



The hormone GLP-1, produced by the gut in response to food intake, serves as a signal to the pancreas to prepare to release insulin (a hormone that lowers blood glucose levels) and to cease production of glucagon (a hormone that raises blood glucose levels). In addition, GLP-1 acts on other tissues, briefly slowing the digestive process and reducing appetite. This combination of effects makes GLP-1 an important contributor to maintaining healthy glucose levels, though its effects are brief as it is degraded rapidly in the blood. Past research has led to the development of both long-lived analogs of GLP-1 as well as inhibitors of GLP-1 degradation, which have become important classes of medication for people with type 2 diabetes. GLP-1 stimulates its effects by binding to a receptor, designated GLP1R, that spans cell membranes and transmits the hormone's signal to the cell's interior. Understanding how GLP1R interacts with GLP-1 on the outside of the cell, and then acts on protein partners called G proteins that carry the GLP-1 signal within the cell, might lead to improvements in therapy that take advantage of this pathway. In research described in the Cross-Cutting chapter of this book, a cutting-edge technique called cryo-electron microscopy was used to determine the structure of GLP1R in complex with GLP-1 and a G protein. In this image, the portion of GLP1R located outside the cell is shown in dark green, and the membrane-spanning portion is light green. The GLP-1 hormone is shown in red, and various parts of the G protein are shown in gold, blue, and purple. GLP1R is similar to other receptors that are important for a variety of functions in the body. A better understanding of these receptors, from this and other studies, may help inform the development of new treatments for multiple diseases.

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# 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, these diseases and conditions affect many millions of Americans and can profoundly decrease quality of life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.*

Not only is diabetes chronic and relentless, but its slow accumulation of insults to the body can rob a person of the ability to see, hear, feel, think, and walk. In addition to increasing the risk for complications of vision loss, kidney failure, and amputation, diabetes doubles risk for heart disease, many forms of cancer, some forms of dementia, hearing loss, erectile dysfunction, urinary incontinence, and many other common diseases.<sup>1</sup> NIDDK is vigorously pursuing research to combat diabetes and its associated health consequences.

Diabetes is a debilitating disease that affects an estimated 30.3 million people in the United States—or 9.4 percent of the total population—and is the seventh leading cause of death.<sup>2</sup> Although rates of diabetes-related complications have declined substantially in the past two decades, and the rate of new cases of diagnosed diabetes has begun to fall, disease burden remains significant as the number of people with diabetes is still very high.<sup>3,4</sup> Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial cost for diagnosed diabetes in the United States in 2012—including costs of medical care, disability, and premature death—was \$245 billion.<sup>5</sup> Effective therapy can prevent or delay diabetic complications, but nearly one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.<sup>2</sup>

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of 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. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that is similar to type 2 diabetes but unique to pregnancy. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the mother and baby before, during, and after delivery.

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of diagnosed diabetes cases in adults, and the majority of diagnosed cases in children and youth.<sup>2</sup> 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 insulin-producing  $\beta$  cells of the pancreas. If left

- <sup>1</sup> *Diabetes in America*, 3rd ed. Cowie CC, et al., Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 17-1468, 2017.
- <sup>2</sup> Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2017*. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2017.
- <sup>3</sup> Gregg EW, et al. *N Engl J Med* 370: 1514-1523, 2014.
- <sup>4</sup> Centers for Disease Control and Prevention. *Diabetes—working to reverse the US epidemic, at a glance 2016*. Atlanta, GA: U.S. Department of Health and Human Services, 2016.
- <sup>5</sup> American Diabetes Association. *Diabetes Care* 36: 1033-1046, 2013.

untreated, type 1 diabetes results in death from starvation: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—to regulate their blood glucose levels. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated with type 1 diabetes. However, despite vigilance in disease management, with current technologies to test blood glucose levels and administer insulin, it is still not possible for people with type 1 diabetes to control blood glucose levels as well as functional pancreatic  $\beta$  cells do. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery. In this regard, a milestone was achieved in 2016 when the U.S. Food and Drug Administration approved the first commercial "hybrid artificial pancreas" device that automatically links glucose monitoring and insulin delivery. The NIDDK supported early research that contributed to the development of the approved device and continues to support research to test and improve artificial pancreas technologies. Researchers are also working to develop  $\beta$  cell replacement therapies, such as islet transplantation, to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases in U.S. adults.<sup>2</sup> The risk for developing type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.<sup>4</sup> Type 2 diabetes occurs at higher rates among racial and ethnic minority populations in the United States, including African Americans, Hispanic and Latino Americans, American Indians, some Asian Americans, and Native Hawaiians and Pacific Islanders.<sup>2</sup> Gestational diabetes is also a risk factor: about half of women with gestational diabetes will develop type 2 diabetes within 5 to 10 years after giving birth.<sup>6</sup>

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic  $\beta$  cells lose their ability to secrete enough insulin to

restore balance, and the timing of insulin secretion becomes abnormal, causing blood glucose levels to rise. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 84 million U.S. adults who have a condition called "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.<sup>2</sup> This population is at elevated risk of developing type 2 diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that people with prediabetes can dramatically reduce their risk of developing type 2 diabetes with diet and exercise changes designed to achieve a 7 percent reduction in body weight. To a more limited degree, the safe and well-tolerated drug metformin can also help prevent or delay type 2 diabetes. Moreover, follow-up research has shown that the benefits of reduced diabetes risk from weight loss or metformin can persist for at least 15 years.

Type 2 diabetes was previously called "adult-onset" diabetes because it is predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects youth from racial and ethnic minority populations in the United States. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. For example, the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial showed that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because the onset and severity of disease complications correlate with both the duration of diabetes and control of blood glucose levels; thus, those with early disease onset are at greater risk with respect to complications than those who develop the disease later in life. In addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and 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 type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes in young women could contribute to a cycle of ever-growing rates of diabetes. Therefore, the advent of type 2 diabetes

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<sup>6</sup> Kim C, et al. *Diabetes Care* 25: 1862-1868, 2002.

in youth has the potential to worsen the enormous health burden that diabetes already places on the United States.

The NIDDK is supporting research to better understand metabolism and the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the NIDDK'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 NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

## NEW INSIGHTS ON THE COMPLICATIONS OF DIABETES

**Personalizing Eye Exam Schedule for People with Type 1 Diabetes:** Researchers have developed an evidence-based screening schedule for an eye disease (retinopathy) in people with type 1 diabetes, with the frequency of screening tailored to an individual's current level of eye disease and hemoglobin (Hb) A1c level, a measure of average blood glucose (sugar) control. Diabetes is the leading cause of new cases of blindness in adults. Vision loss, however, can be prevented if the damage is detected and treated in a timely manner. Currently, for people with type 1 diabetes, annual retinal examinations are recommended to screen for signs of retinopathy, starting 3 to 5 years after diagnosis. Previous results from NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated that a period of intensive blood glucose control lowered the risk of complications, including those involving the eyes. This led researchers to ask whether an annual eye screening is necessary for people with type 1 diabetes who intensively control their blood glucose levels.

In the over 30 years that DCCT/EDIC participants have been followed, data from approximately 24,000 eye examinations were collected along with information about each participant's eye health. From these data, DCCT/EDIC researchers modeled the likelihood that a person would progress from a lower level of retinopathy to very severe retinopathy in specific

periods of time. They found that, for people with no or mild retinopathy, annual examinations might not be necessary. For people with moderate to severe retinopathy, however, more frequent examinations might be needed to detect retinopathy severe enough that timely treatment is needed to prevent vision loss. They also found that the risk of eye disease progression was closely related to the participant's HbA1c level.

With the goal to limit the likelihood of progression to very severe retinopathy between examinations to approximately 5 percent, the scientists developed an eye examination schedule based on a person's current state of retinopathy and additionally on HbA1c level. Averaged over all levels of HbA1c, they estimated that a person could go 4 years between examinations if they had no initial retinopathy, 3 years if they had mild retinopathy, and 6 months if they had moderate retinopathy. For people with severe retinopathy, monitoring more frequently than every 3 months would be necessary to reduce the probability to approximately 15 percent of developing very severe retinopathy before their next examination. People at all levels of retinopathy with higher HbA1c levels were predicted to need more frequent eye exams, as they are at higher risk to develop eye disease. For example, the eye examination schedule for people at a current HbA1c level of 6 percent would be 5 years if they had no initial retinopathy, 5 years if they had mild retinopathy, 6 months if they had moderate retinopathy, and 3 months if they had severe retinopathy; whereas for people at a current HbA1c level of 10 percent, the corresponding schedule would be 3 years, 2 years, 3 months, and 1 month, respectively.

Taking into consideration both the reduced number of screenings the scientists propose for people with no or mild retinopathy and the more frequent examinations needed for people with moderate or severe retinopathy, they also calculated how their schedule would affect the number of screenings overall for people with type 1 diabetes. They found that, over 20 years, screening according to their tailored examination schedule would, on average, result in a 58 percent reduction in number of exams overall, compared to annual screening for everyone. Combining this overall reduction with an approximate \$200 cost for screening and approximate 1 million people with type 1 diabetes, the scientists estimate

that this screening schedule could result in a savings of approximately \$1 billion over 20 years. Although the additional screening for those with worse retinopathy would increase their screening burden, it could also increase the likelihood of detecting further progression of retinopathy, so that therapy proven to preserve vision can be delivered in the timeframe before irreparable vision loss occurs. Importantly, this schedule has yet to be tested in real-life situations in people with type 1 diabetes. In addition, it is not known if it will be appropriate for people with type 2 diabetes, as it remains to be determined whether retinopathy progresses similarly in people with type 2 diabetes and people with type 1 diabetes. Regardless, this risk-based screening schedule has the potential to personalize treatment to reduce both undetected diabetic eye disease and the burden of annual retinal exams for some people, which may result in cost savings overall and better health for people with type 1 diabetes.

*Nathan DM, Beu I, Hainsworth D,...Lachin JM; for the DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med 376: 1507-1516, doi: 10.1056/NEJMoa1612836, 2017.*

**Identification of Signaling Pathway Involved in Diabetic Nerve Damage Leads to Discovery of Promising New Therapy:** Researchers have discovered that blocking a signaling pathway involved in diabetic nerve damage with a drug already being given to people for other conditions could prevent or reverse that damage in mice. People with diabetes can, over time, develop nerve damage throughout the body. The most common type of diabetic nerve damage, called peripheral diabetic neuropathy, causes pain or loss of feeling in the feet, legs, hands, and arms and is a major risk factor for amputation. Currently, people with diabetic nerve damage may be treated with medications to manage pain, but there is great need to find therapies to prevent and reverse this serious complication to reduce its significant health burden.

Toward this goal, scientists screened a library of molecules for those that could enhance repair of male rat nerve cells in laboratory culture by stimulating the outgrowth of neurites, which project from nerve cell bodies and connect the cells to other nerve cells. The more neurite outgrowth the better, in terms of repairing nerve damage. They found that molecules that blocked

“muscarinic acetylcholine type 1 receptors” (M<sub>1</sub>R) stimulated neurite outgrowth. Further experiments confirmed a key role for M<sub>1</sub>R in regulating neurite outgrowth: neurite outgrowth was inhibited when M<sub>1</sub>R protein levels were experimentally increased in cultured rat nerve cells, whereas neurite outgrowth was higher in nerve cells from an experimental mouse model lacking M<sub>1</sub>R compared to control mice. To take these observations a step further, the researchers studied an M<sub>1</sub>R -blocking drug in mouse models of diabetes, focusing on a drug called pirenzepine because it is already used clinically for other conditions. They found that pirenzepine treatment prevented and reversed diabetic nerve damage in male and female mouse models of type 1 and type 2 diabetes. The drug also prevented nerve damage associated with other conditions, such as chemotherapy, suggesting that blocking M<sub>1</sub>R with pirenzepine stimulates nerve repair/regeneration even when the underlying cause of the damage varies in animals.

This research suggests that M<sub>1</sub>R plays a key role in the nerve damage associated with diabetes and other conditions in mice, and that blocking its activity with pirenzepine could prevent or reverse that damage. Interestingly, the scientists found no evidence that the normal M<sub>1</sub>R signaling pathway is altered in diabetes, so the mechanism by which pirenzepine is exerting its effects is not clear. Nonetheless, the promising results of the study are already being translated to people: the NIDDK is funding a pilot clinical trial to test whether another drug (topical oxybutynin) that blocks M<sub>1</sub>R can reverse diabetic neuropathy.

*Calcutt NA, Smith DR, Frizzi K,...Femyhough P. Selective antagonism of muscarinic receptors is neuroprotective in peripheral neuropathy. J Clin Invest 127: 608-622, doi: 10.1172/JCI88321, 2017.*

### **Study Suggests Possible Approach for Early Detection of Diabetic Kidney Disease Risk:**

Researchers have identified a set of molecules that appear to predict loss of kidney function and correlate with kidney damage in people with type 2 diabetes. Diabetes is the leading cause of kidney disease in America and is one of the leading causes of kidney failure. However, early in the course of disease available methods for assessing kidney function are not sufficient to predict who is likely to progress to advanced loss of kidney function; knowing this information could help inform clinical care.

Persistent hyperglycemia, or elevated blood glucose (sugar) levels, is the chief culprit in most diabetes health complications and is thought to wield this effect in part through the production of tissue-damaging chemical byproducts. These molecules are called advanced glycation end products (AGEs) and oxidative end products, and are detectable in the blood. Leveraging biological samples and data from 168 women and men with type 2 diabetes who participated in a kidney-disease-focused clinical trial and follow-up period, researchers tested the hypothesis that increasing levels of one or more of these molecules at an early stage might predict progression of diabetic kidney disease. They found through their analyses that increases in certain AGEs during the 6-year clinical trial predicted a threshold loss of kidney function during the trial or follow-up period. Higher levels of these AGEs correlated with the appearance of kidney lesions typical of diabetic kidney disease that were detected in kidney biopsies from a subset of participants at the end of the clinical trial. Notably, there is evidence that increasing levels of AGEs in the blood are partly due to a vicious cycle in which kidney impairment leads to reduced clearance of these toxic molecules from the body—reinforcing the message of other clinical trials that good control of blood glucose is important to staving off diabetes complications. The participants in this study were Pima Indians of the Gila River Indian Community in Arizona. Future studies may both help determine the clinical utility of AGEs as noninvasive predictive biomarkers of progression of diabetic kidney disease and whether the findings extend to other populations.

*Saulnier P-J, Wheelock KM, Howell S, ...Beisswenger PJ. Advanced glycation end products predict loss of renal function and correlate with lesions of diabetic kidney disease in American Indians with type 2 diabetes.*

*Diabetes* 65: 3744-3753, doi: 10.2337/db16-0310, 2016.

## UNCOVERING CLUES TO METABOLIC CONTROL AND THE DEVELOPMENT OF TYPE 2 DIABETES

### Identification of a Key Metabolic Regulator:

Scientists have determined that the protein  $\beta$ -arrestin-2 plays critical roles in the pancreas and liver to regulate metabolism.  $\beta$ -arrestins are a family of proteins that regulate a wide variety of functions in different tissues in the body. Previous studies, in which mice were genetically engineered to lack  $\beta$ -arrestin-2, suggested

that this protein might be involved in metabolic functions, but it remained unclear where  $\beta$ -arrestin-2 was needed to affect metabolism.

To explore a potential role for  $\beta$ -arrestin-2 in  $\beta$  cells (the pancreatic cells that produce insulin) and in hepatocytes (a cell type in the liver), the researchers genetically engineered mice to lack  $\beta$ -arrestin-2 specifically in  $\beta$  cells or in hepatocytes. The scientists found that male mice lacking  $\beta$ -arrestin-2 only in their  $\beta$  cells showed mild metabolic changes (compared to mice with  $\beta$ -arrestin-2 in their  $\beta$  cells) when fed a normal diet. These mice, however, showed significant metabolic changes when fed a diet that induces obesity and type 2 diabetes in mice. Compared to mice with  $\beta$ -arrestin-2 in their  $\beta$  cells consuming the same diet, the mice without  $\beta$ -arrestin-2 showed an increase in blood glucose (sugar) levels and almost no glucose-stimulated insulin secretion.

To complement these studies, the researchers also genetically engineered mice to have higher levels of  $\beta$ -arrestin-2 than usual. They found that, when fed the diabetes-inducing diet, these mice showed an increase in glucose-stimulated insulin secretion, greatly improved glucose tolerance, and lower blood glucose levels, compared to normal mice on the same diet. This suggested that  $\beta$ -arrestin-2 can counter the metabolic effects of a diet that induces obesity and type 2 diabetes. Importantly, the researchers found that glucose-stimulated insulin secretion was significantly reduced in a human pancreatic  $\beta$  cell line lacking  $\beta$ -arrestin-2, suggesting that  $\beta$ -arrestin-2 may be similarly important to human metabolism.

The researchers found that  $\beta$ -arrestin-2 has a similarly important role in hepatocytes: eliminating the protein in these liver cells in mice fed the diabetes-inducing diet worsened metabolic control, while increasing the protein's levels in the cells helped ameliorate the effects of the diet.

These two studies implicate  $\beta$ -arrestin-2 as a key regulator of  $\beta$  cell and hepatic function in maintaining normal metabolism. Additional research will be necessary to determine the extent to which  $\beta$ -arrestin-2 acts similarly in humans, but this research suggests that strategies to promote  $\beta$ -arrestin-2 activity in  $\beta$  cells and/or hepatocytes

could be clinically useful in the treatment of type 2 diabetes.

Zhu L, Rossi M, Cui Y, ...Wess J. Hepatic  $\beta$ -arrestin 2 is essential for maintaining euglycemia. *J Clin Invest* 127: 2941-2945, doi: 10.1172/JCI92913, 2017.

Zhu L, Almaca J, Dadi PK, ...Wess J.  $\beta$ -arrestin-2 is an essential regulator of pancreatic  $\beta$ -cell function under physiological and pathophysiological conditions. *Nat Commun* 8: 14295, doi: 10.1038/ncomms14295, 2017.

### **Uncovering Cellular Factors Linking the Immune System, Obesity, and Insulin Resistance:**

New research suggests a protein secreted by certain immune system cells not only promotes obesity-associated inflammation, but also drives insulin resistance in key tissues, and identifies a key player in activation of the cells in question. Obesity has long been known to cause chronic inflammation, a state in which macrophages—immune-system cells that help defend the body against infection—are inappropriately and continuously activated in metabolically important tissues such as adipose (fat), muscle, and liver. This obesity-associated chronic inflammation is thought to contribute to the development of insulin resistance—a condition that often leads to type 2 diabetes—possibly through the effects of some of the many proteins macrophages secrete. Although several of these proteins have been investigated, none has clearly been shown to be a major driver of insulin resistance. A new study focuses on the macrophage-secreted galectin-3 (Gal3) protein. Gal3 had previously been shown to be elevated in a mouse model of diet-induced obesity. Gal3 levels in these mice correlated significantly with insulin resistance, so researchers sought to determine whether Gal3 has a role in causing this condition, or whether the correlation was coincidental.

Indeed, through a variety of experiments they found compelling evidence that Gal3 plays a significant role in promoting insulin resistance. For example, mice that lack the gene for making Gal3 remained sensitive to insulin, even when they had diet-induced obesity. Moreover, treating obese mice that have the normal gene for Gal3 with a compound that inhibits the action of the protein improved their insulin sensitivity. In other experiments, exposing laboratory-grown mouse adipose, muscle, or liver cells to Gal3 protein reduced the cells' ability to respond properly to insulin, suggesting that Gal3 could drive insulin

resistance in the absence of other macrophage-secreted substances. Exploring the mechanism by which it may promote insulin resistance, scientists found that Gal3 binds to the insulin receptor, a protein on the surface of cells to which insulin binds to exert its effects. Although it does not seem to prevent insulin from binding to its receptor at the same time, Gal3 seems to inhibit the receptor's capacity to trigger the normal cellular response to insulin. Complementing these findings, the team found evidence that Gal3 promotes the inflammatory state by attracting additional macrophages to tissues where it is being secreted. The experiments in living mice were performed in male animals, so it is possible that there are differences in the effects of Gal3 in female mice.

The researchers also examined Gal3 levels in 52 human volunteers, and found the protein to be elevated in those with obesity, and to correlate significantly with insulin-resistance, suggesting the protein might have a similar effect in human and mouse physiology. It remains unknown whether inhibition of Gal3 could be a safe or effective approach to treating human insulin resistance and type 2 diabetes, but taken together, these experiments suggest it is well worth exploring that possibility.

Understanding how macrophages become activated to cause inflammation and insulin resistance could provide another potential target for battling type 2 diabetes. In a study using male mice and laboratory grown cells, a different group of researchers focused on a cellular protein called fatty acid synthase, or FAS. FAS enables cells to make simple fat molecules, called fatty acids, from precursor molecules. These fatty acids can then become part of the cell membrane, which is the cell's structural boundary and site of interaction with its environment. Mice lacking FAS in their macrophages gained weight similarly to control mice when fed a diet that causes obesity and diabetes, but had fewer macrophages in their fat tissue, less inflammation, and better insulin sensitivity. At the same time, laboratory-grown macrophages with artificially reduced FAS activity also had lower than normal inflammatory responses to a pathogen-derived molecule that should elicit a potent immune response. These and other results suggested that FAS may play a key role in macrophage activation, both in obesity-associated inflammation and in the response to infection. Because macrophage activation involves changes in molecules present in the cell membrane, the scientists compared the composition of FAS-deficient and normal macrophage cell membranes under a variety of conditions. These

experiments indicated that while FAS deficiency does not disturb overall membrane integrity, it disrupts the normal assembly and molecular content of specialized membrane structures that help macrophages migrate into tissues and incite inflammation. Should FAS prove to have a similar role in human macrophage activation as it does in mice, these findings may one day lead to new approaches to preventing inflammation and insulin resistance in people with obesity.

Li P, Liu S, Lu M,...Olefsky JM. Hematopoietic-derived Galectin-3 causes cellular and systemic insulin resistance. *Cell* 167: 973-984. e12, doi: 10.1016/j.cell.2016.10.025, 2016.

Wei X, Song H, Yin L,...Semenkovich CF. Fatty acid synthesis configures the plasma membrane for inflammation in diabetes. *Nature* 539: 294-298, doi: 10.1038/nature20117, 2016.

**In Obesity, an Immune System Signal Can Lead to Loss of Beneficial Bacteria and Loss of Blood Glucose Control:** New research suggests that a key molecular signal produced by immune cells as a result of obesity may worsen blood glucose control through a system that limits the abundance of a beneficial species of bacteria in the gut. The molecular signal in question is interferon gamma (IFN $\gamma$ ), a protein released as part of the inflammatory response to obesity in both mice and humans. Diet-induced obesity can promote type 2 diabetes in mice, as it often does in humans, and previous research had shown that glucose levels remain healthy in obese mice that lack the gene for IFN $\gamma$ .

Because previous research has shown that bacteria in the gut can have a significant impact on glucose levels in their hosts, and because IFN $\gamma$  can modulate the body's immune response to bacteria, it is plausible that the protein might be promoting type 2 diabetes indirectly by causing the immune system to act against beneficial microbes. To test this concept, researchers treated obese male mice with a combination of antibiotics that wipes out nearly all intestinal bacteria. Doing so eliminated differences in glucose levels between mice that had the gene for IFN $\gamma$  and those that did not. Then they assessed the population of gut bacteria in obese male and female mice to find bacterial species that differed in abundance depending on whether the mice have the gene for IFN $\gamma$ . From among the species that were significantly more, or less, abundant, the researchers asked which of these species correlated positively or negatively with glucose levels. This process led them to focus on a type of bacteria called

*Akkermansia muciniphila*, which is commonly found in both the mouse and human gut. Higher levels of *A. muciniphila* in the mouse gut correlated with better blood glucose control. *A. muciniphila* levels were sharply reduced in obese mice that had the IFN $\gamma$  gene, but obese mice lacking IFN $\gamma$  had levels of these bacteria similar to those found in lean mice. Conversely, in obese male mice that lacked *A. muciniphila*, IFN $\gamma$  no longer seemed to affect glucose control: those without IFN $\gamma$  were no healthier than those that could make the protein, until and unless *A. muciniphila* was added back.

Overall, these results suggested that *A. muciniphila* helps mice maintain proper blood glucose control, and that IFN $\gamma$  production, elevated in obesity, worsens blood glucose control through its adverse effects on these beneficial bacteria. The scientists also found evidence that *A. muciniphila* may have a similar beneficial effect on metabolism in people: higher levels of these bacteria correlated modestly but significantly with better blood glucose control in a group of people participating in other metabolic studies. In any case, these results show that inflammation due to obesity can cause changes in the gut microbiome that have a deleterious effect on blood glucose control, and suggest that interventions to support a healthful gut microbiome may one day be a viable approach to helping treat or prevent type 2 diabetes.

Greer RL, Dong X, Moraes AC,...Shulzhenko N. Akkermansia muciniphila mediates negative effects of IFN $\gamma$  on glucose metabolism. *Nat Commun* 7: 13329, doi: 10.1038/ncomms13329, 2016.

## RESEARCH ON CYSTIC FIBROSIS AND OTHER RARE DISEASES

### Protein-folding Chaperones Have Both Positive and Negative Roles To Play in Cystic Fibrosis:

New research has found that proteins involved in ensuring that other proteins are in their proper shapes may have a role to play in mitigating the effects of cystic fibrosis (CF). People with CF lack a functional copy of the *CFTR* gene, and the most common variant of the gene found in people with CF is designated  $\Delta F508$ -*CFTR*. In  $\Delta F508$ -*CFTR*, the absence of a single amino acid interferes with proper folding of the CFTR protein, not only interfering directly with its function as a channel that allows chloride ions to pass through the cell membrane, but also destabilizing the protein and causing it to be a target for degradation. The destruction of the  $\Delta F508$ -CFTR protein is due in



part to the activities of a group of different proteins collectively known as “chaperones,” which help ensure that other proteins are properly folded through a variety of mechanisms. For example, some chaperones assist in the initial folding of a protein, as it is being synthesized by the cell; others identify proteins that have adopted improper shapes, such as  $\Delta F508$ -CFTR, and target them for degradation; and, in some cases, chaperones may be able to refold misfolded proteins into a functional state.

In new research, using cells from both mice and humans, scientists have found that the chaperones Hsc70 and Hsp90 have a limited capacity to nudge  $\Delta F508$ -CFTR closer to the properly folded shape of normal CFTR protein, allowing a modest amount of chloride to flow through the channel. The researchers found that selective, chemical inhibition of Hsc70 caused the amount of  $\Delta F508$ -CFTR in the cell membrane to increase, indicating that this chaperone contributes to the destruction of the misfolded channel. However, this approach further showed that despite there being more of the protein in the membrane, the ability of chloride to move through the membrane either did not rise or diminished slightly depending on the type of cell used for the experiment: this indicates that Hsc70 also has the capacity to help  $\Delta F508$ -CFTR adopt a conformation closer to normal CFTR protein. In other words, the higher levels of protein in the membrane are offset by the fact that the proteins do not work as well, which is why net chloride transmission stays the same or diminishes. Selective inhibition of Hsp90 had little impact on the amount of  $\Delta F508$ -CFTR in the membrane, but significantly reduced the ability of the channels present to transmit chloride, indicating that Hsp90 can help  $\Delta F508$ -CFTR adopt a more functional conformation—presumably closer to that of normal CFTR protein—without promoting its degradation. Inhibiting both chaperones had an even more profound effect, reducing chloride transmission by more than half. Importantly, addition of Hsc70 and Hsp90—along with specific protein partners called co-chaperones—increased the ability of  $\Delta F508$ -CFTR to permit passage of chloride through the membrane. Experiments further suggested that when working with one co-chaperone, Hsc70 may promote  $\Delta F508$ -CFTR destruction, while with another co-chaperone Hsc70 might promote improved channel function.

These discoveries suggest that manipulating the activity of chaperones is worth exploring as a potential means of treating CF and perhaps other diseases caused by destabilized cell surface proteins.

*Bagdany M, Veit G, Fukuda R,...Lukacs GL. Chaperones rescue the energetic landscape of mutant CFTR at single molecule and in cell. Nat Commun 8: 398, doi: 10.1038/s41467-017-00444-4, 2017.*

### **Finding the Genetic Cause of a Form of**

**Hyperparathyroidism:** Researchers have identified genetic differences that can cause familial isolated hyperparathyroidism (FIHP), a discovery that could lead to improved testing for the disorder and may one day lead to improved treatment for people with either too much or too little parathyroid hormone (PTH). PTH stimulates release of calcium from bones when blood calcium levels are too low. FIHP is an inherited disease, and is one of several conditions characterized by high basal levels of PTH that lead to dangerous elevations of blood calcium levels. This calcium dysregulation in FIHP results in symptoms that may include kidney stones, osteoporosis, and neuromuscular problems like weakness, drowsiness, and depression. Other causes of excess PTH that may yield similar symptoms include various distinct syndromes, and most commonly benign or malignant tumors of the parathyroid gland—conditions that may be best treated in different ways. Understanding the genetics of FIHP would potentially allow it to be differentiated more easily and accurately from other causes of excess PTH, allowing clinicians to tailor treatment to patient needs. Toward this goal, researchers studied families that have FIHP to pinpoint specific genetic differences unique to people with this disease.

Focusing initially on a subset of gene regions in DNA from eight unrelated families in which some family members have FIHP, the scientists looked for rare genetic variations that were present in people with FIHP, but not in their family members without the disease. This approach helped them narrow the investigation to 30 genes of interest, which they examined in detail in 32 other families where two or more individuals had symptoms of FIHP. In this way, they discovered that FIHP-affected members of several of the families had one or more rare mutations in the gene *GCM2*. This gene encodes a protein known to be involved in development and function of the parathyroid gland by turning on other genes needed for parathyroid function. Interestingly, other *GCM2* variations had previously been shown to reduce expression of those genes, leaving people without enough PTH; and mice genetically engineered to lack *GCM2* do not develop functional parathyroid glands. Thus, it was surprising that some *GCM2* variations have the opposite effect, leading to too much PTH in people with FIHP. The research team showed that at least some of the *GCM2* mutations found

in families with FIHP increased the activation of other genes by the *GCM2*-encoded protein, resulting in excess PTH. Through additional experiments, they showed that some of the FIHP-associated *GCM2* mutations alter an important regulatory region that is needed to prevent over-activation of the other parathyroid genes.

Importantly, people with FIHP in most of the families that participated in the study were found not to have mutations in *GCM2*, suggesting that other genetic causes of FIHP remain to be discovered. But the discoveries that *GCM2*-activating mutations can cause excess PTH, while inactivating mutations can result in insufficient PTH, suggest this gene or the protein it encodes could be valuable drug targets for treating some people whose PTH levels are either too high or too low.

Guan B, Welch JM, Sapp JC, ...Agarwal SK. *GCM2-activating mutations in familial isolated hyperparathyroidism. Am J Hum Genet* 99: 1034-1044, doi: 10.1016/j.ajhg.2016.08.018, 2016.

### Innovations in Testing for a Rare Genetic

**Disease—Pompe Disease:** Researchers have developed methods that could significantly improve accuracy of testing for a rare genetic disorder called Pompe disease. Pompe disease results from lack of a protein called acid  $\alpha$ -glucosidase (typically abbreviated GAA), and causes progressive muscle weakness, enlarged heart, and other problems—and in severe cases can lead to death in early childhood. Fortunately, the disease is treatable, particularly if GAA deficiency is identified early. Because the disease can cause significant, irreversible damage before symptoms are apparent, it is of great importance to be able to screen newborn children to identify those who would benefit from treatment.

A currently available screening method uses a chemical that becomes fluorescent when acted on by GAA. This screen can clearly distinguish individuals with normal GAA from individuals who have severe Pompe. However, some people are born with intermediate levels of GAA activity. These individuals may have a milder form of Pompe in which symptoms manifest later in development, but they also may not have the disease at all. Because the fluorescence test cannot clearly differentiate these groups from one another, some babies may be treated for Pompe unnecessarily. To get around this problem, researchers developed methods that can distinguish much more subtle differences in GAA activity. In one new study, they used a test method they estimated to be 15

times more sensitive to differences in GAA activity than is the fluorescent method. Using dried blood samples from males and females, including 11 people with early onset Pompe, 12 with more mild, later onset Pompe, and 230 with GAA levels that are lower than normal, but who have no disease, the new screening method correctly identified all of the people who have the disease, while incorrectly identifying just 4 percent of the healthy individuals who have intermediate GAA levels as having possible Pompe disease. That is, there were no false negatives, while there was a very low rate of false positives. In contrast, the fluorescence method had a much higher rate of false positives, incorrectly identifying about 90 percent of samples with intermediate levels of GAA as being from individuals with possible Pompe disease. The new method could be scaled up to allow rapid screening of dried blood spots from newborns, suggesting it could be practical as a standard infant screen for the disease.

Infants with the most severe, early-onset form of Pompe disease require more aggressive treatment than do babies with the milder, late-onset form. To enhance the ability to distinguish small differences in GAA activity, scientists developed a similar test, adding an additional step, and using fresh samples of leukocytes (white blood cells), rather than dried blood spots. This approach yields about a 700-fold improvement in sensitivity relative to the fluorescence method. Because this method requires a fresh blood sample, it is less suitable for initial screening of a large population of newborns than the version that utilizes dried blood spots. But with the more sensitive assay the researchers could clearly distinguish individuals with early-onset from those with late-onset Pompe. Even this highly sensitive approach identified a few individuals with low GAA levels but no symptoms as having possible late-onset Pompe. This suggests that some people may need more GAA than others to maintain health. Further research may be warranted to determine what factors affect susceptibility to late-onset Pompe in people with intermediate levels of GAA.

Liao HC, Chan MJ, Yang CF, ...Gelb MH. *Mass spectrometry but not fluorimetry distinguishes affected and pseudodeficiency patients in newborn screening for Pompe disease. Clin Chem* 63: 1271-1277, doi: 10.1373/clinchem.2016.269027, 2017.

Lin N, Huang J, Violante S, ...Yu C. *Liquid chromatography-tandem mass spectrometry assay of leukocyte acid  $\alpha$ -glucosidase for post-newborn screening evaluation of Pompe disease. Clin Chem* 63: 842-851, doi: 10.1373/clinchem.2016.259036, 2017.

# Medicare To Provide Benefits for Diabetes Prevention and Treatment Stemming from NIDDK-supported Research

In April of 2018, the Centers for Medicare & Medicaid Services (CMS) is beginning coverage of a group-based adaptation of the lifestyle intervention for beneficiaries with prediabetes; this prevention approach was first pioneered in NIDDK's Diabetes Prevention Program (DPP) clinical trial. The original DPP showed that an intensive lifestyle intervention could reduce the likelihood of developing type 2 diabetes by 58 percent over 3 years among people at high-risk for the disease. For DPP participants who were at least 60 years old at the beginning of the clinical trial the intervention was even more effective, reducing the likelihood of developing type 2 diabetes by 71 percent over the same time period. On the strength of these findings, the NIDDK funded research to develop cost-effective adaptations of the intervention that could be delivered efficiently to millions of Americans who would stand to benefit. The Centers for Disease Control and Prevention scaled up one such adaptation, calling it the National Diabetes Prevention Program. CMS tested this adaptation in 2014 and 2015, concluding in a report from the CMS Office of the Actuary on March 14, 2016, that if offered as a benefit nationally, the program would, on average, be expected to save money and lead to better health for beneficiaries. Accordingly, the Secretary of Health and Human Services determined that the benefit would begin in 2018.

Similarly, NIDDK-supported research contributed to the development of continuous glucose monitors (CGMs)—technology that is now being covered

by CMS under Medicare Part B for beneficiaries who take insulin for either type 1 or type 2 diabetes. CGMs automatically test a wearer's blood glucose (sugar) levels every few minutes, helping them ensure that their dose of insulin is keeping them as near as possible to optimal blood glucose levels. The NIDDK has long supported the development of new tools and technologies for managing diabetes, including CGMs. For example, NIDDK-supported research contributed to the seminal finding that glucose levels in "interstitial" fluid in tissues under the skin reflected glucose levels in the blood, enabling the development of CGMs, which rely upon this route for glucose sensing. Today, all current CGM technology on the market benefitted from NIDDK support early in development, such as through grants to small businesses. At first, the U.S. Food and Drug Administration (FDA) only approved CGMs as a supplement to, but not replacement for, conventional monitoring, such as with blood glucose test strips. With the recent FDA approval of at least one CGM as a primary method of blood glucose monitoring for making diabetes treatment decisions, as of January 2017 (CMS-1682-R), CMS is covering certain CGMs.

These examples show ways in which past NIDDK research has led to improvements in care and prevention for people with or at risk for diabetes, and demonstrate how other recent and ongoing discoveries may lead to further improvements in the future.

# The SEARCH for Diabetes in Youth

## Expanding Understanding of Diabetes in Children and Young Adults

Diabetes is one of the most serious health challenges facing the United States, with rising numbers of both adults and children affected. Type 1 and type 2 diabetes can affect many parts of the body and are associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower limb amputation. To combat diabetes and its associated complications, the NIDDK and the Centers for Disease Control and Prevention began the SEARCH for Diabetes in Youth study in 2000. Today, this unique study continues to provide critical information about diabetes among children and young adults in the United States.

Effective diabetes research requires accurate data on the scope and trends of the disease: how many children and adults have diabetes? Does diabetes affect some populations differently than others? What complications do people with diabetes encounter, and how does this disease affect their quality of life? The SEARCH study has been investigating these questions.

Currently, SEARCH is conducted at five centers, with research sites located across seven states. More than 27,000 SEARCH study participants represent a geographically and racially/ethnically diverse group of people who were under 20 years of age when they were diagnosed with type 1 or type 2 diabetes. These volunteers' participation has been critical in determining the extent of diabetes in the United States and its impact on different populations.

In the over 17 years since its inception, SEARCH has provided a wealth of information about the effects of diabetes on children and young adults. SEARCH investigators have assessed trends in diabetes diagnosis, prevalence, and health care, and have gathered data on complication rates and quality of life. SEARCH was instrumental in discovering that diabetes is frequently found among U.S. youth and that rates of both type 1 and type 2 diabetes diagnoses are increasing in both male and female youths of various racial/ethnic backgrounds and ages. SEARCH also demonstrated that many youths with diabetes are at risk for complications such as eye, nerve, heart, and kidney problems, and that this risk is particularly prominent

among those of racial/ethnic minority groups. For example, a recent SEARCH report showed that from 2002 to 2012, the annual increase in type 1 diabetes diagnosis among U.S. youth—when adjusted for age, sex, and racial/ethnic group—was 1.8 percent, and the annual increase in type 2 diabetes diagnosis was 4.8 percent. However, SEARCH investigators found that the increase varied across racial/ethnic groups. A significant annual increase was found in type 2 diabetes diagnoses among all racial and ethnic groups except non-Hispanic Whites. Type 1 diabetes incidence also increased significantly more in Hispanic youths than in non-Hispanic White youths.

SEARCH investigators also recently published several reports on diabetes complications in youth. They estimated that by about age 21, approximately 32 percent of SEARCH study participants with type 1 diabetes and 72 percent of participants with type 2 diabetes would have (or be at high risk for) at least one diabetic complication. SEARCH researchers also described high rates of diabetic peripheral neuropathy in study participants (seven percent and twenty-two percent in youth with type 1 and type 2 diabetes, respectively) and found that poor blood glucose (sugar) control and greater waist-to-height ratio were associated with elevated cholesterol and lipid levels in the blood of youth with type 1 diabetes.

Increases in type 1 and type 2 diabetes diagnoses in youth are worrying because these populations face unique challenges in managing their diabetes and may be at greater risk of complications later in life due to their long disease duration. These findings suggest that early monitoring of youth with diabetes could lead to earlier diagnosis and treatment of complications, and ultimately to better health. Additionally, the variation in diabetes incidence along racial/ethnic lines suggests that the future burden of these diseases and their complications may fall disproportionately upon certain groups.

SEARCH is planned to continue at least through 2020, with SEARCH investigators building upon past progress to investigate important questions about diabetes trends and outcomes in youth.

# NIDDK Director Testifies on Type 1 Diabetes Research

On July 26, 2017, NIDDK Director Dr. Griffin P. Rodgers testified about progress and future directions in type 1 diabetes research before the Senate Special Committee on Aging, which is led by Chairman Susan Collins (R-Maine) and Ranking Member Bob Casey (D-Pennsylvania). The hearing, entitled “Progress Toward a Cure for Type 1 Diabetes: Research and the Artificial Pancreas,” was held in conjunction with the Children’s Congress, an event sponsored every 2 years by JDRF to highlight the value and progress of type 1 diabetes research for children and adults living with this disease.

In his testimony, Dr. Rodgers described research made possible by the *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program)*, which the NIDDK administers on behalf of the Secretary of the Department of Health and Human Services.

Examples of the research include:

- progress toward the development of artificial pancreas technology—devices that automate blood glucose sensing and insulin administration—and four new clinical trials testing these technologies (see Story of Discovery in this chapter);
- results of a clinical trial testing islet transplantation as a treatment approach for people with difficult-to-control type 1 diabetes;
- progress toward engineering a biological cure from NIDDK’s Human Islet Research Network; and
- results of a comparative effectiveness clinical trial testing different treatments for diabetic eye disease.

Testifying with Dr. Rodgers were Mr. Paul Sparks, an actor and patient advocate; JDRF Children’s Congress Chairwoman Ms. Angie Platt; and JDRF Children’s Congress Delegates Charlie Albair, age 10, Lorynn Watt, age 17, and Jonathan Platt, age 14.



Shown at the dais (left to right): Sen. Elizabeth Warren (D-MA), Sen. Bob Casey (D-PA), and Sen. Susan Collins (R-ME, Committee Chair). Photo credit: Larry Lettera



NIDDK Director Dr. Griffin P. Rodgers testifying before the Senate Special Committee on Aging. Also shown at the table (left to right): Actor Paul Sparks, Children’s Congress Delegates Charlie Albair and Lorynn Watt, and 2017 Children’s Congress Family Chair Angie Platt. Photo credit: Larry Lettera

The *Special Diabetes Program*’s current authorization expired September 30, 2017. Should the *Program* be renewed, an extension would provide NIDDK with an opportunity to support new and emerging research in type 1 diabetes and its complications. To solicit input on future directions that could be supported with the new funds, the NIDDK convened a planning meeting in April 2017, which was held under the auspices of the statutory Diabetes Mellitus Interagency Coordinating Committee. At the meeting, a panel of external scientific experts and a lay representative provided input on concepts for potential new research initiatives developed by the NIDDK, other institutes at NIH, and the Centers for Disease Control and Prevention; the panel also provided input on the continuations of programs that are already supported by the *Special Diabetes Program*. Guided by that input, diabetes research strategic plans, and input that the NIDDK receives at venues such as scientific conferences and workshops, the Institute is identifying the most compelling areas of current research opportunity. If the *Special Diabetes Program* is renewed, it would be poised to continue its exceptional track record of supporting cutting-edge type 1 diabetes research.

## Artificial Pancreas for Managing Type 1 Diabetes: Cutting-edge Technology 50 Years in the Making

Aristotle once said: “the whole is greater than the sum of its parts.” This could be said for a revolutionary new management tool for type 1 diabetes: artificial pancreas technology. This technology builds on decades of advances in type 1 diabetes management—such as the advent of insulin pumps and continuous glucose monitors (CGMs). Now, with long-standing support from NIDDK, private funding entities, and industry, researchers have combined these individual “parts” to develop a “whole” device that can benefit people more than each component alone.

A major milestone occurred in 2016 with the first U.S. Food and Drug Administration (FDA) approval of a commercial “hybrid” artificial pancreas device developed by industry; NIDDK-supported research contributed to the early development of the approved device. This milestone promises to be just the beginning of a new era in the development of cutting-edge artificial pancreas technologies that could benefit people with type 1 diabetes.

### What Is an Artificial Pancreas?

Artificial pancreas technology strives to mimic the exquisite control of blood glucose (sugar) maintained by a healthy pancreas. The pancreas produces a number of hormones, including insulin and glucagon, to enable the body to use glucose for fuel and store glucose when it is in excess, or release it from stores when glucose levels get too low. In people with type 1 diabetes, the immune system destroys insulin-producing pancreatic  $\beta$  cells. Thus, people with the disease need to administer

insulin for survival and measure blood glucose levels to determine how much insulin to take.

An artificial pancreas, or “closed-loop system,” is technology that would replace the function of the pancreas that does not work in people with type 1 diabetes: delivering insulin in response to blood glucose levels. It links three technologies: (1) a sensor, such as a CGM, that measures blood glucose levels and sends data to a computer; (2) an insulin delivery device, such as an insulin pump; and (3) a computer that calculates the amount of insulin needed and instructs the pump to deliver it. The goal is that the technology would require minimal human input, thus acting much like a healthy pancreas.

The need for improved type 1 diabetes management tools is underscored by the 1993 results of the NIDDK-supported landmark Diabetes Control and Complications Trial (DCCT). This trial and the ongoing follow-up study showed that intensive blood glucose control greatly reduced the development of eye, kidney, and nerve complications in people with type 1 diabetes, and even suggested that the increased mortality historically seen in those with type 1 diabetes can be reduced or eliminated through careful management of blood glucose. The ongoing follow-up study has continued to demonstrate long-term, improved health benefits of early and intensive glucose control. The intensive control regimen is difficult, however, because it requires that people frequently and carefully monitor blood glucose levels throughout the day with finger sticks or a CGM and determine how much insulin to

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administer. The calculation is a “best guess” that requires monitoring and modification, particularly when everyday experiences like eating, exercising, and illness can affect blood glucose levels in unexpected ways. Additionally, the DCCT showed that intensive control increased people’s immediate risk for hypoglycemia, or dangerously low blood glucose levels. With the difficulties of intensive glucose control and the threat of hypoglycemia, people with type 1 diabetes still rarely achieve recommended glucose levels to reduce the risk of complications. Thus, there is a critical need for better management tools, such as artificial pancreas technology that could help people achieve recommended blood glucose control while preventing hypoglycemia and reducing management burden.

## Early Artificial Pancreas Development

The idea of replacing the pancreas with an artificial one is not new. In fact, the first experimental artificial pancreas was developed in 1964. The device—about the size of a large backpack—measured blood glucose levels and delivered insulin intravenously and thus was not intended for everyday use in free-living conditions. Despite this early effort, the technologies it used to measure blood glucose levels and deliver insulin would take decades to develop for daily, home use. Additional progress was made in the mid- to late-1970s with several research groups publishing results of their closed-loop studies, as well as with the introduction of the first commercial artificial pancreas device intended to be used for inpatient hospital use—the Biostator. These big and bulky devices also used intravenous glucose sensing and insulin administration. While these advances were important for showing that this technology was feasible, much more research was needed to develop artificial pancreas technology that could be used in everyday life.

## Advances in the “Parts” of Artificial Pancreas Technology

Before the artificial pancreas as a whole could be improved, it was necessary to improve the individual parts. One key component of artificial pancreas technology is the insulin pump, which was developed with NIH and industry support. Insulin pumps are small devices that deliver insulin continuously in a small basal amount and provide larger boluses when needed, for example at mealtime. They provide an alternative to multiple injections of insulin and deliver insulin subcutaneously (*i.e.*, under the skin). The first commercially available insulin pump was introduced in 1978, and was bulky and not very user-friendly, relative to more recent devices. However, clinical studies of insulin pump therapy beginning in the late 1970s, and supported by the NIDDK and others, demonstrated that pumps were an effective alternative to multiple daily insulin injections, which helped promote their adoption into clinical practice. The development of insulin pumps made the DCCT possible, and the results of the DCCT demonstrating the importance of intensive blood glucose control stimulated future development of improved pumps.

Insulin pumps are widely used today and have improved over the years. For example, in 2013, the FDA approved a device, consisting of a pump linked to a sensor, that suspends the delivery of insulin when glucose levels reach a preset low threshold. This approach helps reduce the risk of hypoglycemia from excess insulin. Further research has led to newer devices that *predict*, based on trends in the sensor data, when this level will be reached and preemptively suspend insulin delivery. Such devices have been tested in NIDDK-supported studies and are being used in today’s artificial pancreas systems. Advances in insulin engineering, which has produced faster acting and longer duration forms to use in insulin pumps, have also been important to artificial pancreas development.

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Another critical component of artificial pancreas technology is a CGM, which provides a way to measure glucose levels every few minutes. For years, people with diabetes monitored their glucose levels with urine tests, which recognized high but not dangerously low glucose levels and reflected past, not current, glucose levels. By the 1980s, blood glucose meters had been developed and were widely used, enabling people to self-monitor blood glucose levels at home with finger sticks.

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 a device that people could use in their daily lives. Researchers supported by the NIDDK and others found another route that would be safe and practical for continuous monitoring: glucose levels in “interstitial” fluid in tissues under the skin reflected glucose levels in the blood. One aspect of this advance was the development of miniaturized electrodes to measure the reaction of glucose with an enzyme called glucose oxidase to assess glucose levels in the small fluid volumes present under the skin. A continuous monitor was first approved by the FDA in 1999. However, the glucose values obtained from this device could only be assessed retrospectively, not in real time. Further research led to FDA approval, in 2006, of next-generation continuous monitors that allowed real-time glucose sensing. Since then, CGMs have continued to improve, are used by some people with diabetes, and are part of today’s artificial pancreas systems.

With the advances in the two major parts of artificial pancreas systems, also needed was a way to link them together. Thus, at the same time, researchers were working on the mathematical part of artificial pancreas technology by developing algorithms so that a computer can calculate how much insulin is needed based on CGM readings and tell the insulin pump to deliver it. Many algorithms being tested

in some of today’s artificial pancreas devices, called “model predictive control algorithms,” have their roots in an NIDDK-supported 1979 study that evaluated the feasibility of using a mathematical model of glucose disappearance to estimate insulin sensitivity. Additionally, computers themselves have significantly advanced over the last few decades, becoming smaller, more portable, faster, and capable of advanced processing. These technological advancements laid the foundation for research to link together these individual technologies to develop next-generation artificial pancreas devices.

The NIDDK supported development of these components—and continues to support the next generation of these devices—through grant awards to small businesses, as well to academic institutions. Many of the businesses were created by academic investigators to work toward commercializing the new technologies. Often these NIDDK-supported small businesses became larger companies, or the technologies were sold to larger businesses toward bringing the technologies to market. These important investments in small businesses played a significant role in ensuring that these advances moved from the laboratory to the people who could benefit from them.

## **A New Era of Artificial Pancreas Research—Making the Whole Greater Than the Sum of Its Parts**

A new era of research began in the 2000s as these technologies were becoming available. A 2006 NIDDK-supported study conducted by researchers in industry and academia was the first to show the feasibility of simultaneously using a continuous glucose monitor for subcutaneous glucose sensing and a subcutaneous pump for insulin delivery in an artificial pancreas system in people with type 1 diabetes. This study propelled the field toward the advanced trials being conducted today.



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Since that time, there has been tremendous progress in developing artificial pancreas technologies and testing them in people, which has been supported, for example, by the NIDDK, JDRF, the Leona M. and Harry B. Helmsley Charitable Trust, and industry. The first small clinical trials, in the early 2010s, were conducted in hospital or clinical settings using laptops to control the artificial pancreas device and with constant monitoring by researchers and study staff, restricting participants' activity. The trials showed very promising results. For example, in 2010, results from the first randomized controlled trial showed that use of an artificial pancreas device reduced the risk of nighttime hypoglycemia in children and adolescents with type 1 diabetes compared to standard therapy. Two years later, NIDDK-supported studies showed that artificial pancreas technology could improve blood glucose levels without increasing hypoglycemia in adolescents and adults with type 1 diabetes.

The promising results from hospital-based trials, as well as the advent of portable smartphone technology to replace laptops, enabled the next step—moving to “transitional” outpatient settings, such as hotels, that more closely mimicked free-living conditions but still allowed the participants to be monitored closely by study staff. For example, in 2013, NIDDK-supported researchers working with adult participants who had type 1 diabetes showed that smartphone technology could be used to run a closed loop system. Another group of NIDDK-supported researchers tested a “bihormonal” artificial pancreas system that delivers two different pancreatic hormones—insulin to lower blood glucose levels and glucagon to increase them—with the hope of more closely mimicking the function of a healthy pancreas. They tested their wearable, automated device in adults staying at a hotel, and in adolescents at a diabetes camp. Results reported in 2014 showed that compared to usual care, participants had lower mean glucose levels and reduced episodes of hypoglycemia. In fact, the device allowed nearly all participants to achieve

recommended levels of blood glucose control. Armed with positive results from transitional settings, scientists took the next step: moving to at-home studies to replicate real-life conditions. The first studies tested overnight artificial pancreas use, as it is easier for the artificial pancreas to control blood glucose levels when it is not being challenged with daytime activities, like meals and exercise, that cause unpredictable blood glucose swings. In 2014, NIDDK-supported researchers studied adolescents with type 1 diabetes who participated in school and other activities during the day using standard diabetes management tools, and wore an artificial pancreas at home at night. Results showed that unsupervised, *i.e.*, not monitored continually by study staff, closed-loop control at night improved glucose control during the day and night, and reduced the number of episodes of nighttime hypoglycemia.

More recently, researchers have begun to test day and night artificial pancreas use under free-living, home-use conditions, for a short duration in small numbers of people who went about their daily lives (e.g., going to school or work) and had no restrictions on their diet and exercise. For example, in 2016, NIDDK-supported researchers showed that unsupervised day-and-night artificial pancreas use was feasible and safe in adolescents with type 1 diabetes. In 2017, NIDDK-supported researchers found that day-and-night use of a bihormonal artificial pancreas improved blood glucose control compared to conventional insulin pump therapy in adults. The positive results of these and other studies testing 24/7 closed-loop control at home under free-living conditions underscore the promise of this therapy for everyday use. Encouraged by this progress in moving from carefully controlled studies in hospitals to hotels to free-living conditions, researchers are now testing artificial pancreas technologies in even more challenging environments, like the extended vigorous outdoor exercise of snowboarding camp.

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## First FDA Approval of a Hybrid Artificial Pancreas Device

A key milestone in artificial pancreas technology development was achieved in 2016 with the publication of results of an industry-supported trial. It was the largest outpatient artificial pancreas study done to that date, including 124 people with type 1 diabetes ages 14 and older who used the device for 3 months. The study tested a “hybrid” system: although the device automatically adjusts insulin levels, it requires users to count and enter mealtime carbohydrates. Thus, it is not completely automated and still requires human input. The study showed that the hybrid artificial pancreas system was safe for use. Based on the results of the trial, in September 2016 the FDA announced that it approved the device for use in people 14 years of age and older with type 1 diabetes—the first commercial hybrid artificial pancreas to be FDA approved. The NIDDK supported early research that contributed to the development of the approved device, such as testing some initial versions of the different components and algorithms that preceded the currently approved device. To improve upon this approved device, the NIDDK is supporting research comparing the current computer algorithm used in the device to another algorithm that might provide better control.

## Collaborations Stimulate Progress

Critically important to the success of this effort have been partnerships that the NIDDK has forged with FDA, and voluntaries such as JDRF and the Leona M. and Harry B. Helmsley Charitable Trust, all of whom are working toward the same goal of making the technology available to people with type 1 diabetes. For example, the NIDDK, FDA, and JDRF have sponsored a series of scientific workshops that have brought together experts in the field to stimulate discussion of the current state of the art, technical challenges and possible solutions, safety issues, and next steps. Since 2007, the NIDDK

and FDA have also worked together on a federal Interagency Artificial Pancreas Working Group, which has been instrumental in promoting the field. NIDDK collaboration with JDRF and the Leona M. and Harry B. Helmsley Charitable Trust has also resulted in coordinated efforts with more efficient investment of resources and has greatly expedited progress. Many of the studies described above have also had support from these funding entities.

## Future Research Directions

The FDA approval of the hybrid artificial pancreas device is a critical milestone, moving the technology from a research setting to the marketplace. However, there are still limitations with the approved device. For example, it requires users to prick their fingers to determine blood glucose levels to calibrate the device’s glucose sensors. Other approved sensors, however, do not require this type of calibration and may be incorporated into future devices. Also, the device requires users to count carbohydrates and put that information into the system at mealtimes. Thus, the device is not completely automated and still places management burden on patients. Still needed are improved components of artificial pancreas systems, as well as research testing different systems so that people could have choices about which system may best suit their needs and lifestyle.

Toward these goals, the NIDDK continues its vigorous support of artificial pancreas research through grants to small businesses and academia. For example, the Institute is supporting four new clinical trials to test technologies in larger groups, with wider age ranges, over longer periods of time, and in largely unrestricted conditions. These trials are generating data to determine whether the technologies meet the safety and efficacy requirements for FDA approval of these systems. Research is also ongoing toward improving the “parts” of artificial pancreas technology, such as developing implantable glucose

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sensors and novel hormone formulations, which could help overcome some of the limitations of current systems toward making fully automated devices. Additionally, developing implantable components is important toward achieving the goal of giving people with diabetes freedom from having devices attached to their bodies and having to manage the devices. Because new technology will only benefit people if they can use it, research optimizing incorporation of artificial pancreas technologies into clinical care and enhancing their “usability” is essential, so that people are not overwhelmed with excessive data volume or complexity. This includes research on special populations—such as young children, people with more difficult-to-control diabetes or vision complications, pregnant women, and older adults—to ensure that all people with type 1 diabetes could use and benefit from this new technology.

This technology could also be beneficial beyond type 1 diabetes. Many people with type 2 diabetes manage their diabetes with insulin. Hypoglycemia in this population is a major cause of morbidity, and artificial pancreas technology may help people using insulin to manage their type 2 diabetes to avoid this dangerous complication while improving their blood glucose control. A recent study found that adults who used continuous glucose monitoring on a daily or near-daily basis for 6 months showed improved blood glucose control. Another study tested artificial pancreas technology in people with type 2 diabetes

who had not previously used insulin to treat their diabetes. This study found that participants spent more time in the target glucose range and less time in hyperglycemia. This small, short trial suggested that artificial pancreas use in people with type 2 diabetes could improve glucose levels, especially overnight, without increasing the risk of hypoglycemia. There is also potential for these devices to be used in hospital settings to control glycemia; lack of glycemic control is a major problem, even in people who do not have diabetes, but who have hyperglycemia due to trauma or a critical illness.

While the artificial pancreas represents near-term technology that could improve the health of people with type 1 diabetes, it is not a cure. Therefore, the NIDDK also supports research toward a biological cure for type 1 diabetes, such as developing therapies to replace pancreatic  $\beta$  cells that have been destroyed by the immune system.

With the significant progress to date and with additional research, it is expected that the FDA approval of the first hybrid artificial pancreas device is just the beginning of a new era of technologies that can improve the short- and long-term health of people with type 1 diabetes, while also reducing management burden. Artificial pancreases truly represent a life-changing advance for people with this chronic disease.

# PATIENT PROFILE

## Jadah: Paving the Path to Preventing Type 1 Diabetes



Jadah (right) and Travis

“All that matters to me is that I’m making a difference,” explains Jadah matter-of-factly when asked why she is part of type 1 diabetes research. Although she hasn’t been diagnosed with type 1 diabetes, 14-year-old Jadah is at high risk of developing clinical symptoms of the disease, such as high blood sugar (glucose) levels. With the goal of making a difference, she is participating in a clinical trial in the NIDDK’s Type 1 Diabetes TrialNet (TrialNet) to test a strategy for stopping the disease process at its earliest stage. People at this early stage have biological factors (autoantibodies) that characterize the beginning of the disease process and are at very high risk of developing clinical symptoms, but they still have normal blood sugar levels. Researchers are also developing therapies for individuals with diagnosed diabetes, which is marked by high blood sugar levels. Type 1 diabetes is an autoimmune disease in which a

**“All that matters to me is that I’m making a difference,” says Jadah, of her participation in type 1 diabetes research.**

person’s immune system destroys the cells that make insulin. People with the disease (or parents of children with the disease) must carefully monitor blood sugar levels and administer insulin. It is very difficult for people with type 1 diabetes to achieve a balance between too much sugar in the blood and too little. Too much sugar could lead to serious eye, nerve, and kidney complications; too little sugar could lead to confusion, loss of consciousness, and death. While a goal of type 1 diabetes research is a cure for people who have the disease, a way to prevent the disease could spare future generations from type 1 diabetes.

### The Benefits of Learning Type 1 Diabetes Risk

Type 1 diabetes has been part of Jadah’s family life since 2009, when her brother, Travis, was diagnosed. Because people with a first-degree relative with type 1 diabetes have a 15 times greater likelihood of developing the disease, scientists believe that Jadah and others like her could hold the clues for

uncovering how the disease develops and identifying a prevention strategy.

Research has revealed that before type 1 diabetes symptoms appear, the immune system produces specific autoantibodies—proteins that can be detected in the blood. TrialNet’s Pathway to Prevention study screens first- and second-degree relatives of people with type 1 diabetes for these autoantibodies. From the number of different autoantibodies in a person’s blood, they can determine that person’s risk of developing type 1 diabetes. As of January 2018, TrialNet researchers had screened over 160,000

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individuals. TrialNet offers yearly rescreening for children under 18 years of age, so a total of over 250,000 screenings have been conducted to date.

Jadah's mom, Susie, had first seen TrialNet information booths at fundraising walks held by the type 1 diabetes advocacy organization JDRF. Susie was amazed that researchers could determine if there's further risk of type 1 diabetes in her family. But she was also concerned: would she want to know if Jadah were at high risk?

Susie learned that there were several reasons to find out Jadah's risk status. People screened by TrialNet and found to be at high risk are eligible to be monitored for the appearance of more autoantibodies

and/or for an increase in their blood sugar levels, which

would indicate development of type 1 diabetes. TrialNet's tests are likely to detect progression to type 1 diabetes before the appearance of potentially serious clinical symptoms. For example, early detection decreases the likelihood of a life-threatening complication, called diabetic ketoacidosis (DKA), at diagnosis.

Travis had DKA when he was diagnosed, and Susie didn't want the same thing to happen to Jadah. Additionally, if Jadah were found to be at high risk, she could be eligible to participate in a TrialNet prevention trial. Susie realized she did want to know, feeling that "[it] is incredible that you could find out ahead of time if there's a [high] risk [of type 1 diabetes]." But she and Terry, Jadah's dad, felt strongly that it was Jadah's decision.

## From Reluctant Screener to Trial Participant

It wasn't learning about her risk for type 1 diabetes that concerned Jadah most—it was the blood draw needed for the test. "I just hated needles when I was

a kid. I mean, I was so scared of them," she recalls. While visiting Travis at a diabetes camp in 2011, Jadah reluctantly agreed to be screened. Although she did the blood draw, the experience was too much for her. "Right after that I just wanted to leave that camp without even saying goodbye to my brother," she remembers.

Not long after, Susie and Terry received a call from TrialNet telling them that Jadah was at high risk, but that another blood draw was needed to confirm the result. This time Jadah said no. Susie and Terry tried everything they could think of to change Jadah's mind, but she held her ground for 4 years. In the meantime, Susie was constantly worried, wondering if every time Jadah seemed sick she was really showing early signs of type 1 diabetes. Eventually, it was Jadah's

grandmother who changed her mind about the rescreening. "I just thought that

***"It's not like you are in a study. It's like you are hanging out with your friends," says Jadah of her experience in a TrialNet clinical trial.***

I should take her advice," says Jadah, "...I thought this was something that I could do for her, that she would want me to do."

In April 2015, Jadah went to her local University of Minnesota TrialNet site for her second screening and shortly after learned the result, which confirmed the earlier screening: she was at high risk for developing type 1 diabetes. Because she was at high risk for the disease, but had not yet developed it, that September Jadah was offered a unique opportunity to join a clinical trial testing a drug for prevention of type 1 diabetes.

Whether or not to enroll in the trial wasn't a difficult decision for Jadah. She had made friends with the staff at the University of Minnesota TrialNet site and enjoyed spending time with them. "I loved these nurses so much that I wanted to be in the study right away, just so I could be with these nurses," says Jadah. Susie shared her daughter's enthusiasm for the trial, and they enrolled her.

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## Taking Part in the Abatacept Prevention Trial

Jadah is participating in a trial testing the agent CTLA-4lg, also known as abatacept, for its ability to delay or prevent type 1 diabetes in people at high risk for the disease. In 2011, TrialNet investigators found that over a 2-year period, abatacept slowed disease progression for 6 to 9 months, compared to placebo, in people newly diagnosed with type 1 diabetes. This resulted in higher insulin production in the people who had been treated with abatacept. Moreover, this improvement persisted for 1 year after the drug was discontinued. These results suggested that abatacept could be used in combination with other agents for a possibly more robust and prolonged effect in people newly diagnosed with type 1 diabetes,

***“Being able to have the opportunity to be part of this [research] is amazing,” Susie remarks. “We want to stop type 1 diabetes in this generation, and we are excited to be a part of this important research.”***

and that it should be tested for its ability to prevent the disease in those at high risk. This led to the trial in which Jadah is participating.

Jadah's experience in the trial required her to make three visits to the University of Minnesota TrialNet site in the first 4 weeks, then one visit a month for 11 months. Each visit took about 2 hours, including a 30-minute infusion of the drug or a placebo, followed by 1 hour of observation to make sure there were no side effects or complications, like an allergic reaction. Jadah and Susie turned the visits into a bonding experience, going out to breakfast or lunch afterwards before returning Jadah to school.

## A Bond Inspires the Future

Now that Jadah has finished her treatment course, she only returns to TrialNet for blood tests every 3 months and has her blood sugar levels tested every 6 months. She could even do the blood tests at her local clinic, but Jadah quickly said no to that. “Even if you're in there for 5 minutes,” she explains, “it's worth it because they [the nurses at the University of Minnesota TrialNet site] take their

time and they make you feel comfortable... It's not like you are in a study. It's like you are hanging out with your friends.” The TrialNet staff have even inspired her to work toward becoming a pediatrician in the future, as long as she can still have time to visit the lake, camp, and ski.

As for the possibility that she might develop type 1 diabetes, Jadah says, “I know that, even if I do get diagnosed, I'll still have my family, and they're going to know what to do. I'm going to know what to do because I see Travis doing it.”

Susie is so grateful that Jadah has had this wonderful experience and what she views as the chance to

be part of changing history. “Being able to have the opportunity to be part of

this [research] is amazing,” Susie remarks. “We want to stop type 1 diabetes in this generation, and we are excited to be a part of this important research.”

For now, Jadah and her family will continue to raise funds for type 1 diabetes research—with JDRF walks and, for Susie this past summer, through JDRF's Ride to Cure Diabetes—while they eagerly await the results of the abatacept prevention trial. Does Jadah wonder whether she received the drug or placebo? “Nope, I don't wonder at all,” she answers. “I just want to find a cure for all the other people out there who have type 1 diabetes.” Jadah is ready to participate again, if needed, in another prevention trial or in a trial for people who are newly diagnosed, if she develops type 1 diabetes.

Jadah and her family encourage anyone who can to get screened by TrialNet and to consider participating in research. “The sooner people get involved, the better we are going to be in the future,” says Susie. “We can't wait... All we need right now is participants [in clinical trials]. If we get participants, we'll get a prevention and a cure.”

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## Kinyatta: Dedicated to the Search for Better Health for People with Diabetes



**Kinyatta**

Kinyatta is, in her own words, “a helper.” That helping spirit shines through in her work as an instructional assistant co-teaching the first grade. It also shows in her long-standing participation—for 15 years and counting—in the SEARCH for Diabetes in Youth study, a unique research study committed to improving the quality of life of children and young adults with diabetes.

### Learning by Example

Kinyatta's participation in SEARCH is a gift to medical research and all those with diabetes, but it is just one way she works to help children. Kinyatta has always wanted to be an educator. To find the reason, you need look no further than Kinyatta's own first-grade teacher. “She was awesome,” Kinyatta says. One particularly memorable example involved a classroom hamster named Fluffy. In first grade,

Kinyatta loved Fluffy so much that she would cry when she had to go home and leave Fluffy behind. Then, one day, her teacher arrived at her home, with a hamster of her very own for Kinyatta to keep. Referring to that generous gift, Kinyatta says, “Those are the kind of things that I do for my kids.” Whether it is listening to and supporting the children, buying them a snack if they are hungry, or making sure they have the right clothes for a school performance, Kinyatta tries to be there for her students. “I just want to be that teacher that kids can go to with their problems. If they're having a bad day, they can talk to me. That's just the kind of person I am.”

### Living with Type 2 Diabetes

Kinyatta was diagnosed with type 2 diabetes when she was 12 years old. She had gained weight between third and sixth grades, and her mother, a nurse, was concerned. She brought up the issue to Kinyatta's doctor, and a blood test showed that Kinyatta's blood sugar (glucose) level was higher than normal. In type 2 diabetes, the body becomes resistant to the action of insulin, a hormone that controls blood sugar levels, and the pancreatic cells that produce insulin also don't function normally, causing blood sugar levels to rise.

Although her family had a history of type 1 diabetes, Kinyatta didn't know much about type 2 diabetes when she was diagnosed. Her doctors gave her basic information about the disease, showed her how to monitor her blood sugar level with a blood glucose meter, and taught her how to recognize the signs of high and low blood sugar. They also recommended that she manage her weight through diet and exercise. Kinyatta took nutrition classes

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that helped her make changes to her diet, such as controlling her portions and making healthy choices about what to eat.

Kinyatta had already picked up a lot of unhealthy eating habits, so changing what and how much she ate wasn't easy. Her family's support helped. They changed their diet as well, and joined Kinyatta in her efforts to get more exercise. She and her mother would walk every day. A few of her teachers knew what she was going through and supported her, as well.

Still, having type 2 diabetes added an extra complication to the already challenging transition to middle school. Other kids noticed that Kinyatta ate differently than they did, and some asked why she didn't eat candy, for example. Kinyatta didn't want to tell

them she had type 2 diabetes, so she would sometimes try to deflect the questions about her

choice of foods, saying it was just what she liked to eat. "It was little things like that, that I would have to fight off," Kinyatta says. "I've never been a self-conscious person, but...you know, as a child that stuff starts to get to you."

But Kinyatta's efforts paid off: she lost a lot of excess weight over the next few years. She also stayed active throughout high school by participating in color guard and winter guard, marching with the school band, and taking dance classes. "I always tried to just stay healthy," Kinyatta remembers.

## SEARCHing for Better Health

About a year after she was diagnosed, Kinyatta was asked to join a diabetes research study called the SEARCH for Diabetes in Youth.

SEARCH is currently the largest, most diverse study of diabetes among U.S. youth ever conducted. The

study is funded by the Centers for Disease Control and Prevention and the NIDDK, and SEARCH investigators seek to answer questions such as: how many children have type 1 or type 2 diabetes? How does that number change over time? What complications are these children experiencing as they age? How does having diabetes affect their lives? More than 27,000 volunteers with either type 1 or type 2 diabetes have participated in SEARCH, providing the information to help answer these questions.

Kinyatta agreed to become one of them.

Kinyatta says that she always feels well informed during her SEARCH visits. First, SEARCH coordinators contact her to begin the process. She is then sent

paperwork or surveys to fill out beforehand to help expedite her visit. Once she arrives at the

appointment, the SEARCH staff go over the visit with her in detail, describing what questions they are investigating, what tests they will run, and how they will use the results. The visit can take most of the day and can involve a variety of questionnaires and tests depending on the particular information the study is collecting at that time. For Kinyatta, some of those tests have included having her heart monitored, having her eyes examined, screening for depression, and taking part in a sleep study.

Being in SEARCH has also been educational in several ways. The SEARCH staff share Kinyatta's test results with her, giving her information about her own health. She's also learned about type 2 diabetes and strategies to manage the disease. "I'm really thankful for [the study staff], because I wouldn't know what I know now about diabetes if it wasn't for SEARCH."

***When Kinyatta made diet and lifestyle changes after her diagnosis, her family's support helped. They changed their diet as well and joined Kinyatta in her efforts to get more exercise.***



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Since the study began in 2000, SEARCH investigators have used data provided by volunteers like Kinyatta to assess not only how widespread diabetes is in the population, but also clinical and public health implications of the disease. As a result, SEARCH has provided a wealth of information about the effects of diabetes on children and young adults, including data on the total number of youth with diabetes in the United States, the number of new cases per year, and trends in diabetes diagnosis.

Findings from SEARCH are also providing data on the complications youth with diabetes are experiencing and how diabetes

affects their quality of life. For instance, before SEARCH it was unclear how soon signs of various diabetic complications

appear in children and young adults. All SEARCH participants were under 20 years of age when they were diagnosed, and the tests that they have participated in at SEARCH study visits have provided sobering news about diabetes complications in those who develop type 1 or type 2 diabetes early in life. A recent SEARCH analysis estimated that by about age 21, approximately 32 percent of SEARCH participants with type 1 diabetes and 72 percent of participants with type 2 diabetes would have at least one complication from diabetes or would be at high risk for a complication such as kidney, heart, nerve, or eye disease. These findings suggest that screening for risk factors and early monitoring of youth with diabetes could result in prevention or earlier diagnosis and treatment of complications. This could ultimately contribute to the goal of better health over the lifespan.

SEARCH is planned to continue at least through 2020. Such long-term studies offer valuable insights

into health trends over time, and they depend upon volunteers willing to participate for many years, as Kinyatta has. Kinyatta has no plans to quit, either. She says, “to see all the progress that I’ve helped them make is amazing to me.” She’s made strong connections with the SEARCH study staff, and they are often the first to send her a birthday card every year. “It’s just been a good experience,” Kinyatta says.

## Following Her Dreams

Kinyatta says that her diabetes status has not changed much since she was diagnosed. Her

HbA1c (a measure of her blood sugar level over time) has remained steady, and her doctors’ recommendations have been to continue

exercising and eating a healthy diet. Kinyatta takes this advice to heart. She feels that making healthy food choices and staying active helps keep her diabetes under control, which lets her avoid the need for diabetes medications and reduces her chances of having diabetic complications later in life.

Maintaining a healthy lifestyle can still be challenging, and Kinyatta admits that she doesn’t always do as well at it as she’d like. She’ll go through “health kicks” and cravings for unhealthy food the same as anyone else,

but through it all she tries to focus on the long-term goal: staying active and being mindful of what she eats. She goes to the gym and

takes walks, aiming to maintain her weight, and she continues to put those childhood nutrition classes to good use. When it comes to making food choices, she says, “I’m really good at saying, ‘Well, if I had this, I don’t need this.’” Such trade-offs—a not-so-healthy breakfast in the morning, for instance, and then a salad for lunch—help her maintain balance in her diet.

***“I love the connections that I’ve made with the people that work for SEARCH,” Kinyatta says of the research study staff. “It’s just been a good experience.”***

***“That’s the one thing that I’ve gotten out of my life: you can’t let people deter you from your dreams.”***

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Kinyatta still doesn't share the knowledge that she has diabetes widely, and some people she's known her whole life still haven't guessed. Kinyatta thinks it's because many people mistakenly believe that all people who have type 2 diabetes use insulin. But now Kinyatta is more likely to be forthcoming about her own experiences, pointing out that even those not on insulin therapy can have type 2 diabetes.

However, Kinyatta does not let having type 2 diabetes define her. She considers herself to have a normal life. She loves to travel and particularly loves spending time on the water. "I'm very adventurous. I just don't let anything hold me back from trying anything new."

Kinyatta carries that sense of adventure into her career, as well. In addition to her classroom teaching, she is studying for her master's degree in counselor education, so that she can become a school counselor. Her ultimate career goal is to own her own business or run her own school, where she can pursue

her passion for helping inner-city kids. She'd like to focus on teaching writing, reading comprehension, and literature, "because those were my biggest struggles as a child."

She also encourages others to do what they can for their health and to make the most of their lives. No matter what, Kinyatta says, don't give up on yourself. "I never saw myself graduating college: I did it. I never saw myself graduating with honors, and I did. I never thought about getting a master's degree—let alone a Ph.D.—and here I am working on my master's, and I have professors encouraging me to get a Ph.D."

The student has become the teacher, and if there's one thing that Kinyatta wants to pass on, to her students or to others with type 2 diabetes, it's this: do what you're capable of doing, no matter what others say. "That's the one thing that I've gotten out of my life: you can't let people deter you from your dreams."