This is a chapter from the NIDDK’s Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK’s mission and is available at: www.niddk.nih.gov/about-niddk стратегические планы и отчеты niddk-Recent-Advances-Emerging-Opportunities
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NIDDK Recent Advances & Emerging Opportunities 2024
In research described in this chapter, scientists discovered a novel way the gut microbiome signals to the brain to influence motivation to exercise in mice. As depicted above (from left to right), the gut microbiome’s production of metabolites—specifically fatty acid amides—stimulates a subset of gut sensory neurons (labeled here “CB1+ Trpv1+” to indicate a requirement for the proteins CB1 and TRPV1 on these neurons). These neurons signal to a specific part of the brain responsible for motivation (the striatum), reducing production of the protein monoamine oxidase (MAO). Reduction of MAO leads to increased levels of dopamine, a key molecule in the brain that—among other functions—promotes the feeling of reward. In mice, the increased dopamine resulted in enhanced capability for exercise. Additional research is necessary to determine whether a similar gut-brain connection exists in humans, but this research could spur exciting new strategies to modify behaviors, such as motivation to exercise, and help people live healthier lives.

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic, translational, and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, thyroid dysfunction, 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.

Diabetes is a debilitating disease that affects an estimated 38.4 million people in the United States—11.6 percent of the total population—and is the eighth leading cause of death.\(^1\) Although overall rates of diabetes-related complications have declined substantially in recent years, disease burden remains significant, as the number of people with diabetes is still very high.\(^2\) 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 costs of diagnosed diabetes in the United States in 2022—including costs of medical care, disability, and premature death—was $413 billion.\(^3\) Effective therapy can prevent or delay diabetic complications, but 23 percent of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.\(^1\)

Diabetes affects an estimated 38.4 million people in the United States—over 11 percent of the population. Another 97 million U.S. adults have “prediabetes,” which puts them at elevated risk of developing type 2 diabetes.

Diabetes is characterized by the body’s inability to produce and/or respond appropriately to insulin, a hormone that is necessary for cells to absorb and use glucose (sugar) as a 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, type 2 diabetes, and gestational diabetes, a form of diabetes that develops during pregnancy but in many cases resolves after pregnancy.

Diabetes increases the risk for complications such as vision loss, kidney failure, and amputation, as well as doubling the risk for heart disease, many forms of cancer, some forms of dementia, and many other common diseases.

Type 1 diabetes affects approximately 5.7 percent of adults diagnosed with diabetes and the majority of children and youth diagnosed with diabetes.\(^1\) 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 that destroys insulin-producing β (beta) cells in the pancreas. Thus, people with type 1 diabetes require lifelong insulin administration to regulate their blood glucose levels.

NIDDK’s landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that

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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. These results underscore the importance of developing novel technologies that can improve blood glucose management with less burden, such as new methods to improve blood glucose monitoring and insulin delivery. NIDDK has supported pivotal research that contributed to the development or testing of multiple U.S. Food and Drug Administration (FDA)-approved diabetes management technologies, including artificial pancreas devices that automatically link glucose monitoring and insulin delivery. Scientists are also working to further develop and enhance β-cell replacement therapies, such as islet transplantation, that can eliminate the need for insulin injections, toward the ultimate goal of curing type 1 diabetes.

Type 2 diabetes is the most common form of the disease. The risk for developing type 2 diabetes is associated with many factors, including older age, obesity, family history of diabetes, impaired glucose metabolism, and physical inactivity. The percentage of adults with diagnosed diabetes in the United States is highest among racial and ethnic minority populations, including American Indians and Alaska Natives, non-Hispanic Black people, and people of Hispanic origin. Gestational diabetes is also an important risk factor: people who develop gestational diabetes during pregnancy are at increased risk of developing type 2 diabetes in the future.

In people with type 2 diabetes, their muscle, fat, and liver cells do not properly respond to insulin. Gradually, the pancreatic β cells lose their ability to secrete enough insulin, resulting in elevated and abnormal blood glucose levels. Treatment approaches for managing glucose levels include lifestyle modification (i.e., diet and exercise) and oral and injected medications, with insulin often required as the disease progresses. Also, an estimated 97.6 million U.S. adults have prediabetes, in which blood glucose levels are higher than normal but not as high as in diabetes. This population is at elevated risk of developing type 2 diabetes.

Type 2 diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects youth from racial and ethnic minority populations in the United States. NIDDK-supported research has shown that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because those with early disease onset are at especially high risk for developing complications. In addition, increasing rates of type 2 diabetes in youth and adolescents may lead to more people entering pregnancy with diabetes, and diabetes during pregnancy—either gestational diabetes or pre-existing type 2 diabetes—is associated with an increased risk for negative effects on the fetus. Also, diabetes during pregnancy is associated with an increased risk of blood glucose abnormalities in offspring. Thus, the rising rates of diabetes and prediabetes could contribute to a cycle of ever-growing diabetes rates, in addition to increasing risks for pregnancy complications.

NIDDK-supported research contributed to development and testing of new diabetes management technologies, including artificial pancreas devices that automatically link glucose monitoring to insulin delivery.

The most common forms of diabetes, type 1 and type 2, are associated with variations in multiple genes. Some rare forms of diabetes, called monogenic diabetes, result from mutations in a single gene. There are also unusual forms of diabetes, called “atypical diabetes,” that differ from known types. People with atypical diabetes may be diagnosed with and treated for type 1 or type 2 diabetes, but not have a history or signs consistent with their diagnosis. It is critical to study various types of diabetes, including discovering and defining rare and atypical forms of diabetes, to move toward better diagnoses, improved treatments, and potential prevention of these diseases.

NIDDK also supports 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 its mission; such research ultimately will spur the design of potential new intervention strategies. In parallel, based on knowledge from past research investments, NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.
**TRACKING TRENDS IN DIABETES**

**Study Shows That Diabetes in Young People Under the Age of 20 Continues to Rise:** Recent findings from the SEARCH for Diabetes in Youth study (SEARCH) show that the number of young people being diagnosed with diabetes in the United States is rising, with the biggest increases observed among racial and ethnic minority youth. These findings emphasize the importance of identifying ways to prevent diabetes onset in youth, as increasing incidence of type 1 diabetes and type 2 diabetes in young people will result in a growing population of young adults at risk for early complications of diabetes, such as diabetic kidney disease, eye disease, nerve disease, and high blood pressure.

SEARCH—supported by NIDDK, the Centers for Disease Control and Prevention, and the Special Statutory Funding Program for Type 1 Diabetes Research—is a multi-center study that launched in 2000 with the goal to learn more about diabetes and its complications in children and young adults in the United States. Previous findings from SEARCH reported an alarming increase in the incidence of type 1 and type 2 diabetes in children and young people from 2002 to 2015. These recent data extend the previous analyses for an additional 3 years to 2018. The study found that, for U.S. children and young adults, new diagnoses of type 1 diabetes increased by approximately 2 percent every year, while new cases of type 2 diabetes increased by more than 5 percent every year. The rates of increase in both type 1 and type 2 diabetes were higher among American Indian, Asian or Pacific Islander, Hispanic, and non-Hispanic Black populations, compared to the non-Hispanic White population. The study also found a peak in type 1 diabetes diagnoses at 10 years of age and in type 2 diabetes at 16 years of age, providing critical information about a time window when interventions to reduce the diabetes risk in youth might be most effective.

The rise in youth-onset type 2 diabetes could be a consequence of the increasing rates of obesity in youth—a known risk factor for type 2 diabetes—and improved diagnosis and screening. Further research is needed to identify more effective ways to prevent and/or delay onset of diabetes in youth and to address the higher burden of diabetes in children and young people from racial and ethnic minority groups.


**Women With Type 2 Diabetes Face a Higher Burden of Risk Factors Compared to Men:** Researchers have demonstrated that women, particularly younger women, with type 2 diabetes continue to experience a greater burden of cardiometabolic and socioeconomic risk factors than men with the disease. Type 2 diabetes triples the risk of death from cardiovascular disease in women, while it doubles the risk among men with type 2 diabetes. This disparity has been previously documented. However, a better understanding of the factors that contribute to worse outcomes among women is critical to optimize care strategies, effectively reduce risks, and fill treatment gaps for women with type 2 diabetes.

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) was a randomized controlled trial comparing four blood glucose (sugar)-lowering medications (sulfonylurea, dipeptidyl peptidase 4 inhibitor, a glucagon-like receptor agonist, or insulin) on metabolic outcomes in adult men and women with type 2 diabetes who were already taking the drug metformin. While GRADE previously demonstrated that two diabetes drugs (liraglutide or insulin glargine) outperformed others when combined with metformin, the participant cohort continues to provide critical information to understand type 2 diabetes. In a secondary study, researchers sought to examine sex differences in adverse risk factors within the GRADE cohort, which included more than 5,000 individuals from diverse racial and ethnic backgrounds, with more than one-third being women. This analysis showed that, compared to men with similar blood glucose control and duration of type 2 diabetes, women with type 2 diabetes in the GRADE study were younger, yet had more adverse risk factors for cardiovascular disease such as higher body mass index (a measure of weight relative to height), greater prevalence of severe obesity, and higher overall cholesterol levels. Moreover, women were less likely than men to receive treatment for high cholesterol. Women with high blood pressure were equally as likely as men to achieve their target blood pressure; however, women were less likely to receive pharmacological...
treatment for this condition. When the researchers assessed non-traditional, socioeconomic risk factors, they found that women in this cohort were more likely than men to be divorced, separated, or widowed, and they had fewer years of education and lower incomes. In addition, women were more likely than men to take antidepressant medication.

Researchers have demonstrated that women with type 2 diabetes continue to experience a greater burden of cardiometabolic and socioeconomic risk factors than men do.

While decades of research have documented that women with type 2 diabetes are less likely to receive evidence-based care for cardiometabolic risk factor management, the results from this study indicate that disparities continue to persist. In addition, these results demonstrate that substantial differences in adverse socioeconomic factors between women and men remain apparent. Taken together, there is a pressing need to optimize health care strategies to reduce health disparities and fill treatment gaps for women.

Researchers used machine learning analysis to identify panels of biological markers that can predict development of early stages of type 1 diabetes months in advance.

The Environmental Determinants of Diabetes in the Young (TEDDY) study—a long-term study following children at high risk of developing type 1 diabetes—seeks to identify what factors trigger or protect against the disease. TEDDY researchers analyzed samples from hundreds of participants and identified protein biomarkers that predict the various stages of type 1 diabetes. Many of these proteins have functions previously implicated in type 1 diabetes development, such as immune processes, metabolism, digestion, and disposal of damaged cells such as β cells. Eighty-three of these proteins were validated as accurate biomarkers of islet autoimmunity and type 1 diabetes development. Further analysis using innovative machine learning tools identified how subsets of these proteins, when measured together, could predict the development of islet autoimmunity and type 1 diabetes diagnosis up to 6 months in advance. Though the accuracy of this prediction strategy needs to be tested in larger and more diverse groups of people, it could lead to improved methods to detect islet autoimmunity before onset and to determine who is likely to progress to type 1 diabetes. Such information would help doctors monitor changes in people’s health and inform prevention strategies. Additionally, the identified biomarkers highlighted specific biological pathways involved in disease development, providing new clues to what causes type 1 diabetes and how it may be prevented or treated.

Identifying Biomarkers to Predict Type 1 Diabetes:
Analyses of thousands of blood samples from children at high genetic risk of developing type 1 diabetes have identified proteins that can predict early stages of the disease. In type 1 diabetes, the immune system launches a misguided attack, called islet autoimmunity, on the insulin-producing β (beta) cells in the pancreatic islets. Islet autoimmunity marks an early stage of type 1 diabetes that occurs prior to the appearance of other symptoms such as high blood glucose (sugar) levels. In many cases, islet autoimmunity progresses to destruction of β cells, leading to type 1 diabetes symptoms and diagnosis. While islet autoimmunity can be detected via the presence of autoantibodies in the blood, there is currently no way to know if or when islet autoimmunity will develop or if an individual will transition from autoimmunity to type 1 diabetes. Therefore, biological markers (biomarkers) that predict development of islet autoimmunity and/or the onset of type 1 diabetes symptoms are highly needed.


NIDDK Recent Advances & Emerging Opportunities 2024: Diabetes, Endocrinology, and Metabolic Diseases
not delay type 1 diabetes diagnosis. Previous research in people newly diagnosed with type 1 diabetes found that abatacept helped maintain insulin production, possibly by reducing the activation of specific kinds of immune cells and interrupting the misdirected autoimmune attack on β cells. Based on these results, researchers from the Type 1 Diabetes TrialNet tested whether abatacept could delay or prevent progression of the disease at earlier stages. They enrolled 212 men, women, and children ages 6 to 45 years who were relatives of people with type 1 diabetes and had “stage 1” type 1 diabetes. Those with stage 1 diabetes have two or more autoantibodies that indicate early stages of the autoimmune attack but have no clinical symptoms of the disease. Stage 1 eventually progresses to abnormal blood glucose (sugar) levels (stage 2) and then to clinical diagnosis of type 1 diabetes (stage 3).

Trial participants were randomly assigned to receive either intravenous infusions of abatacept or a placebo over 12 months. Scientists monitored the participants’ insulin production, ability to maintain healthy blood glucose levels, and development of additional autoantibodies for signs of type 1 diabetes progression. This 1-year course of abatacept treatment did not significantly prevent progression from stage 1 to stage 2 type 1 diabetes, nor did it delay or prevent clinical diagnosis of type 1 diabetes compared to placebo. However, participants who received abatacept showed immune cell changes indicative of an altered autoimmune response and had improved β-cell function and insulin secretion compared to those who received placebo. These effects were not permanent and were lost once the drug was discontinued.

These results provide important new data about the mechanisms and timing of type 1 diabetes progression. Further research is needed to determine if abatacept’s effects on the immune system can help modify type 1 diabetes progression at a different disease stage, in longer treatment courses, or in combination with another therapy.


**Clinical trials testing artificial pancreas technologies for managing type 1 diabetes in children and adults have reported positive results, with one leading to the approval of a new commercial device.**

In the second trial, scientists studied a different artificial pancreas device, Control-IQ, in very young children—a particularly challenging population when it comes to blood glucose control. Previous NIDDK-supported clinical trials led to FDA approval of the Control-IQ device in people ages 6 and older, so this new trial focused on younger children to provide data for FDA to consider expanding the age range for the device. The trial enrolled 102 female and male participants ages 2 to 5 years and randomly assigned them to either the artificial pancreas group or the standard care
control group. Participants in the control group used a continuous glucose monitor and their pre-study method of insulin delivery—either insulin injections or an insulin pump. During the 13-week trial, participants in the artificial pancreas group spent more time, an increase of about 3 hours per day, with their blood glucose levels in the recommended target range compared to the standard care group. The greatest difference in blood glucose control was seen at nighttime, between 10 p.m. and 6 a.m., with children in the artificial pancreas group spending 18 percent more time within the normal blood glucose range. This is important because nighttime control is especially challenging to maintain in children with type 1 diabetes. Interestingly, the study took place during the COVID-19 pandemic, so most of the trial visits were conducted virtually. Because telemedicine was successfully used to teach families how to use the artificial pancreas device, the study suggests that this technology could be made available to people in areas without nearby specialty care.

Long-term NIDDK support has been instrumental in the development and clinical testing of both devices and has culminated in new commercial technologies. Improved type 1 diabetes management technologies could help people achieve recommended blood glucose levels with less burden, toward improving their short- and long-term health.


STUDYING TYPE 2 DIABETES AND ITS COMPLICATIONS

Providing Additional Lifestyle Intervention Based on Initial Progress Can Improve Weight Loss to Prevent Diabetes: New data suggest that behavioral weight-loss programs that are customized based on the individual’s progress, as opposed to a one-size-fits-all intervention, can improve weight loss results and may help reduce the risk of diabetes more effectively. The Diabetes Prevention Program (DPP), a landmark clinical trial for type 2 diabetes prevention, has previously shown that lifestyle modifications aimed at losing 7 percent of body weight can prevent or delay diabetes in people who are at high risk for developing the disease. However, the lifestyle modification did not result in weight loss for all participants, suggesting that there is an opportunity for a better-tailored diabetes prevention approach based on the individual. In this study, researchers sought to determine whether an additional intervention early in a lifestyle modification program would help people who were not losing weight. Adapted from the DPP, Group Lifestyle Balance (GLB) is a series of group-based sessions that provides education, encouragement, and tools for weight loss through lifestyle changes such as healthy eating and physical activity. All study participants were at high risk for developing diabetes and received GLB for a month. After an initial assessment, people who achieved less than 2.5 percent weight loss after 1 month received GLB+, an adaptive program to provide additional resources and support. Those who did achieve more than 2.5 percent weight loss continued to receive GLB. After following the participants for another 3 months, they found that providing the additional support enabled the GLB+ group to experience significant weight loss, as well as reductions in blood glucose (sugar) levels, although the average weight loss of the GLB group was greater. For both the GLB and GLB+ groups, progress at week 5 predicted their weight loss results at month 4, suggesting that the first month is a critical time window for longer-term weight loss success. Because both groups were predominantly White people and the GLB+ group was 81 percent women, additional research will be necessary to determine whether these results will translate to other populations as well.

These findings come at a time when there is an urgent need for more effective diabetes treatment and prevention strategies, and the science of personalized medicine is increasingly guiding decisions in clinical practice. Considering data from DPP showed that diabetes risk decreases by 10 percent with every percentage point of weight loss achieved, even modest weight loss can help reduce diabetes risk. It may be clinically beneficial to assess weight loss following 1 month of intervention and, when needed, provide an additional, adaptive intervention to help improve weight loss and blood glucose levels.

Novel Liver Organoid Technology Provides Insights About Fatty Liver Disease and Type 2 Diabetes:
Researchers used novel technology to develop mini-livers, or organoids, to gain new understanding about how a genetic variant plays a context-dependent role in fatty liver disease with or without type 2 diabetes. Nonalcoholic fatty liver disease (NAFLD), in which excess fat builds up in the liver, can lead to liver inflammation and damage, and result in a more aggressive disease called nonalcoholic steatohepatitis (NASH). NASH can progress to scarring of the liver, cancer, and liver failure. Many people with NAFLD, however, do not develop NASH, suggesting additional factors, like certain genetic variants and the presence of conditions like type 2 diabetes, might influence susceptibility to severe liver disease. Identification of these factors and how they affect disease progression could inform personalized prevention and treatment strategies.

In new research, scientists used cutting-edge technology to grow liver organoids modeling NAFLD/NASH from induced pluripotent stem cells generated from 24 female and male donors. They used these organoids to examine genetic contributors to NAFLD/NASH, finding that a variant of the glucokinase regulatory protein (GCKR) gene was associated with fat accumulation. Other studies have implicated GCKR in NAFLD/NASH, although its role has been unclear. Building on this finding, the scientists examined clinical data from over 1,000 people with NASH—mostly middle-aged White women with obesity. They were surprised to discover that the presence of the GCKR variant had differing effects on liver health. The presence of the GCKR variant was protective of liver function when a person's hemoglobin A1c (HbA1c; a measure of average blood glucose [sugar]) level was in a non-diabetic range. In contrast, the variant's presence was harmful when HbA1c levels were in a diabetic range. These observations suggest that HbA1c levels may be used to help predict the severity of liver disease progression in people with the GCKR variant—toward developing more personalized medicine approaches. To study the connection between NAFLD and diabetes further, they treated the NAFLD/NASH liver organoids with metformin—the first-line drug for people with type 2 diabetes—and found that metformin may exacerbate liver disease in the presence of the GCKR variant. However, treating the organoids with different drugs appeared to stabilize the organoids’ function, suggesting that people carrying the variant could benefit from alternate diabetes treatments to protect liver health.

These observations—made by integrating data from novel personalized liver organoid analyses with clinical data—give new understanding of how a genetic variant contributes to liver disease severity in people with and without type 2 diabetes. Such insights represent a significant step forward toward identifying people who are at higher risk of developing severe liver disease and informing personalized therapies to protect their liver health.


INVESTIGATING ISLET BIOLOGY

How Eating and Fasting Regulate Insulin: Scientists discovered that eating and fasting prompt cells in mice to ramp up or tamp down insulin secretion by changing the activity of various genes, and that similar insulin adjustments in human cells may be affected by type 2 diabetes, with potential implications for future therapy. Insulin-producing β (beta) cells, which reside in clusters called islets in the pancreas, release more insulin when needed for the body to use nutrients such as glucose (sugar) from food, and less insulin in periods of fasting. This regulation of insulin secretion is critical, as insufficient insulin can result in high blood glucose levels characteristic of diabetes, while excess insulin can lead to dangerously low blood glucose. However, it was not known how islet cells adapt their insulin secretion to nutrient conditions. To investigate this, scientists explored whether these insulin adjustments may result from changes in gene activity and changes to the epigenome, which includes proteins that interact with and package genes along the genome. One of the ways cells can influence gene activity is by chemically modifying these proteins.

The researchers began by analyzing insulin secretion, genes, and the epigenome from islets of mice that had been fed compared to those that had been fasted. They observed higher insulin secretion in islets from fed mice within just a few hours after providing the food. They then identified numerous genes that differed in activity between islets of fed and fasted mice, including genes with roles in nutrient sensing and metabolism, which may help link insulin secretion to feeding. Additionally, feeding increased chemical modifications to epigenomic proteins, consistent with the increased gene activity. Investigating further, they
discovered that a different protein, called Lsd1, has a key role in changing epigenomic modifications and gene activity in β cells in response to nutrient status, leading to reduced insulin secretion during fasting. Finally, the researchers discovered that Lsd1 similarly affects insulin secretion and gene activity in human islets, acting at multiple sites across the genome—including sites where type 2 diabetes genetic variants have been found. The researchers suggest that these diabetes-associated variants might affect nutrient-based regulation of gene activity and resulting insulin secretion. 

This study sheds light on how β cells adapt insulin secretion to the body’s needs, and how type 2 diabetes may disrupt this process. Future research on this pathway of insulin regulation may lead to new approaches for diabetes treatment.


UNDERSTANDING EXERCISE

What Gives Exercise Its Beneficial Effects: Researchers working with mice have identified molecular links between exercise and some of its beneficial effects. Exercise does more than make muscles stronger: it comes with a host of metabolic and psychological benefits. Understanding the mechanisms through which exercise improves health might help us to get more from exercise, or even to obtain some of its health benefits in other ways, without working out. In a new study, scientists considered the possibility that exercise might induce cells in some parts of the body to secrete more or less of various proteins that play a key role in regulating metabolic health. Secreting such proteins into the bloodstream can enable signaling between cells in different parts of the body to affect health.

Accordingly, they developed a method to track changes in protein secretion from 21 different cell types in mice and found that exercise caused changes in the cells’ secretion of numerous proteins into the blood. Among these was a significant increase in the secretion by liver cells of CES2A and CES2C, two closely related proteins called carboxylesterases. To determine whether secreted CES2 proteins play an important role in mediating the effects of exercise, they developed strains of mice with liver cells that secrete CES2A or CES2C whether or not the mice exercise. Both forms of CES2 protein partially protected these mice from the effects of an unhealthy diet that causes weight gain and would otherwise have resulted in type 2 diabetes. The mice that secreted more CES2 from their liver cells gained less weight, and they did not develop signs of diabetes but instead had relatively normal glucose (sugar) levels and remained more responsive to insulin. Secretion of the proteins did not affect weight gain or insulin sensitivity in mice fed a healthier diet, but those secreting CES2C were able to run faster and exercise longer without prior training than mice secreting CES2A or an unrelated control protein. These findings suggest that both CES2 proteins have a role in helping produce some of the beneficial metabolic effects of exercise in mice, and that CES2C might have a role in helping the mice improve exercise performance and endurance.

If carboxylesterases turn out to have a similar impact on metabolism in humans, or if other proteins secreted in response to exercise also influence metabolism, this research could one day lead to approaches that help people get the most metabolic benefit they can from whatever amount of exercise they do.


Guts to Run—How the Microbiome Motivates Exercise: Scientists discovered a novel way the gut signals to the brain to influence motivation to exercise in mice. The importance of physical activity to health is well known, but participating in exercise can be challenging for many, and motivation to start or continue physical activity varies among people. Understanding the factors that drive exercise is critical to developing strategies to help people start and maintain motivation for physical activity.

To discover new regulators of exercise, researchers undertook a systematic approach and documented the genome, metabolome (products of metabolism), intestinal microbiome (the microbes inhabiting the gut), energy metabolism, and exercise profiles of approximately 200 genetically diverse male and female mice to produce over 2 million data points. Because the scientists observed significant variability in the exercise performance of the mice in both treadmill and wheel running, they applied machine-learning techniques to identify factors that correlated with either enhanced or decreased performance. These studies led to a surprising observation: the presence or absence of specific bacteria in the gut microbiome of the mice had a strong predictive power on the mice’s exercise
Further experiments demonstrated that removal of the microbiome by treatment with antibiotics decreased exercise performance, while reconstituting the microbiome by transplantation or stopping the antibiotic treatment restored performance. This suggested that the microbiome contributed to exercise performance in a specific, acute, and reversible way.

Through an impressive body of work, the scientists revealed that gut microbiome production of metabolites—specifically fatty acid amides—promoted exercise in the mice. These metabolites stimulated gut sensory neurons which, in return, signaled to neurons in a specific part of the brain responsible for motivation. This signal enhanced levels of dopamine, a key molecule in the brain that—among other functions—promotes the feeling of reward. In microbiome-depleted mice, levels of dopamine post-exercise were reduced, leading the mice to exercise less. In contrast, activation of dopamine signaling in these mice restored motivation to exercise even in the absence of a gut microbiome.

Scientists revealed a novel connection between the gut microbiome and the brain that influences the motivation to exercise in mice.

This surprising discovery showed that brain activity contributing to exercise motivation is influenced by the gut microbiome, a previously unknown gut-brain connection affecting behavior. Additional research is necessary to determine whether a similar gut-brain connection exists in humans, but this research could spur exciting new strategies to modify behavior through lifestyle interventions, diet, and metabolite supplementation, to help people live healthier lives.


**ADVANCING TREATMENT OF POMPE DISEASE**

*In Utero Therapy Promising for Preventing Prenatal Organ Damage From Rare Genetic Disease:* Scientists found that treating the rare genetic disorder Pompe disease in utero may halt prenatal organ damage and improve health after birth. Pompe disease is caused by genetic changes that reduce the essential enzyme (a type of protein) acid alpha-glucosidase (GAA), and one form of the disease, called infantile-onset Pompe disease, leads to a near-complete lack of GAA. Because GAA is needed to break down glycogen, a form of sugar that fuels muscles, lack of GAA can cause glycogen buildup and irreversible organ damage, particularly to the muscles and heart. Fetal and newborn screening can diagnose infantile-onset Pompe disease, and prompt intravenous treatment after birth with GAA via an approach called enzyme-replacement therapy (ERT) can improve a child’s prognosis. However, improved treatments are needed, since ERT cannot reverse organ damage that occurred in utero, and some infants develop an immune response to ERT and die early in life.

Researchers tested whether treating Pompe disease earlier—via *in utero* ERT (IUERT) with GAA—could prevent prenatal organ damage and circumvent an immune response to the therapy. They teamed up with a family with a history of infantile-onset Pompe disease that was expecting a female child diagnosed with the disease. The researchers used ultrasonic imaging to guide delivery of 6 IUERT infusions into the umbilical cord, one every 2 weeks, starting around 24 weeks gestation. This treatment was safe for the mother and fetus. The infant continued to receive and tolerate ERT treatment after birth and was followed through 13 months of age. Her glycogen buildup levels significantly decreased following ERT, and unlike her siblings who had had Pompe disease, there were no signs of damage to her heart. In stark contrast to other children with this disease, she also displayed age-appropriate motor skills and muscle development, including appropriately meeting milestones such as crawling and walking.

Though this report only covered one case, IUERT appears to have prevented the prenatal organ damage expected in infantile-onset Pompe disease, allowing the treated child to thrive through the first year of life. A larger clinical trial is in progress that will build on this remarkable result and provide more data about IUERT’s safety and efficacy at treating Pompe disease and other, related genetic diseases.

Celebrating the 50th Anniversary of Diabetes Research Centers

The year 2023 marked the 50th anniversary of the NIDDK-supported Diabetes Research Centers that have transformed the field of diabetes research. The Diabetes Research Centers are part of an integrated program of diabetes and related endocrinology and metabolism research and one of NIDDK’s longest running programs. Toward the goal of developing new methods to treat, prevent, and ultimately cure diabetes and its complications, the Centers program supports research institutions with an established existing base of high-quality, diabetes-related research; provides increased, cost-effective collaboration among multidisciplinary groups of investigators; and provides shared access to specialized technical resources and expertise. The Centers are structured around an administrative core with an enrichment program, biomedical research cores, and a pilot and feasibility program to encourage early-stage investigators and researchers new to diabetes.

One of the major contributions made by Diabetes Research Centers is the landmark Diabetes Control and Complications Trial (DCCT) that launched in 1983. DCCT, along with its follow-up study that started in 1994, called the Epidemiology of Diabetes Interventions and Complications (EDIC) study, showed that early and intensive blood glucose (sugar) control lowered the risk for type 1 diabetes complications, including diabetic eye disease, cardiovascular events, kidney disease, and nerve damage. These results transformed the way type 1 diabetes is managed, and researchers continue to learn from DCCT/EDIC participants today. More than four decades later, most of the living, original DCCT participants still contribute to the EDIC study.

In more recent years, Diabetes Research Centers have contributed knowledge to a variety of areas. Some examples include investigating mechanisms by which a recently approved drug, teplizumab, can delay the onset of type 1 diabetes in individuals at high risk; revealing how time-restricted feeding can mitigate obesity in mice or how circadian disruption may contribute to metabolic disease; discovering the metabolic, cardiovascular, and immune changes that occur at the molecular level following acute physical activity; identifying risk factors for diabetic nerve disease in DCCT/EDIC participants; and finding association between worse health outcomes in people admitted with COVID-19 and high blood glucose levels. Despite the challenges of the COVID-19 pandemic, the number and importance of publications that have come out of Diabetes Research Centers continued unabated.

The Centers have also been successful at leveraging their expertise and resources for the greater good.
of the research community, especially when there are other NIDDK-supported Centers nearby. For instance, the Centers have been able to increase synergy through the Centers for Diabetes Translation Research, and in 2022, NIDDK began a program studying cystic fibrosis-related diabetes through the Cystic Fibrosis Centers utilizing diabetes expertise at Diabetes Research Centers. The Mouse Metabolic Phenotyping Centers-Live is another program that collaborates with many Diabetes Research Centers to provide experimental testing services to scientists studying mouse models of diabetes, obesity, diabetic complications, and other metabolic diseases. Lastly, the Medical Student Research Program in Diabetes and Obesity supports summer research opportunities for medical students at one of the current Diabetes Research Centers with the goals of encouraging medical students to pursue research and diversifying the diabetes research workforce.

Diabetes research has come a long way since the Diabetes Research Centers were created 50 years ago. While the goal of the Centers remains the same, the Centers will embrace opportunities to incorporate new areas of science, to increase synergy and better leverage resources across the program and with other NIDDK Centers and programs, to strengthen the key pilot and feasibility program, and to attract new and diverse investigators to the field. Building on the program’s great accomplishments, the Centers will continue to advance the field and evolve as new opportunities and priorities emerge to meet the needs of the diabetes community.
The Special Diabetes Program: 25 Years of Advancing Type 1 Diabetes Research

In 2023, the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program) celebrated 25 years of research progress. Since its inception in 1998, the Special Diabetes Program has demonstrated the value of consistent, long-term research support, enabling NIDDK to expand type 1 diabetes research beyond what was possible with regular appropriations and allowing researchers to conduct clinical trials unlikely to be performed in the private sector. As a result, Special Diabetes Program-funded research has led to life-changing improvements for people with the disease and ushered in a new era of type 1 diabetes management.

Congress established the Special Diabetes Program to support scientific research on the prevention and cure of type 1 diabetes and its complications. This Program has provided a total of about $3.39 billion for Fiscal Year (FY) 1998 through FY 2023. The Program is administered by NIDDK on behalf of the Secretary of the U.S. Department of Health and Human Services, in collaboration with multiple NIH Institutes and Centers and the Centers for Disease Control and Prevention, and with input from the statutory Diabetes Mellitus Interagency Coordinating Committee chaired by NIDDK.

A MULTIFACETED APPROACH TO TYPE 1 DIABETES RESEARCH

NIDDK is pursuing a multipronged approach to type 1 diabetes research, focusing on key questions such as: how can we prevent this disease, how can we improve treatment, and how can we develop a cure? Listed below are major goals pursued by the Special Diabetes Program, accompanied by examples of the extensive progress enabled by Program funding.

**Goal: Identify the genetic and environmental causes of type 1 diabetes**
A person's risk for developing type 1 diabetes is dependent on both genetic and environmental factors. Due to work funded by the Special Diabetes Program and others, over 90 percent of the genetic contributions to type 1 diabetes risk are known in those of European ancestry (who have the highest prevalence of type 1 diabetes), and researchers continue to enhance understanding of risk factors in other backgrounds. To identify environmental factors of type 1 diabetes risk, the long-term clinical research study The Environmental Determinants of Diabetes in the Young (TEDDY) screened over 425,000 newborns, enrolling 8,000 who were at high genetic risk of type 1 diabetes. These children will be followed until they are 15 years old, and they and their families have donated over 4 million biological study samples to date. TEDDY researchers are studying the children's genes, proteins, and metabolites, as well as the microbes they carry and their environmental exposures.

TEDDY analyses have yielded new insights into childhood development, including how the microbes in a child's gut change as they age and how those changes are affected by breastfeeding. TEDDY findings have also increased understanding of how to predict type 1 diabetes, allowing researchers to construct a risk score assessment tool that uses both genetic and immune factors to predict an individual's risk of the disease. New research from TEDDY and other studies has also illustrated how type 1 diabetes is not a single disease but a...
“heterogeneous” one that progresses differently for different people. These and other TEDDY findings could lead to more personalized preventive strategies in the future as we move toward the goal of precision medicine.

**Goal: Prevent or reverse type 1 diabetes**

Long-term research supported by NIH and the Special Diabetes Program recently culminated in the November 2022 U.S. Food and Drug Administration (FDA) approval of teplizumab, the first early, preventive treatment that can delay clinical diagnosis of type 1 diabetes in those at high risk of developing the disease. Key research underlying this FDA approval stemmed from a trial conducted by the Special Diabetes Program-funded Type 1 Diabetes TrialNet, a large international consortium designed to perform clinical trials of therapies to delay or prevent type 1 diabetes progression. TrialNet’s clinical trial of teplizumab found that the drug delayed type 1 diabetes onset by nearly 3 years. (See the type 1 diabetes Personal Perspective in this chapter for more information and for the story of a volunteer who participated in this research.) The landmark FDA approval of teplizumab has ushered in a new era of type 1 diabetes prevention and underscored the value of TrialNet’s unique clinical trial infrastructure.

Teplizumab’s approval was made possible by decades of research—much of it NIH- and Special Diabetes Program-supported—into understanding type 1 diabetes progression and identifying potential therapies. For example, research conducted by the Immune Tolerance Network, led by the National Institute of Allergy and Infectious Diseases (NIAID) with Special Diabetes Program support, showed that teplizumab delayed the loss of insulin production in people with newly diagnosed type 1 diabetes. Additionally, data from TrialNet, TEDDY, and other studies were critical to the discovery that several distinct stages of type 1 diabetes occur before symptoms appear. Being able to identify people in the early stages of disease prior to clinical diagnosis has made type 1 diabetes prevention trials possible.

**Goal: Develop cell replacement therapy**

In type 1 diabetes, the immune system attacks and destroys the insulin-producing β (beta) cells in clusters called islets in the pancreas. Replacing these β cells could be a biological cure for the disease. The Clinical Islet Transplantation Consortium (CIT)—co-led by NIDDK and NIAID—has demonstrated that transplanting donated islets into a person with type 1 diabetes can eliminate severe episodes of low blood glucose (sugar), with some trial participants achieving near-normal average blood glucose levels and an improved quality of life. CIT trial data led to the July 2023 FDA approval of the first cellular therapy made from deceased donor pancreatic cells for the treatment of adults with type 1 diabetes and recurrent severe low blood glucose. This therapy provides an additional treatment option and, in some people, it can result in no longer needing to take insulin. However, islet transplantation’s current limitations—including the need for lifelong immunosuppression and the low availability of donated islets—make it suitable for only a small number of people, and cell replacement strategies that can benefit a wider range of individuals are needed.

Studies through the Beta Cell Biology Consortium and its successor, the Human Islet Research Network (HIRN), are advancing knowledge of how β cells are lost in type 1 diabetes and how they can be protected or replaced in people. HIRN investigations into how β cells develop and mature are allowing scientists to make new β-cell replacements and islet-like mini-organs or “organoids” in the lab. In addition to HIRN activities, other Special Diabetes Program-supported advances have been made in improving transplantation procedures and developing specialized encapsulation technologies to protect β-cell replacements from immune attack. Early Special Diabetes Program investments are providing the technical know-how required for future advances.

**Goal: Improve type 1 diabetes management and care**

The Special Diabetes Program has provided key support for the development of glucose management technologies, from continuous glucose monitors to artificial pancreas systems that automate insulin delivery. As a result, these devices have moved out
of the lab and into people’s daily lives. In the last 8 years, 6 artificial pancreas devices have become commercially available, including devices for children as young as 2 years old. Five of these devices had NIDDK and Special Diabetes Program support during development and/or testing, demonstrating the value of long-term research funding.

The Special Diabetes Program has also played a unique role in expanding research on how new glucose management technologies can benefit everyone with type 1 diabetes, with the goal of having multiple artificial pancreas technologies available to fit diverse needs. Several Program-supported trials have sought to study the use of these devices in groups understudied by industry, such as during pregnancy, in people of certain racial or ethnic groups, and in those for whom managing blood glucose levels is particularly challenging.

**Goal: Prevent or reduce the complications of type 1 diabetes**

Persistent high blood glucose levels can damage nearly every part of the body, leading to life-threatening complications. The Special Diabetes Program has supported a robust portfolio of programs to improve prevention and treatment of these conditions. One particularly successful example is the National Eye Institute-led DRCR Retina Network (previously the Diabetic Retinopathy Clinical Research Network or DRCR.net), which has been transforming diabetic eye care for two decades. One of the DRCR Retina Network’s pivotal findings was that the anti-vascular endothelial growth factor (VEGF) drug, ranibizumab, was more effective than laser treatment at improving visual acuity for the most severe form of diabetic eye disease, proliferative diabetic retinopathy. This result led to ranibizumab being the first new option for treating proliferative diabetic retinopathy in four decades. The Network has also performed comparative effectiveness studies unlikely to be done by industry, confirming that three medications for diabetic macular edema were equally effective, a finding with significant cost implications.

**Goal: Attract new talent and apply new technologies to research on type 1 diabetes**

Tomorrow’s cutting-edge research requires fostering a talented, diverse biomedical workforce today. To this end, the Special Diabetes Program has supported creative new and early-stage investigators pursuing highly innovative new approaches in type 1 diabetes research. It has also helped expand the type 1 diabetes research community through career development and funding opportunities for researchers with specialized skillsets—such as bioengineers, behavioral scientists, and pediatric endocrinologists. Additionally, the Special Diabetes Program supports academic and small business investigators at all stages to help develop ground-breaking technologies. One such partnership resulted in an improved glucagon formulation that does not require refrigeration and thus is suitable for a ready-to-use rescue pen. This device is now commercially available to treat low blood glucose, a daily concern for people with type 1 diabetes.

**BUILDING ON THE PAST, LOOKING TO THE FUTURE**

Through these and many other efforts, the Special Diabetes Program has catalyzed remarkable progress and fostered unique collaborations that have accelerated the pace of type 1 diabetes research. Research funded by the Program has also yielded benefits beyond type 1 diabetes, for example by developing glucose management tools to help those with type 2 diabetes and by offering insights into other autoimmune diseases. Finally, the Special Diabetes Program has supported a pipeline of knowledge that has ushered in a new era of improved health, longevity, and quality of life for people with type 1 diabetes. With continued research, NIDDK looks forward to a future when all people can be free from the burden of type 1 diabetes and its complications.
NIDDK Director Testifies at Congressional Hearing on Type 1 Diabetes Research

On July 11, 2023, NIDDK Director Dr. Griffin P. Rodgers testified about progress and future directions in type 1 diabetes research before the Senate Committee on Appropriations, led by Chair Patty Murray (D-Washington) and Vice Chair Susan Collins (R-Maine). The hearing, entitled “Accelerating Breakthroughs: How the Special Diabetes Program Is Creating Hope for those Living with Type 1 Diabetes,” was co-chaired by Senators Collins and Jeanne Shaheen (D-New Hampshire) who also co-chair the Senate Diabetes Caucus. It was held in conjunction with the Children’s Congress, an event sponsored regularly by JDRF to highlight the value of type 1 diabetes research for children and adults living with this disease.

Testifying with Dr. Rodgers were JDRF Chief Executive Officer Aaron J. Kowalski, Ph.D.; music producer and philanthropist James “Jimmy Jam” Harris; and Children’s Congress delegates Maria Muayad, age 10, and Elise Cataldo, age 15.

In his testimony, Dr. Rodgers gave an update on recent research advances made possible by the Special Diabetes Program, including significant progress in developing artificial pancreas technologies and the landmark FDA approval of the first preventive treatment that can delay clinical diagnosis of type 1 diabetes. Dr. Rodgers thanked members of the Committee and Congress for their support of type 1 diabetes research, and expressed his gratitude to the clinical research participants who have made diabetes research advances possible.
Islet Transplantation for Treating Difficult-to-Manage Type 1 Diabetes in Adults

Decades of research supported by NIDDK and other NIH Institutes recently led to the landmark U.S. Food and Drug Administration (FDA) approval of an entirely new type of therapy for people with type 1 diabetes whose disease cannot be managed using current therapies: islet transplantation. Among its many potential benefits, the procedure may allow someone to go from having difficult-to-manage diabetes to being completely insulin-independent, while substantially lowering the risk of having their glucose (sugar) levels fall dangerously low (hypoglycemia). Before the approval, islet transplantation was only available to people participating in a research study. Now, this therapy is approved for adults with the disease who are unable to approach target hemoglobin A1c levels (a measure of average blood glucose levels over time) because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

Insulin is a life-saving treatment for people with type 1 diabetes, whether taken by injection, insulin pump, or an artificial pancreas device. To estimate how much insulin their body may need, people with the disease must closely monitor their diet, exercise, and daily routine. Despite careful management of diabetes, it is difficult to mimic the exquisite blood glucose control of the pancreas. While taking insulin treats excess glucose in the blood (hyperglycemia), too much insulin can lead to a lack of glucose in the brain and to dangerous situations, including coma and death. Despite vigilant insulin administration, some people have episodes of severe hypoglycemia with memory loss, confusion, altered or irrational behavior, difficulty in awakening, seizures, or loss of consciousness. Such episodes may make activities like driving or caring for young children unsafe. Repeated episodes can lead to impaired awareness of hypoglycemia, where a person does not realize that they have dangerously low blood glucose levels and/or is unable to self-administer treatment, typically by consuming high-sugar foods or drinks or taking a glucose tablet.

To address these challenges, NIDDK vigorously supports research to improve diabetes management. This includes research to advance glucose management technologies, such as artificial pancreas devices that automate insulin delivery in response to blood glucose levels, as well as to develop cell-based approaches, such as islet transplantation, to replace the insulin-producing β (beta) cells that have been destroyed in type 1 diabetes. In islet transplantation, islets (which contain β cells and other cell types) are isolated from donor cadaveric pancreases and transplanted into people with type 1 diabetes. The transplanted islets then start to produce insulin in response to blood glucose levels.

The approval of islet transplantation for people with recurrent severe hypoglycemia is the culmination of decades of collaborative work between NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID), as well as non-governmental organizations and businesses, with oversight and advice from the FDA. The Immune Tolerance Network (ITN), led by NIAID with support from NIDDK and JDRF, tested an approach pioneered in Canada, called the Edmonton Protocol, for injecting transplanted islets into a major vein in the liver and keeping them alive with a novel combination of immunosuppressive
drugs. Often, ITN found, the islets survived for months or even years and either reduced the recipient’s need for injected insulin or eliminated it entirely. NIDDK and NIAID continued and built on ITN’s work through the Clinical Islet Transplantation Consortium (CIT) with support from the Special Statutory Funding Program for Type 1 Diabetes Research.

The CIT has achieved remarkable successes, such as documenting the complete elimination of severe hypoglycemic events in the majority of study participants and demonstrating that islet transplantation enabled them to achieve near-normal average blood glucose levels while improving their quality of life—results that paved the way to the recent FDA approval. Notably, ITN and CIT also identified important limitations to islet transplantation procedures. For example, although the surgery itself is less invasive than the transplant of an intact pancreas, complications from the procedure may still occur. More importantly, the medications needed to suppress immune rejection of the islets must be continued for the life of the transplant, and they come with significant risks. Their use increases susceptibility to bacterial and viral infections; can cause fatigue, decreased kidney function, mouth sores, and gastrointestinal problems; and may increase the long-term risk of developing certain cancers. These immunosuppressants are also thought to affect the long-term viability of the transplanted islets, as studies suggest that they are toxic to the islets over time. Thus, an important future research goal is the achievement of “immunological tolerance” for the transplanted cells, meaning that immunosuppression drugs would only be needed for a short time or even not at all.

Because of its current limitations, and because the needed cadaver-derived islets are in short supply, islet transplantation is only appropriate for a small subset of people with type 1 diabetes. NIDDK is currently supporting research to characterize and generate new sources of insulin-producing cells and to eliminate the need for immunosuppressive medicines. For example, in one strategy, called encapsulation, islets (including those from donors as well as progenitor cell-derived islet-like clusters and organoids grown in the laboratory) are coated with a material that protects them from being attacked by the recipient’s immune system and promotes their healthy functioning. To help overcome the shortage of cadaveric islets, research is building on an NIDDK-supported landmark discovery that progenitor cells could be used to produce large quantities of β-like cells in the laboratory. Further development of this breakthrough is being pursued by industry, including the conduct of human clinical trials testing encapsulated and unencapsulated cells. Both the cell source and biomaterials have been developed from fundamental NIDDK-funded research. These industry trials are utilizing clinical trial approaches and experiences developed by NIDDK-supported research on cadaver-derived islet transplantation that led to the FDA licensure, and are expected to benefit from the now established pathway to product licensure made possible by the CIT and the FDA approval.

Overall, this FDA approval is an important milestone in developing a cell-based therapy as a diabetes treatment, helping people with type 1 diabetes who have recurrent hypoglycemia and cannot manage their disease using other approved therapies. This approval also establishes a regulatory framework that future, more broadly applicable cell therapies could follow once they become available. Continued research to identify and test cells and biomaterials, in parallel with research toward generating and preserving sufficient numbers of islets/cells for implantation, will yield knowledge necessary to achieve further progress.
Diabetes affects more than 38 million people in the United States; an additional 97.6 million American adults have prediabetes and are at increased risk for developing type 2 diabetes in the future. Although diabetes occurs in all populations in the United States, type 2 diabetes disproportionately affects racial and ethnic minority groups and populations with low socioeconomic status or living in rural areas. One approach to address and reduce such health disparities involves meaningful inclusion of individuals and communities of diverse backgrounds in developing the research activities that involve them. However, researchers and others involved in study design and recruitment have not routinely engaged these populations whom the studies are intended to benefit. Enhancing such engagement—which involves areas such as trust building and use of culturally appropriate research designs, questions, and materials—provides an important opportunity to advance type 2 diabetes prevention and treatment with effective interventions that have potential for uptake by people experiencing diabetes-related health disparities.

Toward this goal, NIDDK began a novel research program, called the National Engagement Innovation Center, for advancing equity in type 2 diabetes research. The program aims to incorporate the lived experience of people with or at risk for diabetes, family members, caregivers, and others involved in the research, diagnosis, and treatment of diabetes into all stages of the research process. Its establishment is aligned with the goals of the NIDDK Strategic Plan for Research and the recently published NIDDK report Pathways to Health for All: Health Disparities & Health Equity Research Recommendations & Opportunities.

Overall, the Center will provide specialized research resources to support field investigators in conducting community-engaged research by fully embedding communities, patients, and other groups into their research activities. It will also establish a network consisting of multidisciplinary research investigators, including researchers from underrepresented groups, those with specific expertise in type 2 diabetes and community engagement, experts with lived experiences, and representatives from health and advocacy organizations who can serve a role in addressing disparities and advancing health equity in type 2 diabetes research.

Through the course of the project period, which began in late 2023, the Center will create and build infrastructure for delivering these expert research engagement resources, providing two core services to the research community. The first is engagement “studios” in which the Center designs customized consultation sessions to provide varied partner organization or community input on scientists’ research projects. The goal of these studios is to give researchers valuable collaborator insight about type 2 diabetes community-engaged research objectives and approaches that they otherwise would not have the ability or connections to obtain on their own. The second service provides scientists with structured, expert research consultations with Center faculty at any stage of their grant writing or research project.
Through these efforts, the Center will create a national network that will help individual scientists or teams studying type 2 diabetes facilitate or improve: research methods that allow them to identify and address barriers to care to improve access to resources and optimal outcomes; the use of equity approaches that incorporate community members’ research priorities, values, lived experiences, and challenges into practice, while avoiding harm; engagement strategies; partnerships that promote mutually beneficial outcomes for researchers and partners; and dissemination of effective practices for equitable engagement with collaborators. Ultimately, engaging in these practices will advance health equity in type 2 diabetes research toward improving health for all people.
Advancing Research Toward Understanding Rare and Atypical Types of Diabetes

In diabetes, blood sugar (glucose) levels become elevated due to the body’s inability to produce and/or respond appropriately to insulin. In most cases, diabetes is classified as being in two major categories, such as type 1 or type 2 diabetes. In addition, there is diabetes that is pregnancy-related, called gestational diabetes. However, in some people with diabetes, the disease does not fall neatly into one of these categories or does not respond to treatment in the normally expected ways. NIDDK established the Rare and Atypical Diabetes Network (RADIANT) to obtain the data needed to understand these atypical forms of diabetes. (See inset for the story of an individual with an atypical form of diabetes participating in RADIANT.)

**TYPICAL FORMS OF DIABETES**

Type 1 diabetes is a form of diabetes in which the immune system attacks and destroys cells of the pancreas that are responsible for making insulin. People with type 1 diabetes must administer insulin every day to survive and measure blood sugar levels to adjust insulin for best glucose control. Sustained research efforts supported by NIDDK have contributed to improved technologies for treating type 1 diabetes, including artificial pancreas devices that automate insulin delivery in response to blood sugar levels.

Type 2 diabetes occurs when cells throughout the body respond poorly to insulin and lose the ability to take up glucose from the blood for use as a fuel. The pancreas also may not be making enough insulin to compensate and maintain blood sugar levels in a healthy range. Type 2 diabetes is generally associated with obesity and is more common in older adults, but it can begin at any age. NIDDK-supported research has contributed to type 2 diabetes prevention and treatment approaches, including lifestyle approaches and new classes of drugs that help to control blood sugar levels.

Gestational diabetes is a type of diabetes that develops during pregnancy. It often goes away after delivery but can put both the mother and fetus at higher risk of developing type 2 diabetes in the future.

Less common types of diabetes include those that result from changes in a single gene, termed “monogenic” diabetes, while both type 1 and type 2 diabetes have more complex genetic and other contributors. Diabetes can also result from other conditions that damage the pancreas, such as cystic fibrosis (a progressive, genetic disease that causes mucus buildup in organs) or pancreatitis (inflammation in the pancreas). However, scientists now know that not all types of diabetes fall into these discrete categories.

**ATYPICAL FORMS OF DIABETES—NOT AS CLEARLY DEFINED**

Diabetes is diagnosed by tests that measure one’s blood sugar levels. To differentiate type 1 from type 2 diabetes, health care professionals also look for the presence of other markers in the blood—for example, autoantibodies that attack the pancreas, a characteristic of type 1 diabetes. Additionally, any known causes or risk factors underlying diabetes can also help guide the diagnosis and management of the specific type of diabetes. For instance, risk factors such as prediabetes, smoking, overweight, and obesity increase the likelihood of developing type 2 diabetes.
However, there are many unidentified or uncharacterized forms of diabetes without known causes, risk factors, or usual symptoms typically seen in type 1 or type 2 diabetes. Examples of such cases include people who are diagnosed with type 1 diabetes but do not have the associated autoantibodies, young people diagnosed with type 2 diabetes without having typical risk factors, or people with diabetes who have an unusual response to standard treatments and/or experience atypical disease progression. People with atypical diabetes often have trouble getting a definitive diagnosis or may get the correct diagnosis for their condition only after a long and convoluted journey through the health care system, which can lead to emotional distress and prevent proper and timely treatment. More research is needed to discover and define more clearly the types of diabetes that fall within (or beyond) a spectrum of type 1 and type 2 diabetes.

THE RARE AND ATYPICAL DIABETES NETWORK (RADIANT)

Launched in Fall 2020, the goal of the ongoing RADIANT study is to identify and characterize unusual types of diabetes by gathering detailed health information about participants with atypical forms of diabetes. RADIANT includes 14 clinical centers, 5 specialized laboratories, and a data coordinating center. Moreover, a soon-to-be-established data and biospecimen repository will serve as a resource for the broader research community to better understand how and why diabetes can vary so greatly—also called “heterogeneity” of diabetes.

Toward a goal of recruiting 2,000 study participants, RADIANT has already screened over 1,400 individuals and families with rare and atypical diabetes to characterize their health and perform genetic and other analyses. As of August 2023, among the screened participants, 402 individuals have been found to have a rare or atypical form of diabetes, and researchers have thus far identified 6 new genetic forms of diabetes that result from changes in single genes.

Further in-depth studies that involve deeper characterization and analyses are ongoing and are expected to lead to improved understanding of rare and atypical cases of diabetes. Ultimately, RADIANT findings may allow more precise clinical classification of different forms of diabetes and their underlying causes. This knowledge may also help guide the development of new diagnostic tools and treatment approaches, thus improving the quality of life for those with atypical diabetes. It may also help advance the understanding and treatment of more common forms of diabetes.

MOVING TOWARD A PRECISION MEDICINE APPROACH TO TREATING DIABETES

Recent advancements in diabetes research, through RADIANT and other efforts, have led to growing recognition that it will be imperative to move toward a more individualized approach to treatment based on the whole person. Such treatment would address an individual's specific form of diabetes, any associated health conditions, and factors such as genes, environmental contributors (including social determinants of health), and lifestyle. To make this precision medicine approach a reality, better understanding of mechanisms that contribute to heterogeneity of diabetes is needed. For example, in 2023, NIDDK announced a new effort to stimulate research to discover novel measures for subtypes of type 2 diabetes for an improved diabetes classification strategy, which will help determine the most effective treatment based on the classification. Also, NIDDK recently established a Working Group of its Advisory Council on diabetes heterogeneity to identify research gaps and to inform on future research opportunities that can stimulate research efforts to develop more discrete definitions of subtypes of diabetes. Through these and other research efforts, NIDDK aims to improve the health of all people with diabetes.

For additional information on the Rare and Atypical Diabetes Network (RADIANT), please visit its website at: www.atypicaldiabetesnetwork.org.
PERSONAL PERSPECTIVE

Mike’s Story

Mike’s diabetes journey has not been like that of most people with type 1 or type 2 diabetes. A couple days before his 28th birthday, he decided to sign up for a life insurance policy because his friend who worked for an insurance company had asked for help meeting a quota. As part of his application, Mike had to go to the doctor for a physical exam. A few weeks later, he got an unexpected phone call from that same friend. “He told me I needed to go to a hospital right then, like I will die if I don’t,” he remembers.

When he went to the emergency room, doctors measured his blood sugar (glucose) levels and found that they were unusually high. Extremely high blood sugar levels are a symptom of a life-threatening condition called diabetic ketoacidosis, which is why his friend was so worried. The doctors immediately diagnosed him with diabetes, but it was clear from the beginning that his case was not a conventional type of diabetes—neither type 1 nor type 2. Despite the high blood sugar levels, he had no obvious symptoms at the time. He did not have autoantibodies attacking the insulin-producing cells of his pancreas, as is associated with type 1 diabetes. One year before, his blood sugar levels were perfectly fine. He was young and healthy and kept an active lifestyle. However, he did note that he was losing weight, which he later realized was a symptom of diabetes.

“I said, ‘Well, that’s awful because if I can’t name my disease, how am I supposed to fight it or do anything with it?’” remembers Mike, after his primary care physician told him that he had an atypical form of diabetes.

When asked about how he felt while trying to get a proper diagnosis, Mike responds, “I got rejected from probably 80 percent of the diabetes studies I tried to enter over the course of 3 years.” It was frustrating for him because it wasn’t always clear from the study criteria whether he was eligible to enroll. Also, some health care professionals whom he interacted with treated him like a typical type 2 diabetes patient. “I think that the frustration really came from just trying so hard to figure out a part of yourself that you don’t know anything about,” he says.

And then the same diagnosis happened to his two younger brothers. Two years after Mike’s diagnosis, his middle brother found out he also had diabetes that was atypical, just like Mike’s. His brother was in
the middle of training for a marathon, running 13-14 miles a day. It wasn’t surprising that he had lost a lot of weight, but it turned out that the weight loss was a symptom of diabetes. After that, Mike was not surprised when his youngest brother also got the same diagnosis.

“I think that the frustration really came from just trying so hard to figure out a part of yourself that you don’t know anything about,” Mike says, talking about navigating the health care system with an atypical form of diabetes.

In his early forties now, Mike—a chemical engineer by training—works at a company that makes industrial printers. Outside of work, he is a member of his City Council and likes to keep himself busy by getting involved in activities in his tight-knit community when he isn’t parenting his 1-year-old son. When asked about how he has been managing his diabetes, he responds that he considers himself fortunate because the artificial pancreas technology that he uses “is amazing.” Mike, his middle brother who has a geophysics degree, and their youngest brother who has a degree in aeronautical engineering are “all nerds together,” taking a very scientific approach to managing diabetes, and they appreciate the technological advances that allow them to manage their diabetes with less burden.

In fact, it was one of Mike’s brothers who first found out about NIDDK’s Rare and Atypical Diabetes Network (RADIANT). Given his past experiences of not being eligible for most research studies, Mike discovered that RADIANT was tailor-made for people like him and his brothers—the Network was studying people with atypical forms of diabetes. All three brothers are now RADIANT study participants, and Mike participates at Massachusetts General Hospital, one of the 14 RADIANT clinical centers. As part of RADIANT, Mike was asked to fill out questionnaires, visit the clinical center to undergo physical exams and provide blood samples, and complete other tests so that scientists could build a comprehensive resource of genetic, clinical, and descriptive data. Scientists will then study the data from the dedicated RADIANT volunteers, including Mike and his brothers, to begin to understand how and why diabetes can vary so greatly. Such knowledge could help to establish new diagnostic criteria for diabetes, find new markers for screening, or identify drug targets for new therapies that could bring more precision to diabetes treatment.

Mike mentions that, even though the study is relatively new, it has been helpful in that participants have been able to get health information and data about themselves already. The three brothers got the same results on all the tests, so they know for certain that they have the same condition. For Mike, the experience that he and his brothers share in being in the same study has been great as well. A few weeks after Mike and his brothers went through a very comprehensive physical exam, they got to meet up at a family gathering and compare notes. He says that it feels good to be able to share results and speculate with his siblings about whether it may have been a specific environmental factor in their childhood or a genetic factor that contributed to them developing diabetes. They are hoping that RADIANT will give them some answers.

“I can help the future of science and hopefully be able to learn something about myself,” says Mike, speaking about his participation in NIDDK’s Rare and Atypical Diabetes Network (RADIANT).

Mike also hopes that the data he contributes to RADIANT will be used not just for him but for other people who may have similar symptoms. “It would be really neat to be able to make those connections,” Mike says. Moreover, he hopes that one day, researchers will be able to put a name to his type of diabetes. For what he’s learned already and for what the future promises, his excitement about being
a RADIANT study participant is clear: “I can help the future of science and hopefully be able to learn something about myself.”

Looking back at his diabetes journey now, Mike finds some silver linings. He was able to rekindle a friendship with someone whom he had met a few years before he was diagnosed with diabetes. After learning about his diagnosis, the friend reached out to Mike out of the blue and told him about a couple of clinical studies he might be interested in. When everyone else in his life was pitying him about his diabetes, she said, "Here, do some science with it," which he appreciated. Ten years later, she became his wife. Mike says, "It is wild to think that this disease that has complicated my life significantly has indirectly caused ... a lot of the best things in my life, too, and it is a constant reminder that these things aren't necessarily the end... I might as well smile about it and look at all the good things it's done for me."
Contributing to Research Leading to the First Preventive Therapy for Type 1 Diabetes

In type 1 diabetes, the insulin-producing β (beta) cells of the pancreas are destroyed by a misguided immune system attack. A major goal of NIDDK-supported research has been to develop and test therapies to intervene in this autoimmune attack, protect β cells, and prevent or delay type 1 diabetes disease progression. Since 2001, NIDDK’s Type 1 Diabetes TrialNet has been conducting clinical trials studying such therapies. In 2019, TrialNet reported that the immune-targeting drug teplizumab delayed onset of clinical type 1 diabetes in people at high risk of developing the disease. Based on these positive results, the U.S. Food and Drug Administration (FDA) approved teplizumab in November 2022 as the first drug that delays onset of clinical type 1 diabetes. This landmark progress was made possible by the critical contributions of dedicated volunteers in clinical trials testing new disease-modifying therapies for type 1 diabetes. (See inset for the story of a participant in TrialNet’s teplizumab clinical trial.)

NEW KNOWLEDGE ABOUT THE TYPE 1 DIABETES DISEASE PROCESS

The NIDDK-led TrialNet, which also receives support from the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program), is an international network of clinical research centers and affiliate sites, as well as a hub and a coordinating center. TrialNet involves hundreds of scientists and staff and, most importantly, thousands of clinical research participants. TrialNet has conducted multiple studies of agents to delay progression of type 1 diabetes in people with or at risk for the disease.

TrialNet has also contributed key insights into understanding the type 1 diabetes disease process. For example, data from TrialNet and other studies revealed that progression to clinical type 1 diabetes proceeds through distinct stages prior to onset of symptoms and clinical diagnosis (see Figure 1). Stage 1 is defined as the presence of two or more different types of autoantibodies (proteins made by the immune system) with normal blood sugar (glucose) levels; stage 2 is defined as the presence of two or more autoantibodies and abnormal blood sugar levels without symptoms such as increased thirst and urination; and stage 3 is when symptoms of type 1 diabetes are usually present and a clinical diagnosis is received. People at stages 1 and 2 are at high risk of developing clinical (stage 3) type 1 diabetes in the future. This staging has provided a critical framework for the research and development of preventive therapies conducted through TrialNet.

Crucial for identifying people eligible for prevention trials is TrialNet’s “Pathway to Prevention” study that screens relatives of people with type 1 diabetes. Because type 1 diabetes has a genetic component, relatives of people with the disease have a greatly increased risk of developing it. This screening, which uses a simple blood test to measure the levels of five different autoantibodies associated with type 1 diabetes, benefits people by providing knowledge about their risk for developing type 1 diabetes in the future. Additionally, people who are in the early stages (stage 1 or 2) of type 1 diabetes may be eligible to enroll in a TrialNet trial to prevent or delay onset of clinical disease. The Pathway to Prevention study, which has screened over 200,000 people to date, makes TrialNet a unique infrastructure for conducting type 1 diabetes prevention trials.
TESTING TEPLIZUMAB IN A TRIALNET CLINICAL TRIAL

One such prevention trial was based on previous NIDDK- and Special Diabetes Program-supported research demonstrating that treatment with teplizumab slowed β-cell loss in people with recent-onset stage 3 type 1 diabetes. Teplizumab targets T cells in the immune system that are known to play a role in the type 1 diabetes autoimmune attack. However, the drug had never been tested in people without clinical disease, so it was unknown whether or not it could also slow β-cell loss earlier in the course of type 1 diabetes and thus prevent clinical disease onset.

To address this gap in knowledge, TrialNet conducted a trial in which they enrolled 76 participants ages 8 to 49 years who were relatives of people with type 1 diabetes. Most participants were White, and over 70 percent were 18 years old or younger. The participants had stage 2 disease, putting them at high risk of developing clinical type 1 diabetes. Participants were randomly assigned to receive either a 14-day course of teplizumab or placebo, administered intravenously. The results were striking: during the trial, 72 percent of people in the placebo group developed clinical type 1 diabetes, compared to only 43 percent of the teplizumab group. The median time for people in the placebo group to develop clinical disease was just over 24 months, compared to 48 months in the treatment group. This study was the first to show that clinical type 1 diabetes can be delayed for at least 2 years among people who are at high risk. Continued follow-up of trial participants has shown that the benefits of teplizumab extend to at least 3 years.

Figure 1: This graphic illustrates how type 1 diabetes (T1D) progresses. Genetic risk, combined with an unknown environmental trigger(s), is followed by inappropriate activation of the immune system to attack the insulin-producing β cells. The appearance of more than one islet-cell autoantibody in a person’s blood indicates that the immune system has been activated and the person has a high risk of developing type 1 diabetes. Stages 1 and 2 are considered the start of type 1 diabetes, even before the appearance of clinical symptoms and before the clinical diagnosis of diabetes is made. Research by Type 1 Diabetes TrialNet contributed to this new knowledge of type 1 diabetes staging, and TrialNet’s goal is to test agents to prevent or delay the disease at all stages. (Graphic courtesy of Type 1 Diabetes TrialNet.)
LANDMARK FDA APPROVAL OF TEPLIZUMAB

Based on the positive TrialNet clinical trial data, in November 2022 the FDA approved teplizumab (marketed as Tzield™) as the first drug to delay the onset of stage 3 clinical type 1 diabetes in adults and children 8 years and older who have stage 2 type 1 diabetes. This FDA approval provides a much-needed therapeutic option for people at risk of developing type 1 diabetes. It also underscores the importance of TrialNet as a unique and critical network for testing novel type 1 diabetes prevention therapies.

HOPE THROUGH RESEARCH

TrialNet's teplizumab trial was made possible by decades of sustained NIDDK- and Special Diabetes Program-supported research to understand type 1 diabetes progression and to identify and study novel therapeutic targets and agents. Building on this success, TrialNet is now testing other disease-modifying therapies in people with stage 1, 2, or 3 type 1 diabetes. Many additional promising therapies are in TrialNet's pipeline, with even more expected in the future as new knowledge about the underlying mechanisms of type 1 diabetes development and progression are uncovered.

With continued research, the longer-term goal of preventing type 1 diabetes—permanently and in anyone who could develop the disease—now seems possible after decades of contributions from countless scientists and dedicated clinical trial participants.
Mikayla’s Story

In 2016, Mikayla was told that she was about 6 months away from having clinical type 1 diabetes and being dependent on insulin. Seven years later, at age 21, she is still free of clinical disease and is insulin independent, a happy result she attributes to her participation in a clinical trial through Type 1 Diabetes TrialNet.

A SIBLING’S HARROWING TYPE 1 DIABETES DIAGNOSIS

Mikayla’s experiences with type 1 diabetes began in 2016, when her younger sister, Mia, was diagnosed with the disease at age 9 while the family was living in Colorado. Mikayla was 14 at the time and recalls the harrowing experience. “We went to the doctor for me because I sprained my knee,” Mikayla remembers. At the same time, her sister was not feeling well. When the family got home, Mikayla’s mother quickly realized that Mia needed emergency care and rushed her to the hospital. Mikayla’s father was in Florida for work, so Mikayla and her younger brother went to a neighbor’s house. When Mikayla called her mother to check on Mia, the first thing her mother said was that her sister was being airlifted to another hospital.

Mia had diabetic ketoacidosis (DKA), a life-threatening condition that is sometimes the first sign of type 1 diabetes in people who have not yet been diagnosed. The helicopter medical transport took Mia to the Barbara Davis Center for Childhood Diabetes, where she was in the intensive care unit for several days with kidney failure and other life-threatening complications. “It was very scary because my sister is a very bubbly personality, and during that time she was not, so you knew something was wrong,” recalls Mikayla. Thankfully, Mia received the medical care she needed, and the family began managing her newly diagnosed type 1 diabetes at home after she was released from the hospital. Mikayla says that Mia is doing great today.

PARTICIPATING IN TYPE 1 DIABETES TRIALNET

Shortly after Mia’s diagnosis, staff at the Barbara Davis Center—one of 22 clinical research centers participating in TrialNet—suggested that Mikayla, her
parents, and her brother be screened for early signs of type 1 diabetes, “to make sure that nobody else was at risk,” Mikayla says. Because type 1 diabetes has a genetic component, relatives of people with the disease have an increased risk of developing it. The screening involved a blood test to look for the presence of five autoantibodies that are early markers of type 1 diabetes. When the screening results came back a few days before the family was scheduled to move to Florida, Mikayla found out that “everyone was clear but me…. I had four of the five markers.” She had stage 2 type 1 diabetes, putting her at high risk of developing clinical (or stage 3) disease. At that time, the scientists told her that it would be about 6 months before she needed to start taking insulin.

Mikayla and her parents also learned that she was eligible to enroll in a new TrialNet clinical trial testing a drug targeting the immune system, called teplizumab, to see if it could delay progression to clinical type 1 diabetes. Because of their move, they were referred to the University of Florida (UF) TrialNet center, where Mikayla enrolled in the trial “to prevent what happened to [my sister] from happening to other people.” She didn’t worry about the possibility of getting randomly selected to the placebo arm of the trial and not receiving teplizumab. She remembers thinking that getting the placebo would be fine, but “if I get the drug, awesome.”

“During the study, the doctors and the nurses were very nice… They made it very welcoming,” says Mikayla, speaking about her experiences with TrialNet scientists and staff. Mikayla and her mom stayed at a hotel and went to the UF TrialNet clinic each day for the 14-day intervention. “Every day for those 2 weeks, I would sit in the hospital bed,” says Mikayla, where the staff would give her an intravenous infusion treatment that she said lasted 4-5 hours. After the treatment, Mikayla and her mom went to lunch and then rested in the hotel, as sometimes Mikayla had side effects from the treatment. Mikayla remembers the TrialNet staff warmly. “During the study, the doctors and the nurses were very nice…. They made it very welcoming.”

After the intervention part of the trial, Mikayla went to follow-up visits every few months so the TrialNet scientists could measure her blood sugar levels and assess how well her body was producing insulin. (She continues to have follow-up visits yearly.) After a couple years, she was told by the researchers that she had received teplizumab as part of the trial.

TEPLIZUMAB TRIAL RESULTS AND FDA APPROVAL

In 2019, TrialNet announced that the trial Mikayla participated in showed that teplizumab could delay diagnosis of clinical type 1 diabetes by 2 or more years among people who were at high risk. The results have since been extended to an average 3-year delay in clinical diabetes onset.

However, Mikayla has that number beat. Nearly 7 years after receiving teplizumab infusions, she is still free of clinical disease and remains insulin independent. “I don't know how long that’s going to last, but I hope it lasts a little bit longer,” she says. She is grateful that she has been able to navigate her high school and college years without needing to manage type 1 diabetes, knowing first-hand the burden that disease management places on individuals and their families.

More exciting news came in 2022, when the U.S. Food and Drug Administration (FDA) announced that it approved teplizumab as the first drug to delay the onset of clinical type 1 diabetes in adults and children 8 years and older who have stage 2 type 1 diabetes. Mikayla says that for her, the approval “means that people can at least prolong not having to take insulin,
not having to check blood sugar…. I'm very happy about that.” She's particularly excited about what a preventive therapy means for children and families. “It gives parents, especially, a sense of relief because managing type 1 diabetes in a kid is very stressful.” When asked if she would encourage others to participate in a clinical trial, she replies, “Yes, I would. If you have the requirements to meet it and you’re available, I would recommend it.”

For Mikayla, the FDA approval of teplizumab “means that people can at least prolong not having to take insulin, not having to check blood sugar…. I'm very happy about that.”

Now a college senior, Mikayla is pursuing her career goal of becoming a medical illustrator—combining her love of drawing with her passion for anatomy. She is an avid reader and a huge Harry Potter fan. During college, she has served as a resource for friends diagnosed with type 1 diabetes by giving them information about the disease and its management. “They say 'how do you know all this' and I say, 'it's a long story,'” she recalls with a laugh.

Mikayla also recognizes that she is likely to develop clinical type 1 diabetes in the future. “I do know I'm going to get it eventually. I don't know when, but I'm more mentally prepared and more physically prepared…. I'm just happy it hasn't happened yet.” Through her dedication to research, Mikayla has not only benefitted from her participation in the trial, but has achieved her goal of helping other people at risk for developing type 1 diabetes.