspect of closing the loop between glucose sensing and insulin delivery in a mechanical artificial pancreas is the development of “instruction sets” for computers, called algorithms. In the case of the artificial pancreas, these computer programs are needed to interpret continuous glucose sensor data and instruct the insulin pump to dose the proper amount of insulin. Two primary algorithm approaches have been generated and are under investigation. The further development of these algorithms is essential for the rapid implementation of closed-loop glucose control. Another advance propelling progress toward an artificial pancreas is the development of *in silico* (computer-based) models as a resource for pre-clinical testing. In 2008, FDA accepted the use of an *in silico* model of diabetes as a pre-clinical testing tool for closed-loop research. This and other optimized simulators will facilitate the development of new control algorithms by enabling researchers to test and refine artificial pancreas algorithms quickly; it will allow for computer-based algorithm comparisons; and it may eliminate or minimize the need for animal testing, allowing investigators to focus instead on in-hospital human clinical trials, which may save time and money. This may also lead to a more expedited and better defined process of receiving regulatory approval for human trials of closed-loop systems. As the simulator is equipped with a wide array of tools for precise fine-tuning, it should help bring promising algorithms closer to perfection in a shorter time frame. Other studies are also pushing this field forward. Recently a study of 19 youth with type 1 diabetes suggested that closed-loop

systems could reduce the risk of nocturnal hypoglycemia. Tests of a bi-hormonal closed-loop artificial pancreas, one that delivers both insulin and glucagon, are also reporting promising results. Together these important advances are bringing the field closer to the development of an artificial pancreas.

To further accelerate the development of an artificial pancreas, there is close coordination among NIH, JDRF, and FDA. The NIH and JDRF fund research in this area, and FDA advises researchers as they develop new technologies needed to make the artificial pancreas a reality and assists them as they design studies to evaluate safety and effectiveness. In July 2008, NIH, in collaboration with FDA and JDRF, organized a workshop to discuss current advances and remaining challenges toward the development of an artificial pancreas. This workshop concluded that a mechanical artificial pancreas system has enormous potential benefit for a substantial proportion of people with diabetes. However, important technological obstacles impede long-term use of these devices and new and promising technologies are needed toward the development of an artificial pancreas. Therefore, NIH re-solicited cutting edge research conducted by small businesses leading to the development of innovative technologies toward an artificial pancreas and several *Program*-supported grants were awarded. The clinical testing of currently available closed-loop platforms and the development of innovative algorithms by academic investigators are also supported by the *Program*. While the results of this research remain to be determined, it is anticipated that this research will significantly contribute to making the artificial pancreas a reality for people with type 1 diabetes.

## SUMMARY

During the past 3 decades, in part due to support from the *Program*, a variety of technological advances have been introduced that have significantly improved the ability of people with diabetes and their physicians to treat diabetes with insulin, including home glucose monitoring devices that allow periodic measurements of blood glucose levels; improved insulin formulations; portable insulin pumps that provide continuous insulin delivery in a more controlled manner; and, most recently, early-phase CGMs that rely on inserting glucose sensors under the skin. The *Program*-supported DirecNet has filled an industry gap by testing these CGMs in children

and has used these devices in studies that have produced practical suggestions to reduce the risk of nocturnal hypoglycemia. Research on counterregulatory hormones has provided new information about how hypoglycemia is normally prevented and what goes awry in people with type 1 diabetes. This knowledge could lead to the development of new strategies to prevent hypoglycemia. Finally, the pace of research to close the loop is more rapid due to support from the *Program*. Research efforts and advances in this Goal have improved diabetes care today and offer considerable potential for the creation of an artificial mechanical pancreas for the treatment of diabetes in the future.

### RESEARCH CONSORTIUM RELATED TO THE PREVENTION OR REDUCTION OF HYPOGLYCEMIA

Details of the DirecNet evaluation are found in Appendix C. Highlights are summarized below.

**Diabetes Research in Children Network (DirecNet):** DirecNet is a multicenter clinical research network investigating the use of technology advances in the management of type 1 diabetes in children and adolescents. DirecNet filled an industry gap by testing new continuous glucose monitoring technology in children and has utilized six different brands of CGMs in its completion of nine different protocols. DirecNet has also yielded practical suggestions for people with diabetes and their caregivers to maintain healthy blood glucose levels more safely and effectively by managing diet and exercise.

## Story of Discovery: New Technology for Managing Type 1 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 support from the *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program or Program)*, NIH, industry, and others, these new, wearable continuous glucose monitors (CGMs) 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 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, and by eating or taking other action to raise low blood glucose. The monitors also have potential to help some other populations—such as people with type 2 diabetes—control their blood glucose levels. Finally, the realization of continuous glucose monitoring technology is a key step toward developing a mechanical replacement for insulin-producing pancreatic beta cells.

Decades ago, reliable and practical methods for glucose monitoring were not available, yet control of glucose levels in the body is crucial. 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, people with type 1 diabetes 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. However, the need for tools for more frequent monitoring of blood glucose continued to drive research toward developing this technology. The availability of improved glucose-monitoring devices in the early 1980s was critical to enabling scientists to test the importance of blood glucose control to the prevention of the devastating complications of diabetes.

### **The Importance of Intensive Blood Glucose Control**

The tremendous health benefits of intensive blood glucose control were demonstrated in the early 1990s by a landmark, NIH-supported clinical trial, the Diabetes Control and Complications Trial (DCCT). This trial showed that intensive control greatly reduced development of diabetic eye disease, kidney disease,

and nerve damage in people with type 1 diabetes, and an ongoing follow-up study 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 and frequent insulin administration. 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, people with type 1 diabetes still rarely achieve recommended glucose levels. The DCCT thus also underscored the critical importance of research to improve methods for blood glucose control.

Despite the impressive results obtained using glucose meters, these devices are far from optimal. By way of analogy, patients can see a few “snapshots” of their glucose levels per day with glucose meters, but miss what happens in between; with CGMs, 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 key 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 NIH and industry. A continuous monitor was first approved by the U.S. Food and Drug Administration (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.

### Producing a “Real-time” Continuous Glucose Monitor

The NIH and the *Special Diabetes Program* have accelerated the pace of research on glucose sensing technologies through research solicitations and investigator-initiated projects. Over the last decade, these efforts have led investigators in academia and industry to explore a variety of approaches to continuous glucose monitoring, including devices to measure glucose in body fluid extracted from skin, in eye fluid using a contact lens as a sensor, noninvasively with optical sensing of glucose in the blood, and with minimally invasive sensors inserted into the skin. Researchers have also been exploring the benefits and drawbacks of sensors designed for external use versus more permanent, fully implantable devices. Studies have also focused on validating and optimizing the different technologies.

This research culminated in FDA approval in 2006 of new CGMs for people with diabetes. These devices represented a significant improvement over the first devices approved by FDA. NIH support was instrumental in technology development for the new devices. The new monitors employ a slender sensor that can detect the biochemical reaction of glucose with an enzyme (glucose oxidase) present on the sensor tip. Inserted under the skin, these minimally-invasive sensors provide glucose readings in “real time,” every few minutes; display trend data so patients know whether their glucose levels are rising or falling—and how quickly; 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 still need to confirm readings

from these new monitors with a traditional finger stick and blood glucose meter. However, the burden of care can be significantly reduced and further improvements in these devices can be expected with additional research and development.

### **The Potential of Continuous Glucose Monitors To Improve Outcomes**

An ongoing and critical area of NIH-funded research is the evaluation of these monitors for use in children. New insights about the use of continuous glucose monitoring technologies have been gained from the Diabetes Research in Children Network (DirecNet) which is led by NICHD and supported by the *Program*. DirecNet is investigating the use of technological advances in the management of type 1 diabetes in children and adolescents and has carried out several independent and scientifically rigorous studies to determine the true benefit of continuous glucose monitoring technologies, including their accuracy and efficacy.

Clinical studies supported by the Juvenile Diabetes Research Foundation International have now shown significant benefits of CGM use by people with diabetes. To determine whether CGM can aid people who are already receiving intensive insulin therapy, researchers conducted a 26-week, randomized multi-center clinical trial in which one group of volunteers used CGMs, while a control group performed home monitoring with a blood glucose meter. The primary outcome, improved glucose control, as measured by hemoglobin A1c (HbA1c), was mainly achieved in people who were older than 25 years. HbA1c is a component of blood that is a good surrogate measure of long-term blood glucose control and, as such, reflects risk of diabetic complications. In children, benefit was seen specifically in those who used CGMs near-daily, underscoring the need to identify barriers to

CGM use in children and adolescents. Hypoglycemia did not increase, even in participants who improved blood glucose control. These encouraging results were reinforced by a second randomized, multi-center clinical trial. This study found that using CGM devices enables people who are already achieving excellent glucose control to spend more time per day in the target blood glucose range, while spending less time per day with glucose values in the potentially dangerous hypoglycemic range. A recent industry-supported study found that use of an insulin pump paired with a CGM, enabling users to adjust insulin doses based on glucose sensor values, resulted in much greater improvement in blood glucose control than the standard injection regimen. Most significantly, more people achieved recommended HbA1c targets with sensor/pump technology than with injection therapy, with no increase in hypoglycemia. It was especially encouraging that children had many fewer hypoglycemia episodes with the sensor/pump strategy than were seen, for example, in the DCCT. These trials have shown that CGMs, when used near-daily, not only help people with type 1 diabetes get into control—which can have a significant positive impact on lowering the risk of complications—but also enables them to stay in control without increasing the near-term risk of hypoglycemia.

In addition to facilitating self-monitoring of glucose levels by individuals, scientists are using CGMs to answer important research questions. Already an important lesson learned from the use of glucose sensor technology is the realization that blood glucose actually varies to a much greater extent during the course of the day than was previously thought, even in presumed “well-controlled” individuals. Further studies about the impact of this “glycemic variability”—both low- and

high glucose—and not simply average glucose levels will provide important information on the development or progression of diabetes complications. CGMs also provide, for the first time, the opportunity to measure glycemic variability and undetected hypoglycemic events during insulin treatment in people with type 2 diabetes. Additionally, CGMs could be extremely beneficial in the management of individuals with gastroparesis, a slow emptying of food from the stomach caused by nerve damage from diabetic hyperglycemia. People with gastroparesis have great difficulty controlling glucose levels because meal absorption is variable. CGMs could be used to modify insulin delivery to prevent early hypoglycemia following a meal and delayed hyperglycemia. This technology has enormous potential to aid many different patient populations and extend its benefit beyond people with type 1 diabetes.

Today, the combined number of people who use CGMs is estimated to have reached several thousand and is still growing. There are still a number of caveats and limitations to current devices, however. For example, the sensor signals are not entirely specific for glucose and are adversely affected by a combination of factors, such as the body's wound healing and foreign body response, inactivation of the enzyme, and biochemical interference. As a result of these limitations, the sensors must be frequently recalibrated by the user based on finger stick glucose assays, and have not been approved by FDA as the primary standard for glucose measurement. Also, current glucose sensors cannot be fully relied upon for early hypoglycemia detection or warning. While CGMs have significantly benefitted many people with type 1 diabetes, research opportunities remain to improve these devices. Many of these emerging opportunities are

described in Appendix F. Further research to overcome limitations to current devices, improve their usability, and expand their utility will be essential to capitalize on the progress to date and lead to the development of an artificial pancreas.

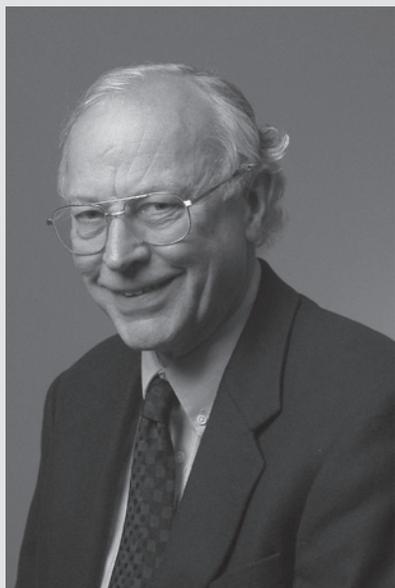
### **Pushing Continuous Glucose Monitoring Toward the Development of an Artificial Pancreas**

An artificial pancreas—which would automate insulin delivery in response to the body's needs—requires, at a minimum, three basic components: a continuous blood glucose sensor, an insulin delivery system, and a way to link the two in a loop. Such a system would automatically turn the measurement of blood glucose levels into a practical, precise, and “real-time” insulin-dosing system for patients. Importantly, a key feature of one of the approved continuous glucose monitors is that it has been “paired” with an insulin pump through a wireless transmitter and transmits its data to the pump, making it easier for the patient to adjust the insulin dose. Although not an artificial pancreas since patients still must be actively involved in determining their insulin doses, this first pairing of a continuous monitor and pump has major implications. It represents the first step in joining glucose monitoring and insulin delivery systems using the most advanced current technology. To help “close the loop,” the *Program* has awarded grants to small business and academic investigators to develop and test innovative technologies—like improved glucose sensors and more physiological algorithms—that may advance progress toward an artificial pancreas. Even before an artificial pancreas is developed, patients can improve their health now, with the unprecedented knowledge gained from continuous glucose monitors.

## Investigator Profile

### **Bruce Buckingham, M.D.**

*Testing Closed-Loop Technology To Preserve Insulin Production in Children Newly Diagnosed with Type 1 Diabetes*



### **Bruce Buckingham, M.D.**

*Bruce Buckingham, M.D., is a Professor in the Department of Pediatrics at Stanford University and a renowned diabetes researcher. He participates in the Diabetes Research in Children Network (DirecNet) and Type 1 Diabetes TrialNet, which are led by NICHD and NIDDK, respectively, and are supported by the Special Statutory Funding Program for Type 1 Diabetes Research. Dr. Buckingham is the Principal Investigator of a clinical trial jointly conducted by DirecNet and TrialNet that is testing intensive glucose control at type 1 diabetes onset using a closed-loop system. This profile describes his experiences in the trial and his research testing new glucose monitoring technologies on a wide-range of patients.*

### **A Clinical Trial in Newly Diagnosed Type 1 Diabetes Patients**

Dr. Buckingham is leading a new clinical trial that, he says, “Is moving several fields forward.”

He is testing whether early and intensive blood glucose control using a closed-loop artificial pancreas system can protect patients’ remaining insulin-producing beta cells from the toxic effects of high blood glucose. “There are some earlier studies showing that, if the blood glucose is maintained fairly close to normal from disease onset, you have better and more prolonged insulin secretion, a prolonged ‘honeymoon’ phase,” explains Dr. Buckingham. The “honeymoon” is the period of time shortly after diagnosis when patients still make significant amounts of their own insulin. Previous research has shown that preserving insulin production can have dramatic, long-term health benefits, which is why researchers are trying to intervene early in the disease.

“We enroll children within the first week of diabetes onset and put them on a closed-loop artificial pancreas. In this system, there is a subcutaneous sensor measuring glucose levels every minute and this information is sent to an algorithm which determines how much insulin they need,” says Dr. Buckingham. The system then automatically delivers insulin to the patient. “When the blood glucose is going up, it delivers more insulin, when the blood glucose is going down, it decreases insulin delivery. By doing this over several days we can bring their blood glucose levels very close to the normal range,” explains Dr. Buckingham.

After the children are treated for 3-4 days on the closed-loop system in the hospital, the intensive treatment continues at home for the next 2 years. “We send them home on a sensor-augmented pump, which is an insulin

pump paired with a continuous glucose sensor,” says Dr. Buckingham. This technology does not automatically deliver insulin based on glucose levels, but “It allows patients to see the fluctuations in their glucose, which are often not seen with routine blood glucose monitoring,” explains Dr. Buckingham. Routine blood glucose monitoring involves a finger stick that measures blood glucose at a single point in time, but the continuous glucose sensor measures glucose levels every few minutes, giving the patients a more complete picture of how their levels are changing throughout the day and night. It also sounds an alarm if glucose levels are above or below glucose targets. “We thought that if they could see all their glucose levels, they could correct any elevations and continue to maintain their glucose values close to normal,” notes Dr. Buckingham.

The trial is comparing outcomes (e.g., insulin production) in these “intensively treated” children to outcomes in children who, from disease onset, use routine blood glucose monitoring to manage their diabetes. Both groups will be followed for 2 years to determine if early, intensive treatment promotes and prolongs the “honeymoon” phase. “The concept is that if someone is exposed to high glucose, those sugars may be toxic to the remaining islet cells,” explains Dr. Buckingham. In addition, “The immune attack [underlying type 1 diabetes] may be more aggressive/effective when the islets are in a high glucose environment,” he says. Therefore, the hope is that keeping blood glucose levels close to normal for the duration of the 2 year trial will protect the islet cells from the toxic effects of high glucose, allowing them to continue to make insulin and this, in turn, makes it easier for them to maintain better glucose levels (a virtual circle).

### **The Benefits to Participants**

The children in this clinical trial are doing very well, says Dr. Buckingham. “It’s been very exciting, and for the kids who have entered a honeymoon, their blood glucose levels are almost a flat line throughout the day,” which refers to the fact that the patients are not experiencing the high and low blood glucose excursions typical of type 1 diabetes.

It also turns out that the intensive treatment that these children receive doesn’t just refer to their blood glucose levels, but also refers to the personal treatment they receive from the dedicated clinical research team. Because the closed-loop system is an experimental therapy, the U.S. Food and Drug Administration requires that, “A pediatric endocrinologist or someone trained in diabetes is at the patient’s bedside 24 hours a day during their inpatient stay,” explains Dr. Buckingham.

This dedication has not been overlooked by the children and their families—Dr. Buckingham has received a lot of positive feedback from them. He says that, because the children have just been diagnosed with diabetes, they and their parents are understandably a little overwhelmed. “We then provide them intensive education about how to use an insulin pump and how to use continuous glucose monitoring. They get a lot of one-on-one teaching. When they leave, I think they feel much more comfortable and in charge of their diabetes.”

He also says that the patients and their parents appreciate using the new technology when they leave the hospital. “Having the glucose values all the time has been very helpful to them. It’s nice to know that there is going to be an alarm at night to wake you if your blood

glucose is low. They have been very appreciative and have done very well,” explains Dr. Buckingham. In fact, the kids are doing so well that, “They have very few alarms because the majority of their blood glucose levels are in the normal range,” he happily remarks.

### **The Benefits of Collaboration**

The clinical trial is a collaboration between DirecNet, which has expertise in studying continuous glucose monitoring technologies, and TrialNet, which has expertise in recruiting and studying people with newly diagnosed type 1 diabetes. “It takes the expertise of both coordinating centers to really make this happen,” notes Dr. Buckingham.

The strength of the DirecNet coordinating center is in collecting and analyzing large amounts of data from monitors and pumps. “When you think about it,” Dr. Buckingham explains, “most of these monitors are measuring glucose levels every minute or every 5 minutes each day. With 5 minute measurements, that is 288 time points of data per day. Since the patients are also using an insulin pump, there is also data on insulin boluses and basal infusion rates that need to be integrated with the glucose data. This is a huge amount of data over 2 years. The DirecNet coordinating center has developed excellent methods of obtaining uploads from these devices, putting the data in a database, and verifying and validating the data as it arrives.”

“On the other hand,” continues Dr. Buckingham, “the trial is looking at the onset of diabetes and trying to prolong the honeymoon phase, which is one of the goals of TrialNet. TrialNet is also interested in how the treatment may affect the immune attack on islet cells, so we are collecting samples through TrialNet to look at immunologic markers to see if there are differences

between the treatment and control groups to begin to see how the immune system was affected.” Thus, the trial is utilizing the expertise of both networks and also saving resources by building on existing infrastructures.

### **Moving Several Fields Forward**

“I think this is a big study in terms of the technical state-of-the-art,” Dr. Buckingham explains, “in that the closed-loop studies are still pretty new. The sensor-augmented pump technology has been around a little while but it’s still relatively new and using it in new-onset patients is also new.”

Thus, this trial is moving several fields forward. First, it is advancing knowledge about closed-loop systems, which can provide insights regarding how to improve the technology to ultimately reach the goal of developing an artificial pancreas that can be used by patients outside of a hospital setting. Second, the trial is testing intensive therapy shortly after disease onset using the new technologies. If effective, it paves the way for people to use new technologies upon diagnosis to not only help manage their diabetes, but also to improve their health outcomes. “These studies could not have been done without NIH funding or without support of the *Special Diabetes Program*,” says Dr. Buckingham.

### **Using New Technologies To Help a Wide-range of Patients**

In the clinical trial described above, Dr. Buckingham is testing new technologies in children and youth who have just been diagnosed with type 1 diabetes. In other research, he is testing the technologies in a very different population—adults with type 1 or type 2 diabetes who have a disease-associated complication called

gastroparesis. This complication is caused by nerve damage which may result from high blood glucose levels, and causes delayed emptying of food from the stomach. Thus, it is difficult for people with gastroparesis to predict when the sugar from food will enter their blood and when their body will need insulin. “It’s hard for people with gastroparesis to administer insulin and keep their blood glucose in good control without having significant episodes of hyperglycemia and hypoglycemia,” explains Dr. Buckingham, “so these patients have a really difficult time with their diabetes. We’re going to utilize—for the first time in a clinical trial—continuous glucose monitoring and an insulin infusion pump therapy for these patients.” By allowing patients to see their glucose values in real time, as well as having alarms to signal a low glucose, “It can hopefully help them keep their glucose values more in a normal range which could even potentially improve

their gastroparesis,” Dr. Buckingham predicts. Thus, the new technologies have high potential for helping a wide-range of patients, from newly diagnosed children to people with late-stage disease complications.

### Looking to the Future

With support from the *Special Diabetes Program*, Dr. Buckingham is conducting state-of-the-art research that can have a major impact on the health and quality of life of people with type 1 diabetes. Not only do new glucose monitoring and insulin-delivery technologies have the potential to make it easier for patients to manage their disease, but they may also improve health outcomes. Dr. Buckingham’s dedication to testing the new technologies in a wide-range of patients can help this potential come to fruition.

## Patient Profile

### Gina Ferrari

#### *Participating in a Clinical Trial Testing a Closed-Loop System To Slow Progression of Type 1 Diabetes*

##### How a Life Can Change in an Instant

"I was eating more than I ever had before, but I kept losing weight," notes Gina Ferrari. It happened at the end of Gina's junior year in high school, just before her ballet showcase and final exams. A simple blood test at the doctor's office changed her life in an instant with a diagnosis she never saw coming—type 1 diabetes.

Gina had no family history of diabetes, so she was surprised and overwhelmed upon receiving the news that she had the disease. She remembers that while she was still processing her diagnosis, she was also a bit relieved. "I was just grateful to know what was wrong with me," says Gina. "I was convinced that, together with my family, I could beat this." Gina was fortunate to be referred through a family friend to Dr. Bruce Buckingham at Stanford University. During her first appointment with Dr. Buckingham, she learned about type 1 diabetes. Because of the daily need to monitor her diet and physical activity, and also closely monitor her blood glucose (sugar) levels and administer insulin, she quickly realized that type 1 diabetes was going to be a formidable opponent.

During that first appointment, Gina also learned about a clinical trial that Dr. Buckingham was leading to test the benefits of early and intensive blood glucose control in people with newly diagnosed type 1 diabetes. Gina's



**Gina Ferrari**

dad Tom remembers, "Dr. Buckingham wanted us to know everything about diabetes and the trial up front. We went from having no information at all to a tidal wave of information in 1 day."

Joining the study required a commitment of 4 days in the hospital within 1 week of Gina's diagnosis. After the hospital stay, she would be sent home with an insulin pump and a continuous glucose monitor to use as part of the trial for the next 2 years. During that time, she would have doctor's appointments every 3 months. After 2 years, if her body is still producing insulin, Gina may continue to participate in the trial for another 2 years. "I was scared to commit so much so soon to a disease I knew so little about," Gina recalls. But she did not have much time to make her decision; participants must be enrolled in the trial within 1 week of their diagnosis. Her parents wanted Gina to participate, but they knew that it had to be her decision. "As hard as it was at the time, Tom and I didn't pressure her and allowed her to process all of the information we were given and arrive at her own

decision,” says her mom Lori. “Needless to say, we were relieved when she told us she wanted to sign up.” The day after Gina learned about the trial she decided to participate.

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**“I am convinced that Gina is doing so well because of her participation in the trial,” says Lori.**

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### **Participation in the Trial: Being Part of Something Special**

The trial, which is supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, is a collaboration between the NIDDK-led Type 1 Diabetes TrialNet and the NICHD-led DirecNet to test whether intensive blood glucose control upon diagnosis can prolong a person’s ability to produce insulin. Previous research demonstrated that preserving this ability can have positive, long-term health benefits in delaying the devastating complications of the disease. This trial employs a “closed-loop” system—a continuous glucose monitor linked to an insulin pump. In this system, a subcutaneous glucose sensor measures blood glucose levels every minute, and that information is transmitted to a computer that calculates how much insulin the pump should deliver. The insulin is delivered automatically based on the blood glucose readings.

The goals of this intensive management using a closed-loop system are to enable the research team to bring the participant’s blood glucose levels close to normal range within the first week of diagnosis and hopefully to preserve the ability of the pancreas to produce some of its own insulin. Because the closed-loop system is experimental and not approved for home use, participants must remain in the hospital while using the system and be closely monitored by the research team,

which is why Gina was in the hospital for the first 4 days of the trial.

The first morning in the hospital was all about education. “We received a phenomenal amount of information and received one-on-one training by experts in the field,” Lori remembers. “As the team was training Gina, Tom and I were learning, too.” “We saw quickly that Gina was capable of managing her diabetes with the new technology and this was very comforting to us,” notes Tom. “She took charge from the very beginning, and I think that helped to give her a sense of control over an overwhelming diagnosis.” Gina remembers, “I spent the first 4 days of my summer in the hospital getting my blood sugar levels under control and learning everything I needed to know about the most advanced ways to manage my diabetes.”

Gina was the second person to enroll in the study, and the excitement of the entire research team was evident to her and her family from the first day. “I love Dr. Buckingham. He was so excited about the trial. He would stay in the hospital with me all night and constantly check on me,” remembers Gina. She recalls that Dr. Buckingham explained how eating different foods would affect her blood glucose levels. He also showed her how to use the continuous glucose monitor to watch how her blood glucose levels were rising and falling. “I knew that he was really busy, but he made me feel like I was his only patient,” says Gina. “The whole team was excited about the trial. We really felt like we were part of something special, something much bigger than Gina’s diabetes,” says Tom. Gina remembers her hospital stay during the first part of the trial as a very positive experience. “My friends were able to come and stay with me in the hospital and as I was learning I was also teaching them about diabetes. I

remember feeling more confident each day that I was in control of my diabetes,” says Gina.

Gina received much more than knowledge about how to use the advanced technology to manage her type 1 diabetes. During her time in the hospital, the research team and Dr. Buckingham helped Gina to understand and believe that she could continue to live her life the way she wanted after leaving the hospital. “I think that after managing my diabetes, the most important thing that Dr. Buckingham and his team taught me was that I can continue to do what I want to do,” says Gina. “Things become more complicated with diabetes and require more planning, but I left the hospital believing that diabetes doesn’t have to slow me down.”

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**“I remember feeling more confident each day that I was in control of my diabetes,” says Gina.**

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Gina admits that she was a little scared when it was time to leave the hospital and go home. “I knew that I was prepared, and my parents and I stayed in close contact with Dr. Buckingham and his team. That helped a lot and was very comforting to all of us,” remembers Gina. She was sent home with an insulin pump paired with a continuous glucose monitor to manage her type 1 diabetes. Unlike the closed-loop system that automatically delivered insulin, the new system required Gina to administer her own insulin. However, the hope is that the technology will help Gina achieve good control of her diabetes and preserve her ability to produce her own insulin. To help with this transition from hospital to home, Gina would get frequent calls from Dr. Buckingham and his team to check on her. “Even when he was traveling outside of the country he would call us. It was an incredible source of comfort for us all,” says Lori.

Before type 1 diabetes, Gina’s day would consist of waking up, going to school, dancing, more dancing, and then doing homework before bed. Now her days are back to that routine, but with the added responsibility and complexity of testing her blood glucose levels 8-10 times a day. All of this information—the amounts of insulin that Gina administers, her blood glucose readings—is uploaded from Gina’s insulin pump and continuous glucose monitor and sent to Dr. Buckingham and his research team so they can monitor and analyze the data.

### **Finding the Silver Lining**

At the time this profile was written, Gina had been participating in the trial for 15 months. The family reports that her doctors say that she is doing extremely well and continues to produce some of her own insulin. Her hemoglobin A1C, a measure reflective of blood glucose control over the preceding 2-3 months, is in the normal, “nondiabetic” range. “I am convinced that Gina is doing so well because of her participation in the trial,” says Lori.

Gina was getting ready to leave for college at the time this article was written. She was excited about starting this new chapter in her life. “I try to not let diabetes define me, but my life is different now. Not only do I carry my insulin pump, glucose meter, medical bracelet, glucose tablets, syringes, and glucagon with me wherever I go,” notes Gina, “but I carry the responsibility of managing a potentially lethal disease, one where a small mistake on my part could put me in the hospital and a big mistake could lead to death.”

Living with type 1 diabetes and being part of the clinical trial have given Gina a new outlook on life. She worked hard the summer after her diagnosis to regain her strength and to get back to dancing. “Now I am back to

where I was before diabetes," Gina says. "Going through this experience and having diabetes has made me really appreciate what I am able to do. I am not nervous before my dance performances like I used to be. Now, I am just

grateful that I can perform." Her proud mother adds, "I am constantly amazed by Gina's positive attitude throughout this experience. She has found the silver lining in what could have been a devastating diagnosis."

## **EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE *SPECIAL DIABETES PROGRAM***

The *Special Statutory Funding Program for Type 1 Diabetes Research* has fueled the emergence of a wide range of research opportunities. These opportunities were identified in a strategic planning process as being critically important for overcoming current barriers and achieving progress in diabetes research. Key questions and research opportunities relevant to type 1 diabetes, including those related to the prevention or reversal of hypoglycemia, are outlined in Appendix F.

