

# NIDDK

## Recent Advances & Emerging Opportunities

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National Institute of  
Diabetes and Digestive  
and Kidney Diseases

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# Message from the Director



As the Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I am pleased to present the 24<sup>th</sup> edition of our annual report, *NIDDK Recent Advances and Emerging Opportunities*, highlighting the research efforts and programs supported by the Institute. NIDDK has a broad research responsibility that includes some of the most common, debilitating, and costly conditions affecting Americans. These conditions include diabetes and other endocrine and metabolic diseases; liver disease and other digestive diseases and conditions, such as inflammatory bowel disease and irritable bowel syndrome; nutritional disorders; obesity; kidney diseases, such as polycystic kidney disease and glomerular disease; urologic diseases and conditions, such as interstitial cystitis/bladder pain syndrome, prostatitis, and urinary tract infection; and blood diseases.

Many of the conditions within the NIDDK research mission disproportionately affect different groups or communities. These groups include those who have been historically marginalized by structural and systemic racism and other forms of discrimination, and those who experience injustice today. In Spring 2023, NIDDK released [Pathways to Health for All](#), a new report developed by the Health Disparities and Health Equity Research Working Group of the National Diabetes and Digestive and Kidney Diseases Advisory Council. *Pathways to Health for All* makes innovative recommendations to advance research in health equity and health disparities. The recommendations are detailed in the “Cross-Cutting Science” section of this annual report.

In addition, this report describes recent NIDDK-supported scientific advances such as:

- Two clinical trials testing artificial pancreas technologies for managing type 1 diabetes that have shown positive results, with one leading to the FDA approval of a new commercial device
- Experiments in mice and human cells that shed light on how insulin-producing  $\beta$  (beta) cells adapt insulin secretion to the body's needs, and how type 2 diabetes may disrupt this process
- Finding that people who are at high risk of developing type 2 diabetes but do not lose weight easily with a group lifestyle intervention may benefit from an additional adaptive lifestyle intervention that helps achieve more weight loss and reduces diabetes risk
- Demonstration that treating the rare genetic disorder Pompe disease *in utero* may halt prenatal organ damage and improve health after birth
- Finding that time-restricted eating was feasible for firefighters on 24-hour shift work and led to health benefits for those with cardiometabolic risks
- Identification of a substance produced by the gut that links surgical and dietary weight-loss therapies to improvements in metabolic and digestive health in mice
- Uncovering biological pathways that link stress to worsening inflammatory bowel disease (IBD) symptoms
- Identification of new risk factors for IBD in individuals from countries in East Asia, which helps to understand and predict the disease across diverse populations
- Finding that an FDA mandate limiting the amount of acetaminophen in combination opioid-acetaminophen pain relievers was associated with lower rates of liver failure from these combination medicines, although rates of liver failure from acetaminophen alone increased
- Creation of the most comprehensive atlas of the human kidney to date, which can be used to help identify kidney disease subgroups and discover new, personalized treatments
- Identification of a previously unknown role of glucose uptake in polycystic kidney disease through development of a novel model system from two innovative techniques

- Revelation that two manifestations of overactive bladder may reflect a spectrum of symptom severity rather than two distinct subtypes of urinary urgency with or without incontinence

The advances, initiatives, workshops, and other efforts featured in this annual report reflect progress in research aligned with the goals and cross-cutting areas of the [NIDDK Strategic Plan for Research](#). The Strategic Plan continues to guide the Institute and presents a broad vision for accelerating research toward pathways to health for all.

This report also includes personal perspectives of those who have given time and effort to participate in NIDDK-sponsored clinical research. A young woman at high risk for developing clinical type 1 diabetes describes how her participation in a clinical trial has helped stave off the disease. A man tells of his experience with atypical diabetes, and how participating in a clinical study could lead to new insights and treatments for this unusual form of the disease. Two cousins—one a kidney donor, the other the recipient—share their experiences with a study that

is aiming to improve outcomes after kidney donation and kidney transplantation. A woman describes what it is like to live with serious pancreatitis, and how she is volunteering in a study that will help to understand and treat this disease.

NIDDK continues efforts to ensure that knowledge gained from its research is disseminated to health care providers, patients, and the public. We develop science-based information on diseases and disorders within the NIDDK mission and share it through our website and other channels. I invite you to visit us at [www.niddk.nih.gov](http://www.niddk.nih.gov). You can also find health information, news, and scientific advances related to NIDDK research by following the links to our social media feeds below.

This report reflects only a fraction of the immense body of NIDDK-funded research across the country, performed by basic scientists, clinical investigators, and study volunteers. Moving forward, we remain committed to supporting these important areas of research and translating scientific discoveries into improvements in the health and quality of life of all people.

The efforts featured in this publication reflect the core mission of NIDDK, including the Director’s guiding principles:

- Maintain a vigorous investigator-initiated research portfolio
- Support pivotal clinical studies and trials
- Promote a steady and diverse pool of talented new investigators
- Foster exceptional research training and mentoring opportunities
- Ensure knowledge dissemination through outreach and communications

More information on how NIDDK supports these core values can be found in the [Funding Trends and Support of Core Values](#) section of the [NIDDK website](#).

## Griffin P. Rodgers, M.D., M.A.C.P.

Director  
National Institute of Diabetes and Digestive and Kidney Diseases  
National Institutes of Health  
U.S. Department of Health and Human Services



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Health equity means that everyone has opportunities to live long, healthy, productive lives—no matter who they are, how they identify, or where they live. NIDDK is committed to advancing health equity by supporting research to enable all communities affected by NIDDK diseases and conditions to thrive. To that end, as highlighted in this chapter, a new report outlines research recommendations from the NIDDK Working Group of Council on Health Disparities and Health Equity Research. These recommendations complement other NIDDK strategic planning efforts with high-impact opportunities and equity-focused principles to advance the Institute’s mission and to pursue pathways to health for all.



# Cross-Cutting Science

*Medical advances are not usually achieved in great, intuitive leaps. More often, new prevention strategies, treatments, and cures result from a long, gradual accumulation of knowledge from years of scientific research. Insights into fundamental biological building blocks and processes—genes, the proteins they encode, the inner workings of cells, and the ways cells communicate with each other—can have broad and far-reaching implications. Indeed, many significant advances in our understanding and treatment of disease can be traced to laboratory studies whose relevance to health could not have been fully known or appreciated at the time they were conducted.*

NIDDK's research mission is broad and includes some of the most chronic, common, consequential, and costly diseases and conditions affecting people in the United States. Many of these diseases and conditions are associated with health disparities, and innovative new ways to combat these disparities are needed to promote health equity. Additionally, while scientific talent is well represented in people of all backgrounds, opportunity is not. Thus, NIDDK strives today to promote a steady and diverse pool of talented investigators who can make tomorrow's innovative breakthroughs.

Described in this chapter are examples of NIDDK efforts to overcome these critical challenges through research and scientific workforce development. In these ways and others, NIDDK works toward its goal of building a pathway to health for all.

## DELVING INTO DNA STRUCTURE AND REPAIR

### **Insights Into Cellular Regulation of Chromosome “Caps”:**

Researchers identified a key regulator of human telomere length with potential implications for diseases and disorders of telomere biology as well as broadly for human health. Telomeres are sequences of DNA found on the ends of chromosomes—the structures in which DNA is organized within a cell. When a cell divides, a bit of DNA sequence from the chromosome end is lost naturally. This shortening is counteracted by a protein that synthesizes new telomeric DNA, so telomeres act as a “cap” to protect the critical genetic information from degradation and keep chromosomes stable. Natural telomere shortening is a hallmark of aging and is associated with increased incidence of disease, including age-related

diseases, and poorer outcomes. In addition, disruption of telomere maintenance (such as through inherited genetic alterations) can cause a number of conditions including bone marrow failure, cardiovascular disease, lung disease, liver cirrhosis, and cancer. Bone marrow failure syndromes, also known as telomere biology disorders, lead to impaired blood production. Therefore, understanding the regulation of human telomere length is vital to developing treatments for a variety of diseases and disorders and promoting human health.

Using an approach that allowed them to screen a large number of genes for effects on telomere length in human cells in the laboratory, scientists identified the molecule thymidine (one of the building blocks [bases] of DNA), and genes that affect levels of thymidine, as important regulators. When genes predicted to promote production of thymidine were turned off, the scientists observed short telomeres in the cells. Conversely, when genes predicted to decrease levels of thymidine, such as the thymidine-degrading gene *SAMHD1*, were turned off, they found longer telomeres. Interestingly, this regulation appeared to be specific and unique to thymidine; altering the levels of the other three DNA bases did not have the same effect. The researchers also demonstrated similar effects when supplementing the cells with thymidine or treating the cells with small molecules that decreased thymidine production. These results suggest a novel and key role for thymidine in regulating telomere length.

*Identification of a key regulator of telomere length reveals a new potential strategy to treat a variety of diseases and disorders.*

Given that some current therapies for cancer and other diseases alter production of molecules like thymidine, the scientists tested whether a similar approach might have potential to treat telomere biology disorders. They found that supplementation of thymidine in cells from people with different telomere biology disorders promoted telomere lengthening, suggesting the possibility of a new therapeutic strategy. This promising approach will need to be studied in animals, including humans, to determine whether the effects are similar to those observed in the laboratory and to develop further this exciting advance.

*Mannherz W and Agarwal S. Thymidine nucleotide metabolism controls human telomere length. Nat Genet 55: 568-580, 2023.*

**Molecular Structures Provide Insight Into Key Players in DNA Damage Repair:** New research from scientists in NIDDK's Intramural Research Program has provided useful insight into the function of proteins involved in repair of damaged DNA. DNA is one of the basic building blocks of life, providing the genetic code to make every cell in our bodies. We encounter environments and situations daily that can damage our DNA, such as exposure to certain chemicals, UV radiation, and errors cells make in replicating their DNA. Additionally, some chemotherapeutic drugs intentionally damage DNA to effectively kill cancer cells. If left unchecked, DNA damage itself can lead to genetic alterations that can contribute to the development of several inheritable disorders and even some cancers. Therefore, the body uses different strategies to repair the various types of DNA damage, including one strategy called nucleotide excision repair (NER). NER involves several different proteins within the cell working together to recognize and cut out the damaged area of DNA. Understanding the details of this process could unlock new ways to treat or prevent some disorders and cancers.

Using synthetic mimics of different types of DNA damage, together with proteins known to be involved in NER in humans, the researchers created detailed molecular images of the protein interactions with the damaged DNA site. Detection of damaged DNA in the cell can occur through two different pathways: through stalling of the process by which cells create RNA copies of DNA, or through recognition by a group of proteins that scan the genome for potential damage. These proteins are called xeroderma pigmentosum complementation group C, or XPC, named after one type of condition in which NER is compromised, resulting in extreme sensitivity to UV light. After recognition via either pathway, a new group of

NER-related proteins is recruited to the site to take over the process of removing the damage. The researchers discovered that these proteins work together to separate the two strands of DNA, much like unzipping a zipper from the center, to create a space—or “bubble”—where proteins can confirm the damaged strand of DNA and cut it out.

The findings from this study have revealed key roles for several proteins involved in the NER process for repairing DNA damage. The importance of these proteins in maintaining health is highlighted by cases where compromised protein function is associated with certain cancers and disorders. NER is also thought to contribute to resistance to some chemotherapy drugs. This study's findings could enable the development of more effective cancer treatments and potential genetic therapies targeting the NER process.

*Kim J, Li CL, Chen X,...Yang W. Lesion recognition by XPC, TFIIH and XPA in DNA excision repair. Nature 617: 170-175, 2023.*

## BUILDING BETTER RESEARCH TOOLS

**Improved RNA Detection Technique Enhances Ability to Monitor Cellular Messages:** Scientists have improved an existing technique to detect RNA messages inside cells, making it faster and cheaper to simultaneously track the activity of multiple genes. Messenger RNAs (mRNAs) carry protein assembly instructions from genes to the cellular machinery where proteins are made. Technologies that track which mRNAs are in what cells at what time can be powerful, versatile tools. These tools can help researchers better understand the roles of the proteins the mRNAs encode, especially in processes where the activity of many genes changes at once, such as when healthy cells are disrupted by disease.

*Researchers streamlined a cutting-edge RNA detection method to make it cheaper, faster, and more flexible.*

Researchers have now reported on improvements to one RNA detection method, called clampFISH. This technique uses a series of probes customized to stick to mRNAs encoding instructions for a specific protein of interest. A large molecular scaffold is then built over the mRNA, binding fluorescent dyes that amplify the

relatively weak “signal” from a single mRNA so it can be detected by microscopy. A weakness of the original “clampFISH 1.0” procedure, however, was that it was relatively expensive and time-consuming, especially when detecting multiple different mRNAs at once.

To create clampFISH 2.0, the scientists modified the structure of the scaffold and streamlined the protocol to make it faster and cheaper. They verified that clampFISH 2.0 still accurately and precisely detected targeted mRNAs and that it could pinpoint an mRNA's location within a cell. clampFISH 2.0 also generated a strong enough signal to allow imaging by lower-powered microscopes with wider fields of view, which allowed researchers to analyze cells faster. This feature was particularly useful in studying rare

events. For example, scientists used clampFISH 2.0 in a very large tumor cell sample to measure the simultaneous activity of 10 genes, observing for the first time how those genes activate together in rare instances that can lead to drug resistance. Researchers also performed a similar analysis on preserved tumor tissue, such as would be generated by a cancer biopsy.

Overall, the streamlined clampFISH 2.0 procedure was shown to be a rapid and flexible tool to efficiently detect multiple mRNAs at once, allowing the study of research questions previously hindered by technical limitations.

*Dardani I, Emert BL, Goyal Y,...Raj A. ClampFISH 2.0 enables rapid, scalable amplified RNA detection in situ. Nat Methods 19: 1403-1410, 2022.*

# FEATURE

## Pathways to Health for All: A New Report From NIDDK's Health Disparities and Health Equity Research Working Group of Council

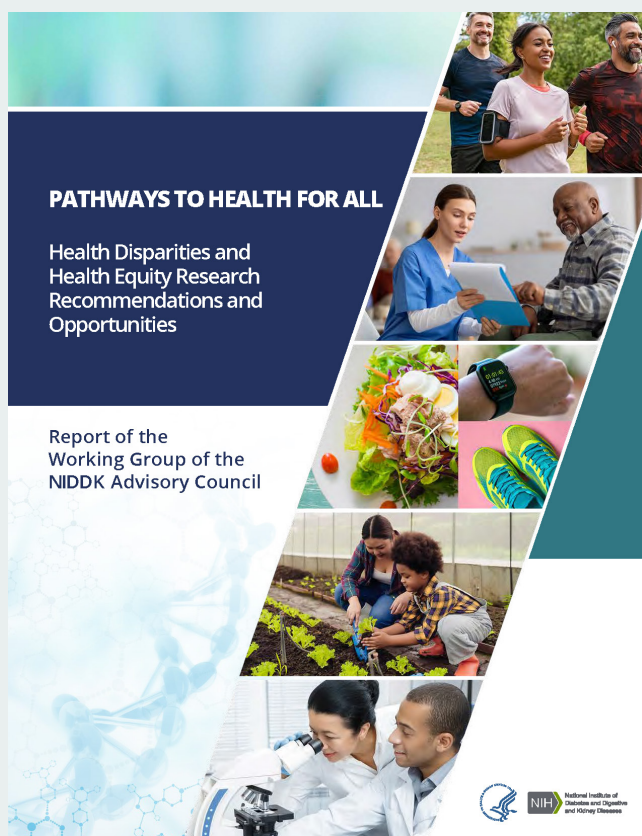
In Spring 2023, NIDDK announced the release of [Pathways to Health for All](#), a new report from the Health Disparities and Health Equity Research Working Group of the NIDDK Advisory Council. The Report makes innovative recommendations to advance research in health equity and health disparities. It also includes guiding principles for embedding equity into research

and tips for researchers, both at NIDDK and externally, who plan to engage in robust health equity research.

Many of the diseases and conditions in NIDDK's research mission disproportionately affect racial and ethnic minority populations and others who are medically underserved or marginalized. Health equity means that people of all backgrounds and ages have fair and just opportunities to live long, healthy, productive lives. The social and structural drivers of health disparities operate in multiple sectors and at levels beyond NIDDK's traditional scope, but research can make a valuable contribution toward advancing health equity. Importantly, social determinants of health—the conditions in which people are born, grow, work, live, and age—can be primary contributors to health inequities among groups that are socially or economically marginalized.

The report presents five overarching research recommendations, each with corresponding opportunities, for high-impact research and actionable strategies:

1. Strengthen community engagement through partnership, power sharing, and capacity building to improve research
2. Advance research on the mechanisms by which biological, behavioral, environmental, and structural factors interact to affect health, disease, and resilience



# FEATURE

3. Advance research on interventions and studies to address racism, health-related social needs, and social determinants of health
4. Promote new methods, measures, tools, and technologies to accelerate achievement of health equity research goals
5. Enhance NIDDK collaboration, structures, and programs to support robust research in health equity

Community members—including patients, caregivers, and others living with or at risk for diseases within NIDDK’s mission—were involved throughout the report development process as Working Group members who shared their lived experiences, perspectives, values, and priorities. These insights are featured in call-out boxes throughout the report. One member commented, “It made me proud and honored that my opinion was

valued, and it made me want to go out and do research in the community to see what is missing or where we can help or fill the void to respond to the community’s voice or the community’s calling.” Another remarked, “I believe participating in this group will facilitate change for us that feel we have been left behind.”

NIDDK thanks the Working Group participants, including Council members, community members, patients, caregivers, NIDDK staff, and external researchers across the country, who contributed their time, expertise, and perspectives to this project. NIDDK research can foster scientific breakthroughs, provide the evidence base needed for equitable and effective clinical practice, and inform public health programs and policies. NIDDK is poised to act—both within its traditional scope and with innovative strategies and collaborations—to implement the recommendations in the report to effect meaningful change within its research mission.

# Mentorship and the NIDDK Commitment to Increasing Scientific Workforce Diversity

Strengthening biomedical research workforce diversity and training is a cross-cutting theme in the [NIDDK Strategic Plan for Research](#), and the importance of nurturing a diverse, world-class workforce is one of the core values described in NIDDK's report [Pathways to Health for All](#). This is because research shows that diverse teams working together and capitalizing on innovative ideas and distinct perspectives outperform homogenous teams. Scientists and trainees from diverse backgrounds and life experiences bring different perspectives, creativity, and individual interests to address complex problems. In this way, they foster scientific innovation, enhance global competitiveness, contribute to robust learning environments, improve the quality of research, enhance public trust, and increase the likelihood that health disparities and the needs of underserved populations are addressed in biomedical research.

Studies also show that robust mentorship is an important predictor of success for researchers, including the ability to obtain research funding. Indeed, effective mentoring is critical for career advancement in biomedical research, particularly at early career stages and for individuals from underrepresented backgrounds. A National Academy of Sciences, Engineering, and Medicine report on the science of effective mentorship in science, technology, engineering, mathematics, and medicine highlights mentorship as a catalytic factor in an individual's participation, persistence, and success in these fields. They also found that although mentorship has a particularly positive effect on individuals from underrepresented backgrounds, these individuals were also less likely to receive mentoring than were trainees from well-represented groups.

For these reasons, NIDDK has a long-standing commitment to fostering training and mentorship for diverse students interested in research careers and is continuously testing new approaches and maintaining existing programs, such as the Institute's flagship partnership with the Network of Minority Health Research Investigators (NMRI). NMRI has had support from NIDDK through its Office of Minority Health Research Coordination for more than 20 years, but is "owned" by its members. NMRI's success begins with the dedication of senior investigators to mentor and serve as role models for junior investigators and continues with their ongoing participation and with recruitment of new members.

Testimonials of those members are evidence for the power of this approach. For example, Deidra Crews, M.D., a professor in the Division of Nephrology at the Johns Hopkins University School of Medicine said, "NMRI has provided me with a network of colleagues across the country who are dedicated to improving the health of socially marginalized communities and has served as a collective source of mentorship and sponsorship throughout my career." Likewise, Susan Brown, Ph.D., an associate professor in the University of California Davis Department of Internal Medicine calls NMRI "a gem. This community of generous and accomplished scholars offers a new entry intellectual home, where you can bring your whole self. NMRI offers a sense of connection and purpose that helped sustain me through the critical early years of my research career. This has been equally true during challenging times of professional transition, pandemic, and national social upheaval. It's an honor and a privilege to continue as a member."

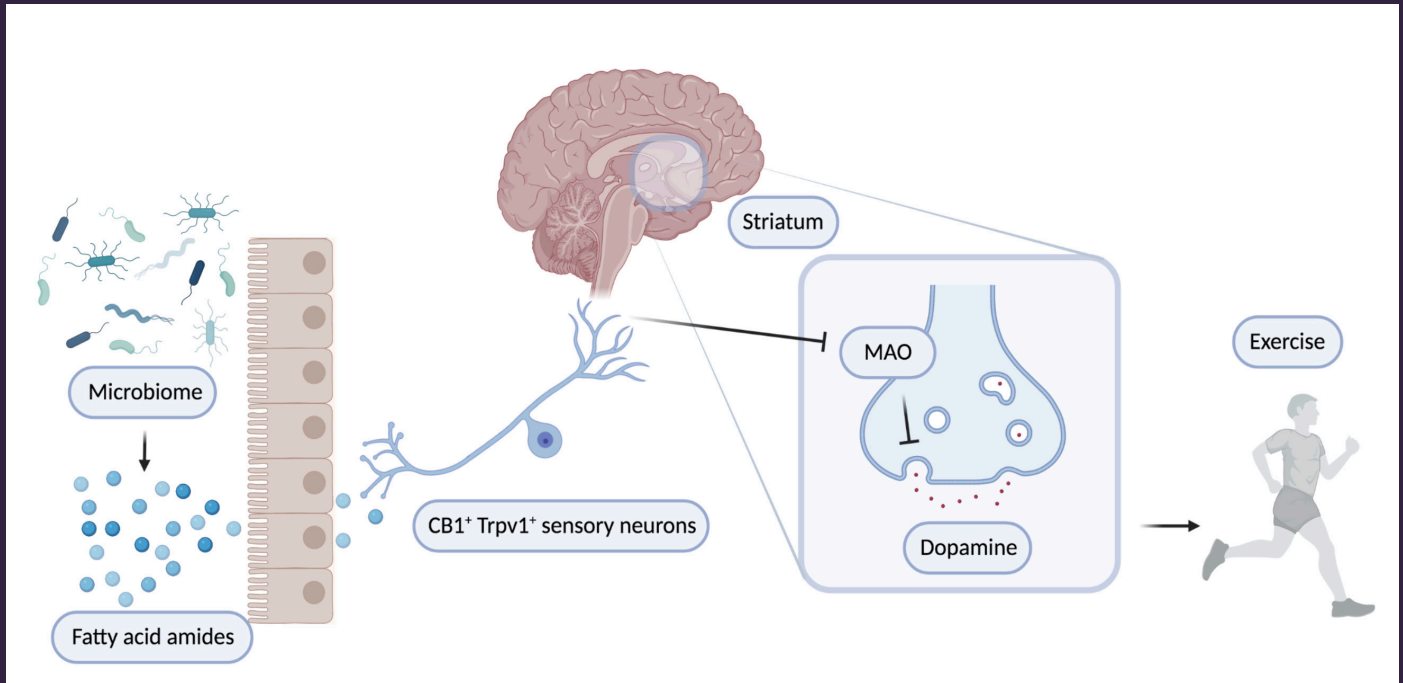
# FEATURE

Lina Huerta-Saenz, M.D., an assistant professor in the Department of Pediatrics, Division of Endocrinology at the Pennsylvania State University, recalls “a time during my career training in the United States when nobody looked like me in a room, and it was very hard to visualize myself in a future leadership position.... Now, I can see myself as a future leader because I know it is possible.” This transformation of outlook demonstrates why NMRI and other NIDDK scientific workforce diversity programs remain so important: as NIDDK Director Dr. Griffin Rodgers has noted, scientific ability is broadly distributed around the country and the world, but opportunity to build a successful scientific career is not.

Accordingly, NMRI is just one of the many approaches that NIDDK takes to advance scientific workforce diversity and mentorship. Others include the Diversity Supplement Program, which covers 2 years of costs, materials, and salaries for young researchers from backgrounds underrepresented in the biomedical workforce, and providing travel awards to attend the annual conferences of the National Medical Association and the National Hispanic Medical Association.

These efforts are complemented by diversity efforts supported by the extramural and intramural NIDDK Divisions. Recently, the Institute expanded such efforts with Helping to Accelerate Research Potential, a program designed to provide opportunities and mentorship for current NIDDK grantees, especially postdoctoral scholars and junior faculty from diverse backgrounds, to enhance their skills in areas that are critical for establishing and maintaining successful independent academic research careers. In addition, NIDDK Investigator Awards to Support Mentoring of Early Career Researchers from Diverse Backgrounds is an initiative designed to provide high-quality mentoring to graduate students and postdoctoral fellows from diverse backgrounds, including those from underrepresented groups, by established, NIDDK-funded scientists.

Together, each of these programs is helping to advance NIDDK’s research mission by developing a scientific workforce that realizes the tremendous, untapped potential of future scholars from every background and region of the Nation.



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<sup>+</sup> Trpv1<sup>+</sup>” 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.

Reprinted from *Nature* 612, Dohnalová, L. et al, A microbiome-dependent gut-brain pathway regulates motivation for exercise, 739–747, Copyright 2022, with permission from Springer *Nature*. Image provided courtesy of Dr. Christoph Thaiss, University of Pennsylvania.



# 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.<sup>1</sup> 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.<sup>2</sup> Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial costs of diagnosed diabetes in the United States in 2022—including costs of medical care, disability, and premature death—was \$413 billion.<sup>3</sup> Effective therapy can prevent or delay diabetic complications, but 23 percent of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.<sup>1</sup>

*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.<sup>1</sup> It most often develops during childhood but may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack that destroys insulin-producing  $\beta$  (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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<sup>1</sup> Centers for Disease Control and Prevention. National Diabetes Statistics Report. <https://www.cdc.gov/diabetes/data/statistics-report/index.html>. Accessed November 21, 2023.

<sup>2</sup> Cowie CC, et al., Eds. Diabetes in America, 3rd edition. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication Number 17-1468, 2018.

<sup>3</sup> American Diabetes Association. Economic costs of diabetes in the U.S. in 2022. *Diabetes Care* 2023, dci230085.

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  $\beta$ -cell replacement therapies, such as islet transplantation, that can eliminate the need for insulin injections, toward the ultimate goal of curing type 1 diabetes.

*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.*

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.<sup>1</sup> 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  $\beta$  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.<sup>1</sup> 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.

*Type 2 diabetes is increasingly being diagnosed in children and adolescents, disproportionately affecting American youth from racial and ethnic minority populations.*

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.

*From 2002 to 2018 in the United States, youth type 1 diabetes diagnoses increased by 2 percent per year, and type 2 diabetes diagnoses increased by over 5 percent per year.*

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.

*Wagenknecht LE, Lawrence JM, Isom S,...Divers J, for the SEARCH for Diabetes in Youth study. Trends in incidence of youth-onset type 1 and type 2 diabetes in the USA, 2002–18: results from the population-based SEARCH for Diabetes in Youth study. Lancet Diabetes Endocrinol 11: 242–250, 2023.*

**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.

*Gulanski BI, Butera NM, Krause-Steinrauf H,...Aroda VR; for the GRADE Research Group. Higher burden of cardiometabolic and socioeconomic risk factors in women with type 2 diabetes: an analysis of the Glycemic Reduction Approaches in Diabetes (GRADE) baseline cohort. BMJ Open Diabetes Res Care 11: e003159, 2023.*

## **PREDICTING, PREVENTING, AND TREATING TYPE 1 DIABETES**

### **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  $\beta$  (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  $\beta$  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.

*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  $\beta$  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.

*Nakayasu ES, Bramer LM, Ansong C,...Metz TO, the TEDDY Study Group. Plasma protein biomarkers predict the development of persistent autoantibodies and type 1 diabetes 6 months prior to the onset of autoimmunity. Cell Rep Med 4: 101093, 2023.*

### **Immune-Targeting Drug Improves Insulin Production and Alters Autoimmune Response but Does Not Delay Type 1 Diabetes:**

A clinical trial testing the immune-targeting drug abatacept in people at high risk of developing type 1 diabetes demonstrated that the drug had beneficial effects on  $\beta$  (beta) cell function but did

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  $\beta$  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  $\beta$ -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.

*Russell WE, Bundy BN, Anderson MS,...Herold KC, and the Type 1 Diabetes TrialNet Study Group. Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. Diabetes Care 46: 1005-1013, 2023.*

**Advances in Artificial Pancreas Technologies for Managing Type 1 Diabetes:** Two clinical trials testing artificial pancreas technologies for managing type 1 diabetes have reported positive results, with one

leading to the approval of a new commercial device. A major goal of NIDDK-supported research has been to develop artificial pancreas devices—also called closed-loop systems or bionic pancreases—that automate type 1 diabetes management and help people with the disease keep their blood glucose (sugar) levels in a healthy range with minimal burden. There has been significant progress, with closed-loop systems now on the market. Two recent multi-center clinical trials tested technologies to expand the availability of closed-loop devices.

In the first trial, scientists tested an experimental bionic pancreas device, which requires less user input and provides more automation compared to other available closed-loop technologies. The trial enrolled 326 female and male participants ages 6 to 79 years with type 1 diabetes. They were randomly assigned to either the bionic pancreas group or a standard care control group. Participants in the control group used a continuous glucose monitor along with their personal pre-study insulin delivery method, which for nearly one-third of them was a commercially available artificial pancreas device. After the 13-week trial, children and adults using the bionic pancreas had improved hemoglobin A1c (a measure of average blood glucose levels) compared to participants in the control group. The bionic pancreas users also spent more time, an increase of about 2.5 hours per day, with their blood glucose levels in the recommended target range. Based on these positive data, the U.S. Food and Drug Administration (FDA) approved the device for use in people with type 1 diabetes ages 6 and older.

*Clinical trials testing artificial pancreas technologies for managing type 1 diabetes in children and adults have reported positive results, with one leading to the FDA 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.

*Russell SJ, Beck RW, Damiano ER,...Dauber A; for the Bionic Pancreas Research Group. Multicenter, randomized trial of a bionic pancreas in type 1 diabetes. N Engl J Med 387: 1161-1172, 2022.*

*Wadwa RP, Reed ZW, Buckingham BA,...Breton MD; for the PEDAP Trial Study Group. Trial of hybrid closed-loop control in young children with type 1 diabetes. N Engl J Med 388: 991-1001, 2023.*

## **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.

*Miller CK, Nagaraja HN, Cheavens J, Fujita K, and Lazarus S. Impact of a novel diabetes prevention intervention for early slow weight loss responders among adults with prediabetes: an adaptive trial. Diabetes Care 45: 2452-2455, 2022.*

### **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, 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.

*Kimura M, Iguchi T, Iwasawa K, ...Takebe T. En masse organoid phenotyping informs metabolic-associated genetic susceptibility to NASH. Cell 185: 4216-4232.e16, 2022.*

## **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  $\beta$  (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  $\beta$  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  $\beta$  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.

Wortham M, Liu F, Harrington AR,...Sander M. Nutrient regulation of the islet epigenome controls adaptive insulin secretion. *J Clin Invest* 133: e165208, 2023.

## 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.

Wei W, Riley NM, Lyu X,...Long JZ. Organism-wide, cell-type-specific secretome mapping of exercise training in mice. *Cell Metab* 35: 1261-1279.e11, 2023.

**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



performance. 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.

Dohnalová L, Lundgren P, Carty JRE, ...Thaiss CA. A microbiome-dependent gut-brain pathway regulates motivation for exercise. *Nature* 612: 739-747, 2022.

## 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.

*Treating the rare genetic disorder Pompe disease in utero may halt prenatal organ damage and improve health after birth.*

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.

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## Celebrating the 50<sup>th</sup> Anniversary of Diabetes Research Centers



The year 2023 marked the 50<sup>th</sup> 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.

It all started with the vision, prescience, and advocacy of Dr. Robert H. Williams, Professor and Chairman of the Department of Medicine at the University of Washington in Seattle. In the early 1970s, Dr. Williams convinced his friend and patient Senator Warren G. Magnuson that diabetes research should be done via a multidisciplinary approach. Senator Magnuson liked this idea and championed establishment of the first Diabetes Endocrinology Research Center at Vanderbilt University in 1973. Since then, the program has grown to support Research Centers at 17 different institutions across the country.

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

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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

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“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  $\beta$  (beta) cells in clusters called islets in the pancreas. Replacing these  $\beta$  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  $\beta$  cells are lost in type 1 diabetes and how they can be protected or replaced in people. HIRN investigations into how  $\beta$  cells develop and mature are allowing scientists to make new  $\beta$ -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  $\beta$ -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

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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



*Shown left to right: NIDDK Director Dr. Griffin P. Rodgers, Sen. Susan Collins (R-ME, Committee Vice Chair), Maria Muayad, James "Jimmy Jam" Harris, Elise Cataldo, Dr. Aaron J. Kowalski, and Sen. Patty Murray (D-WA, Committee Chair), at the July 11, 2023 hearing before the Senate Committee on Appropriations. Photo credit: Getty Images for JDRF.*

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  $\beta$  (beta) cells that have been destroyed in type 1 diabetes. In islet transplantation, islets (which contain  $\beta$  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



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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  $\beta$ -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.

## New National Engagement Innovation Center to Advance Health Equity Research in Type 2 Diabetes

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.

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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.

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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](http://www.atypicaldiabetesnetwork.org).*

## Mike's Story



Mike (left) and his two brothers participate in the NIDDK-supported RADIANT study

Mike's diabetes journey has not been like that of most people with type 1 or type 2 diabetes. A couple days before his 28<sup>th</sup> 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.***

Mike's primary care physician at the time told him that based on test results he had characteristics of both type 1 and type 2 diabetes, but his disease was not either type definitively. "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?'" he recalls. 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

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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

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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  $\beta$  (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  $\beta$  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.

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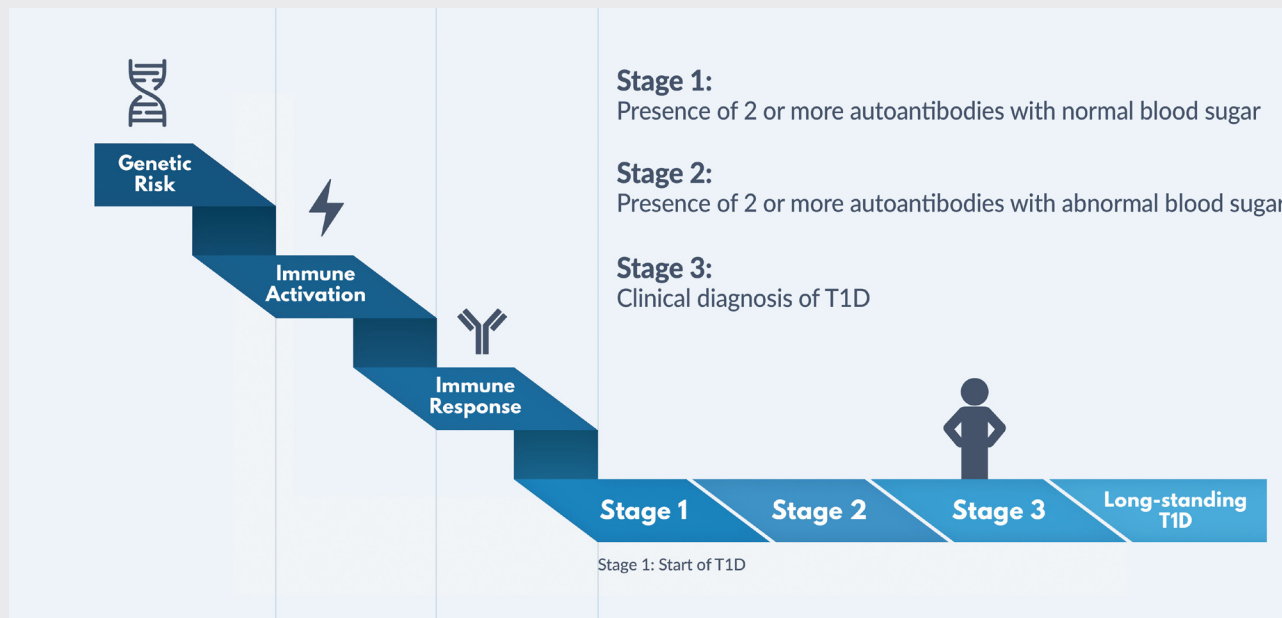


Figure 1: This graphic illustrates how type 1 diabetes (T1D) progresses. Genetic risk, combined with an unknown environmental trigger(s), is followed by inappropriate activation of the immune system to attack the insulin-producing  $\beta$  cells. The appearance of more than one islet-cell autoantibody 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.)

## 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  $\beta$ -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  $\beta$ -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.

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## 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



*Mikayla participated in a Type 1 Diabetes TrialNet clinical trial testing teplizumab*

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.

***Mikayla enrolled in the teplizumab TrialNet clinical trial "to prevent what happened to [my sister] from happening to other people."***

### **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

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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,

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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."***

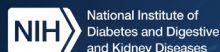
Now a college senior, Mikayla is pursuing her career goal of becoming a medical illustrator—combining her love of drawing with her passion for anatomy. She is an avid reader and a huge

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.

NIH Obesity Research Task Force Symposium

## Medications to Treat Obesity: Past, Present, and Future



September 8, 2023

Natcher Conference Center • Building 45 • NIH Campus • Bethesda, MD



The NIH-wide Obesity Research Task Force was established to accelerate progress in obesity research across NIH, given the importance of the obesity epidemic as a major public health problem and its relevance to the missions of most of the NIH Institutes, Centers, and Offices. The Task Force is co-chaired by the Director of NIDDK, Dr. Griffin P. Rodgers; the Director of the National Heart, Lung, and Blood Institute, Dr. Gary H. Gibbons; and the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Dr. Diana W. Bianchi. The Task Force holds two seminars each year, covering a broad range of topics. On September 8, 2023, the Task Force convened a symposium on medications to treat obesity where seven distinguished scientists highlighted their research in this field, and two individuals who have used these medications shared their personal perspectives and experiences. A summary of this seminar is in this chapter.

# Obesity

***Obesity has risen to epidemic levels in the United States. Individuals who have obesity may develop devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within NIDDK's mission. Nearly 42 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.<sup>1,2</sup> Nearly 20 percent of children and adolescents also have obesity, and thus are at increased risk for developing serious diseases both during their youth and later in adulthood.<sup>1,3</sup> Obesity disproportionately affects people from certain racial and ethnic groups and those who are socioeconomically disadvantaged.***

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment (social determinants of health) such as a lack of healthy, affordable food and places to exercise in many communities; sedentary jobs; and other conditions that influence what, when, and how much people eat. Diet, activity, and aspects of our environment also may modify biological factors in ways that promote obesity. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions.

NIDDK supports a multidimensional research portfolio on obesity, spanning basic, clinical, and translational research. This research is coordinated through NIDDK's Office of Obesity Research and supported by NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases and Division of Digestive Diseases and Nutrition. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental interventions for children and adults in health care, home, community, and other settings using a variety of approaches and technologies, surgical interventions, and combinations of strategies. In parallel, NIDDK-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches.

***Nearly 42 percent of U.S. adults and nearly 20 percent of children and adolescents have obesity.***

NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices to promote collaboration and enhance obesity research across NIH.

***NIDDK supports basic, clinical, and translational research to discover how body weight is regulated and to design and evaluate approaches for preventing and treating obesity.***

<sup>1</sup> Stierman B, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files—Development of files and prevalence estimates for selected health outcomes. Centers for Disease Control and Prevention. National Health Statistics Reports 158, 2021.

<sup>2</sup> Although higher BMI levels generally reflect higher levels of body fat on a population level, BMI does not directly measure body fat or take into consideration age, biological sex, or health risks of populations other than non-Hispanic White.

<sup>3</sup> For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).



## TIMING MEALS TO IMPROVE HEALTH

**How Meal Timing May Reduce Obesity and Improve Metabolic Health:** Scientists have revealed a mechanism behind why eating late at night can be linked to weight gain and metabolic disease in a study in mice. The connection between meal timing, sleep, and obesity is well known, but poorly understood. Research shows that eating during inactive periods (at night for people and during the day for nocturnal mice) can disrupt the body's internal molecular "clock," leading to an impairment of numerous physiological processes across the day/night cycle, including energy (calorie) intake and energy expenditure. This mistimed feeding can also alter fat tissue and contribute to weight gain. Understanding how meal timing affects metabolism could help the development of interventions for obesity.

To explore the reasons behind mistimed feeding and weight gain, researchers fed male mice a high-fat diet either exclusively during their inactive or their active period. Within 1 week, mice fed during their inactive period gained more weight and experienced decreased energy expenditure compared to those fed only in the active period, replicating what has been previously shown. This result led the team to investigate whether fat tissue metabolism differed based on the meal timing. Using mice that were genetically altered to have enhanced thermogenesis—or heat released by fat cells burning calories—they found that the mice fed during the inactive period did not gain weight and had improved glucose (sugar) tolerance, a measure of metabolic health, compared to mice without enhanced thermogenesis fed the same food during the same time of day, suggesting that thermogenesis protects against weight gain resulting from inactive period meals. Next, they sought to determine the specific metabolic underpinnings of this protection and identified the molecule creatine, which the body stores to use as energy, as the likely metabolic mechanism through which restricting feeding to the active period improves health. Indeed, genetic disruption of creatine synthesis in fat cells reduced the metabolic benefits of feeding restricted to the active period.

*Scientists have revealed a mechanism behind why eating at night can be linked to weight gain and metabolic disease.*

Taken together, these results expand upon our knowledge of the mechanisms that underlie the benefits of restricting eating to active periods. Time-restricted feeding in people is a promising approach to decrease body weight and improve metabolic health with few side effects. However, given that many people are unable to maintain this schedule for reasons including shift work, sleep loss, and the social aspect that people tend to dine in the evening, more research could help inform the design of behavioral and therapeutic interventions.

*Hepler C, Weidemann BJ, Waldeck NJ,...Bass J. Time-restricted feeding mitigates obesity through adipocyte thermogenesis. Science 378: 276-284, 2022.*

**Limiting Eating Times to Improve Health of People Who Work Around the Clock:** In a study to improve the health of people who do shift work, researchers found that time-restricted eating was feasible for firefighters on 24-hour schedules and led to cardiometabolic benefits, particularly for those who had health risks when the study began. Shift work disrupts cycles of sleeping, eating, and activity, and it is associated with cardiovascular and metabolic disease. Thus, the researchers developed an intervention to reduce these health risks while being compatible with shift-work schedules and the nature of firefighting work, and they tested this in a clinical trial.

*Researchers found that time-restricted eating was feasible for firefighters on 24-hour shift work and led to health benefits for those with cardiometabolic risks.*

The intervention focused on time-restricted eating (TRE), limiting calorie intake to a 10-hour window per day most days of the week for 12 weeks. As an innovative strategy to inform recruitment and other aspects of the study design, the researchers consulted with fire departments and related organizations and did a 24-hour ride-along to understand the participants' shift-work lifestyle. The study participants, 137 firefighters working 24-hour shifts, were recruited from a local fire-rescue department. Over 90 percent were male, reflecting the fire department's demographics, and were from different racial groups and ethnicities; a majority were White though race was unknown for some participants. The researchers randomly assigned the participants to either the TRE group or a standard of care group. They advised both groups to follow a Mediterranean diet (e.g.,

eating more fruits and vegetables, olive oil, and fish); collected thousands of time-stamped food and beverage records, which the firefighters logged using an app on their smartphones; and examined health measures. The results showed that TRE was feasible, as the firefighters in the TRE group reduced their eating time from around 14 hours per day when the study began to about 11 hours per day. Among the subset of participants who had elevated risk factors before the intervention began, those in the TRE group had improved blood glucose (sugar) and diastolic blood pressure by the end of the study, compared to the standard of care group. Among all the participants, those in the TRE group had improvements in a blood lipid, VLDL, and better quality of life measures compared to the standard of care group. Some health improvements were seen in both groups (e.g., systolic blood pressure), possibly associated with dietary changes. No adverse events were reported.

These encouraging results show health benefits of time-restricted eating for people doing shift work and open the way to potential future studies with larger numbers of participants, including more women, and that explore longer-term health effects.

*Manoogian ENC, Zadourian A, Lo HC,...Panda S. Feasibility of time-restricted eating and impacts on cardiometabolic health in 24-h shift workers: the Healthy Heroes randomized control trial. Cell Metab 34: 1442-1456.e7, 2022.*

## EXAMINING THE EFFECTS OF WEIGHT-LOSS SURGERIES

**Weight-Loss Surgery That Reprograms the Body's Internal Clock to Improve Metabolism and Eating Behavior:** Scientists studying gastric bypass surgery, a treatment for severe obesity that also ameliorates type 2 diabetes, discovered that, in mice, this surgery reprograms the biological day/night "clock" to adjust the timing and amount of food consumption and improve glucose (sugar) metabolism. In designing the study, they sought to explore a potential connection between weight-loss surgery and the body's innate molecular clock based on previous research. Past studies showed that this clock synchronizes metabolism, eating, and other processes with 24-hour day/night cycles, and that risks for obesity and type 2 diabetes increase when day/night cycles are disrupted, for example, when people do shift work.

For their study, the researchers compared mice that had Roux-en-Y gastric bypass (RYGB) surgery to those of

similar body weight that did not have the surgery, with both groups on a high-fat diet. While a high-fat diet typically alters the amount and timing of food intake in mice, those that had RYGB surgery ate less overall and shifted more of their food consumption to the time in the day/night cycle when mice normally eat. The researchers then analyzed different tissues for potential effects on genes encoding clock functions, which exist throughout the body, and found that RYGB surgery led to changes in the activity of clock genes in the liver, an organ with important roles in glucose metabolism. To further test the relevance of the clock to surgical outcomes, they examined mice that lacked a key clock gene. They discovered that, compared to other mice, the clock-deficient mice lost less weight after RYGB surgery and did not have improvements in glucose metabolism. Thus, a functional clock was needed for these beneficial effects.

This study in mice demonstrates the role of the body's molecular clock in weight loss, eating times, and glucose metabolism after RYGB surgery for obesity. If the molecular clock has a similar role in RYGB surgical outcomes in humans, researchers could study whether adjusting meal and snack times may yield more health benefits. Further research on the effects of different bariatric (weight loss) surgical procedures could also lead to new, less invasive treatment approaches.

*Ye Y, Abu El Hajja M, Obeid R,...Mokadem M. Gastric bypass alters diurnal feeding behavior and reprograms the hepatic clock to regulate endogenous glucose flux. JCI Insight 8: e166618, 2023.*

**Substance Produced by Gut Following Bariatric Surgery Regulates Metabolic Health in Mice:** New research in mice has identified a key player produced by the gut that links surgical and dietary weight-loss therapies to improvements in metabolic and digestive health. Interventions such as bariatric surgery or a high-fiber diet can protect against the development of metabolic diseases like type 2 diabetes. Some health benefits from bariatric surgery can even occur independently from weight loss, although exactly how this happens is not clear. Further research on mechanisms underlying these effects may one day lead to new ways to treat metabolic diseases.

*A substance produced by the gut called Reg3g is important for conferring improvements in metabolic and digestive health following bariatric surgery.*

Reg3g is an antimicrobial peptide (a mini version of a protein) produced in the small intestine to help prevent resident bacteria from invading the intestinal wall. Because previous studies have shown that Reg3g confers health benefits in addition to its antibacterial properties, the researchers sought to examine whether Reg3g can also contribute to the health effects of bariatric surgery or a high-fiber diet and offer protection against metabolic diseases like type 2 diabetes. The researchers found that levels of Reg3g ramp up in mice after a type of bariatric surgery called vertical sleeve gastrectomy (VSG). To determine if Reg3g was responsible for the beneficial metabolic effects of VSG, the researchers performed VSG on male mice that were genetically altered to lack Reg3g. When compared to normal mice, the mice lacking Reg3g slowly regained weight and did not show improvements in blood glucose (sugar) levels and insulin production, implicating Reg3g in weight loss maintenance and better metabolic health after bariatric surgery. The researchers also saw improved metabolic health when they administered Reg3g to mice who did not undergo surgery, pointing to a possible role for Reg3g in protection against

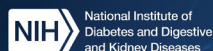
type 2 diabetes. When the researchers looked at the microbiome (the community of microbes in the gut) following VSG or a high-fiber diet, they found that these interventions changed the composition of the microbiome by boosting levels of certain beneficial bacteria, which in turn stimulated Reg3g production. Furthermore, Reg3g was found to play an important role in improving gut function, such as strengthening the gut barrier and reducing cellular stress in the small intestine.

These results suggest that changes to the microbiome due to bariatric surgery or a high-fiber diet stimulate production of Reg3g, which in turn mediates a variety of health benefits. Interestingly, the researchers also found that Reg3g is elevated following VSG in young people with obesity. If Reg3g causes similar metabolic effects in humans as in mice, it could mean that Reg3g-based treatments might have therapeutic value for people with metabolic diseases like type 2 diabetes.

*Shin JH, Bozadjieva-Kramer N, Shao Y,...Seeley RJ. The gut peptide Reg3g links the small intestine microbiome to the regulation of energy balance, glucose levels, and gut function. Cell Metab 34: 1765-1778, 2022.*

NIH Obesity Research Task Force Symposium

## Medications to Treat Obesity: Past, Present, and Future



September 8, 2023

Natcher Conference Center • Building 45 • NIH Campus • Bethesda, MD



# Medications to Treat Obesity: Past, Present, and Future

The epidemic of obesity continues to rise in the United States in adults and children. Obesity increases risk for diseases and conditions such as type 2 diabetes, cardiovascular disease, and some types of cancer and cancer-related death, and it also complicates the management of a myriad of diseases. While enormous progress has been made in the pharmacological management of diseases and conditions closely integrated with excess body weight, such as hypertension and type 2 diabetes, the treatment of obesity itself has proven largely resistant to therapy, with anti-obesity medications of the past often delivering insufficient efficacy and safety concerns that limited use and resulted in the removal of drugs from the market. While lifestyle and behavioral interventions help many people lose weight, some people cannot lose enough weight to improve health with lifestyle treatments alone, and even among those who do, weight loss is often difficult to maintain. Recent advances are now inspiring the pursuit of next-generation anti-obesity medications that appear capable of safely achieving significant and sustained body weight loss. With increasing knowledge, there is real potential to vastly expand therapeutic options for obesity treatment, allowing for more personalized and effective approaches to care. To that end, seven leading scientists highlighted their research at a September 2023 symposium organized as part of the NIH Obesity Research Task Force Seminar Series.

The research presented was supported by NIDDK, other NIH Institutes, and other sources.

Dr. Matthias Tschöp of the German research center Helmholtz Zentrum München presented an overview of obesity drug development ranging from diet pills of the past up to the current transformative era of obesity pharmacotherapies capable of safely inducing substantial amounts of weight loss. One class of medications that is particularly promising for the management of obesity is incretin-based therapies. Incretins are hormones secreted by the gut in response to food ingestion, which then regulate blood glucose (sugar) and delay stomach emptying, but also have effects on multiple other organs, including the brain. Medications that mimic these hormones have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes for more than a decade, but due to their significant effects on body weight, some have also been approved for obesity treatment. Some of the new medications lead to weight losses approaching those seen with bariatric surgery, and recent preliminary data suggest they may also reduce the risk of cardiovascular disease and death for some people with obesity. Additional medications are in the research and development pipeline, including hormones targeting multiple receptors and combination therapies, with a goal of increasing efficacy while minimizing adverse effects.

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Dr. Randy Seeley of the University of Michigan presented his research on the mechanisms by which incretin-based drugs work in the brain to treat obesity. He described the concept of a “set point,” a term that describes a weight range the body strives to maintain, and one which is elevated in a setting of obesity. The set point is regulated by key hormones that act in the brain and by genetics, as well as by calorie intake and expenditure, and it provides a potential explanation for why it can be difficult for people on a diet to maintain weight loss over time as the body is driven back toward a predetermined set point. Through a series of experiments in rodents, Dr. Seeley showed that overfeeding or calorie restriction will expectedly cause weight gain or loss, respectively. However, when the animals returned to eating normally, they very quickly returned to their set point. He went on to show that when rodents were administered obesity medications that target the brain, their set points appeared to become lower, leading to substantial weight loss that was maintained while receiving the drug.

Dr. Domenica Rubino of the Washington Center for Weight Management and Research presented her research on the incretin-based drug semaglutide for obesity treatment in adults through the Semaglutide Treatment Effect in People with obesity (STEP) clinical trials. The STEP program evaluates the safety and efficacy of semaglutide in a diverse population of adults with obesity and with or without type 2 diabetes. Semaglutide resulted in significant and sustained weight loss of 15 to 20 percent of body weight. In addition, the treatment improved cardiac risk factors such as blood pressure, reduced blood glucose levels, and decreased incidence of fatty liver. Participants reported improvements in health-related quality of life and a better sense of control over cravings, along with well-tolerated, primarily gastrointestinal side effects such as nausea, which can be affected by adjusting the dose. Evidence thus far supports the efficacious and safe use of semaglutide for weight management in adults with obesity.

Dr. Ania Jastreboff of Yale University School of Medicine presented her research on the incretin-based drug tirzepatide for obesity treatment in

adults, and she also provided a glimpse at new medications in the drug development pipeline. In a randomized, controlled clinical trial that enrolled more than 2,500 participants, nearly all participants lost weight while taking tirzepatide, while close to half of those lost more than 25 percent of their body weight. Participants on tirzepatide had a greater percent reduction in fat body mass than lean body mass, resulting in an overall improvement in body composition. Furthermore, of the participants who had prediabetes, nearly all reverted to normal blood glucose levels while taking tirzepatide, and cardiometabolic measures such as blood pressure improved. Participants taking the medication reported mild to moderate gastrointestinal adverse effects, and thus there is a need to titrate the dose for each patient. The efficacy, tolerability, and safety profiles of tirzepatide appear consistent with those of similar anti-obesity medications. Dr. Jastreboff previewed several new incretin-based and small molecule drugs currently in phase 2 and 3 clinical trials in the drug development pipeline.

Dr. Jack Yanovski of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at NIH highlighted his research on medications for the treatment of obesity in children and adolescents and gave an overview of the field. There are currently five FDA-approved drugs to treat obesity in children aged 12 to 16 years and one medication approved for children under age 12 years. Several approved medications to treat obesity in youth have limited efficacy and are associated with adverse side effects that could impede adherence. However, the same incretin-based drugs that work well in adults appear effective for weight reduction in adolescents when combined with lifestyle modification. Dr. Yanovski noted that highly effective approaches currently being studied in adults with obesity represent a treatment gap for children, especially for those under the age of 12 years. More research is necessary to gain a greater understanding of the biology of why obesity medications do not work for some youths, and a prime focus of research should also be to develop effective prevention strategies.

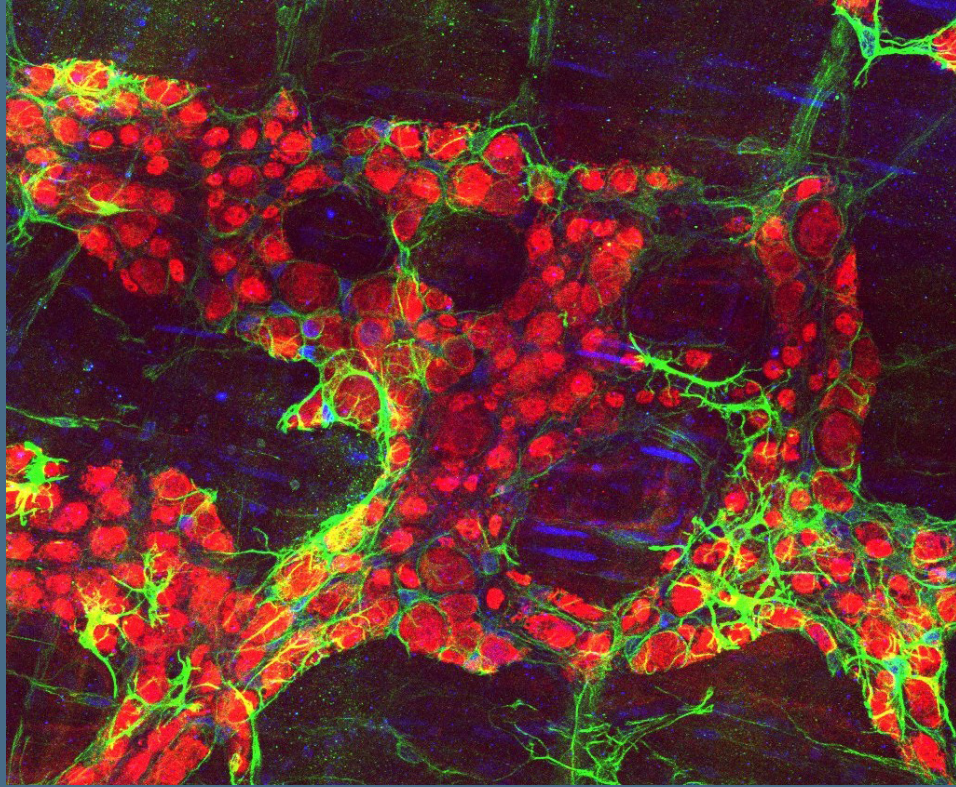
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Dr. Louis Aronne of Weill Cornell Medicine presented his work on using medications to treat obesity in clinical practice. He described key principles to prescribing medication to treat obesity such as considering the patient's severity of disease, any comorbidities that may require medications that cause weight gain, potential adverse side effects and how to manage them, and affordability of the treatment. Dr. Aronne stressed the importance of an individualized, multipronged, stepwise approach. For example, the clinician should start a patient on a low dose of medication and slowly increase to assess tolerability and efficacy; if one medication is not effective, switch to another; and combination therapies can be evaluated to improve results. Dr. Aronne also highlighted case studies from his clinic that illustrate effective use of anti-obesity medications.

Dr. Ilhuoma Eneli of Children's Hospital Colorado presented research on access to obesity treatment and health equity. She described how disparities and inequity contribute to obesity through historical, social, economic, and policy contexts that have systematic effects on weight-related outcomes. Health care-related factors that drive disparities include the often high cost of treatment; location of treatment centers, with many in large, urban areas, limiting access to rural

populations; access to insurance; inadequate provider training; suboptimal diagnostic criteria that may not reflect health risks across different populations (e.g., Asian American populations); and bias/stigma. A related factor is insufficient diversity in clinical trials. Dr. Eneli discussed potential solutions to address structural and systemic factors that lead to inequity in obesity treatment, such as policy change to ensure affordable and accessible options for all. Solutions remain complex and nuanced, and they must occur at the individual, community, and structural levels and in health care environments to effectively address inequities as they pertain to obesity prevention and treatment strategies.

The seminar concluded with a panel discussion featuring two women with experience using obesity medications who shared their personal perspectives. Following their poignant testimonies, they were joined on the panel by the scientific speakers for a lively discussion with participants, moderated by Dr. Susan Yanovski, NIDDK, on current challenges and opportunities in this evolving landscape of transformative obesity medicine. Continued research could reveal better strategies to prevent and treat obesity with personalized approaches to improve health care for all.



The nervous system in the gut—such as the neurons (shown in red) and glia (shown in green) in the microscopy image above—relays signals between the brain and the immune system. As described in this chapter, scientists have demonstrated that stress exacerbated intestinal inflammation in different mouse models of inflammatory bowel disease (IBD) and found evidence for the specific molecular pathways responsible. The researchers found evidence that these pathways likely play the same role in IBD in people as well, a finding that sheds light on the underlying mechanisms linking stress to IBD flare-ups.

*Image used courtesy of the lab of Dr. Christoph Thaiss, University of Pennsylvania. Image credit: Markus Schneider, Klaas Bahnsen, and Niklas Blank.*

# Digestive Diseases and Nutrition

*Digestive diseases are among the leading causes of doctor visits, hospitalizations, and disability in the United States each year. These conditions span a wide spectrum of disorders that affect the gastrointestinal (GI) tract, liver, gallbladder, and pancreas, as well as obesity and other nutrition-related disorders. To reduce the burden of digestive diseases, NIDDK-supported scientists are pursuing research to better understand how widespread these diseases are across the United States and in specific population groups; identify their causes and how they progress; and test new interventions for prevention and treatment, including drugs, surgery, and behavior modification.*

Digestive diseases can exact a significant toll on individuals across the lifespan, resulting in a lower quality of life, years lost due to premature death, and costs associated with hospitalization and pharmaceutical and surgical interventions. The burden of digestive diseases in the United States is substantial: based on recent data, it is estimated that digestive disease is the primary diagnosis in a total of 66.4 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments in the United States each year.<sup>1</sup> Similarly, analyses with 2020 national inpatient samples identified 3.5 million hospitalizations with a primary diagnosis of digestive diseases and 15.1 million hospitalizations with a primary or secondary diagnosis of digestive diseases.<sup>2</sup> In addition, analyses focusing specifically on the clinical and economic burden of emergency department visits identified 15.5 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling \$113 billion in 2020.<sup>3</sup> (Note that the 2020 statistics are likely underestimates due to pandemic-related health care challenges.)

*Annual estimates of the burden of digestive diseases list these diseases as the primary diagnosis in 66.4 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments.*

Inflammatory bowel disease (IBD), an umbrella term for chronic and painful intestinal diseases that include Crohn's disease and ulcerative colitis, is marked by damaging intestinal inflammation that can cause rectal bleeding, diarrhea, nutritional deficiencies, and other

serious complications. IBD often strikes early in life, with a peak age of onset in adolescence or young adulthood. The continued discovery of predisposing genetic variations, potential autoimmune and microbial influences, and new methods to repair damaged intestinal tissue will help predict the best course of treatment and catalyze the design of novel, more personalized therapeutic strategies.

*Scientists are investigating the complex interactions among the genetic, environmental, immune, microbial, and other factors that contribute to, or protect against, the development of inflammatory bowel disease.*

Diseases of the stomach and intestines also include peptic ulcer disease, which is typically caused by infection with the bacterium *Helicobacter pylori* or use of nonsteroidal anti-inflammatory drugs. Other stomach and intestinal disorders include functional

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<sup>1</sup> Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). <http://www.cdc.gov/nchs/ahcd/index.htm>. Accessed October 17, 2023.

<sup>2</sup> Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS). <http://www.hcup-us.ahrq.gov/nisoverview.jsp>. Accessed October 17, 2023.

<sup>3</sup> Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS). <http://www.hcup-us.ahrq.gov/nedsoverview.jsp>. Accessed October 17, 2023.



GI disorders, such as irritable bowel syndrome (IBS), which can cause abdominal pain and altered bowel habits. Gastroesophageal reflux disease, in which caustic stomach acids rise up into the esophagus, can lead to a heightened risk of esophageal cancer. Gastroparesis is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. Fecal incontinence, or impaired bowel control, is a very prevalent condition, and because it is difficult to talk about, many people suffer without seeking treatment. Scientists continue to strive for a deeper understanding of the causes of GI disorders, which will lead to improvements in diagnosis and management.

In individuals with celiac disease, the immune system reacts to ingestion of gluten—a protein component of wheat, barley, and rye—resulting in chronic diarrhea, bloating, anemia, and, in children, slower growth and short stature. The only current treatment for celiac disease is maintenance of a strict gluten-free diet, which is difficult for many people. Research advances in the understanding of genes and environmental triggers that are involved in the development of celiac disease may contribute to improved diagnosis and treatment.

*Research to advance understanding of genes and environmental triggers involved in the development of celiac disease may contribute to improved diagnosis and therapy.*

The microbes that inhabit the GI tract—also known as the intestinal microbiome—are important in maintaining the balance between digestive health and disease. These bacteria, viruses, and other microorganisms can affect long-term health and nutritional status, depending on their interactions with each other, with intestinal cells, and with nutrients ingested by their human host. Disruptions in this microbial ecosystem are associated with diseases such as IBD or infections by the harmful bacterium *Clostridium difficile*. Scientists are gaining insights into the ways these GI microbes influence the development and function of the digestive tract and other systems throughout the body, such as those with immune and metabolic functions, as well as how the composition of the GI microbial community changes with factors such as age, geography, diet, and antibiotic usage.

In acute and chronic pancreatitis, digestive enzymes attack the pancreas from within, causing inflammation,

loss of function, and severe pain. Advanced pancreatitis can be debilitating and may lead to cancer or diabetes, and because pancreatitis is difficult to detect in its early stages, many cases are advanced by the time they are diagnosed. Research has elucidated genetic and other factors contributing to pancreatitis that may lead to ways to treat or prevent this disease.

Serious adverse health effects can occur when the liver is functionally compromised by disease, which sometimes leads to scarring. Severe scarring (cirrhosis) can result in complete liver failure (end-stage liver disease). Some liver diseases primarily affect children, such as biliary atresia (a progressive inflammatory liver disease), while others generally affect adults, such as nonalcoholic fatty liver disease (NAFLD) or its more severe form, nonalcoholic steatohepatitis. In recent years, however, NAFLD in the United States has been increasingly diagnosed in children as well, concurrent with rising rates of overweight and obesity. NAFLD is also associated with health disparities: while the disease occurs in people of all races and ethnicities, in the United States it is more likely to affect those of Hispanic ethnicity. Some forms of liver disease are caused by viral infection, as in most cases of hepatitis, or by genetic mutations such as alpha-1-antitrypsin deficiency; others arise from factors such as autoimmune reactions, drug toxicity, bile duct obstruction, and other triggers, some of which are unknown. Many liver diseases, such as chronic hepatitis B and C, place individuals at elevated risk for developing liver cancer. When liver disease reaches the end stage, the only effective treatment is a liver transplant. Research is critical to identify liver disease early, find methods to preserve liver function in people with liver disease, and develop and further study new treatment options, including experimental, cell-based approaches to liver regeneration.

*In recent years, nonalcoholic fatty liver disease has been increasingly diagnosed in children and adults in the United States, concurrent with rising rates of overweight and obesity.*

NIDDK also funds research on nutrition-related disorders that involve specific, inherited alterations in nutrient metabolism. NIDDK-supported research has enhanced knowledge of how these nutritional disorders develop and how they can best be treated. Investigators also conduct basic, clinical, and translational research on the requirements, bioavailability, and metabolism of

nutrients and other dietary components to understand dietary needs in health and disease. NIDDK staff work collaboratively with representatives from across NIH, including in NIH's Office of Nutrition Research, to advance nutrition research efforts.

## EXPLORING INTESTINAL FUNCTION IN HEALTH AND DISEASE

### Signals Between Nervous System and Intestinal Cells Control Protective Mucus Layer Production in Gut:

New research in mice has discovered connections between the nerve cells of the gastrointestinal tract and mucus production in the gut, pointing to a role for these nerves in protecting the intestinal lining from damage and inflammation. Inflammation in the gut (e.g., colitis) can cause abdominal pain, a hallmark of many gastrointestinal diseases and disorders. Pain-sensing nerve cells—called nociceptors—envelop the gut, however their interactions with the cells of the gut itself are not fully understood. By better understanding the “cross-talk” between these cells, researchers could find new ways to help resolve the inflammation or to protect the intestines from further damage. It could also help scientists understand and treat painful gastrointestinal conditions like inflammatory bowel disease.

*Newly found connections between the nervous system and intestinal cells can control mucus production in the gut, helping to maintain the intestinal barrier and digestive health.*

Researchers working with a mouse model recently found that nociceptors come into close contact with goblet cells—cup-shaped cells in the intestinal lining that secrete mucus to coat the inside of the gut—suggesting that signals from nociceptors might control mucus production. The mucus layer provides nutrients and a habitat for bacteria that aid digestion. It also creates an important physical barrier to protect the gut from those bacteria, so mucus production is critical for both preventing intestinal damage and maintaining a healthy microbiome. The researchers found that male and female mice that were genetically engineered to lack nociceptors had thinner mucus layers on their intestinal linings compared to mice with an intact intestinal nervous system, demonstrating that nociceptors do indeed control mucus production. The researchers also found that capsaicin (the “spicy” chemical in peppers)

or products from gut bacteria triggered the release of a chemical signal called calcitonin gene-related peptide (CGRP) from nociceptors, and the goblet cells responded to this signal by secreting mucus. This means that when the gut is exposed to potentially damaging agents—either from the diet or bacteria—nociceptors can bolster the gut's defenses by stimulating more mucus production. Not surprisingly, the mice with thinner mucus layers also had disrupted microbiomes and were more susceptible to experimentally induced intestinal inflammation (colitis), but the mice were protected from inflammation when the researchers administered CGRP to compensate for the lack of nociceptors.

These results identify a pathway whereby nociceptors can sense insults to the gut and respond not only with pain but also with a signal to help protect the gut. More work is needed to confirm that a similar pathway exists in humans, but these insights could help researchers develop new ways to treat intestinal inflammation and abdominal pain while minimizing disruptions to the intestinal barrier.

*Yang D, Jacobson A, Meerschaert KA, ...Chiu IM. Nociceptor neurons direct goblet cells via a CGRP-RAMP1 axis to drive mucus production and gut barrier protection. Cell 185: 4190-4205, 2022.*

### A Link Between Cellular Stress and Gut Inflammation:

Scientists determined how a state of cellular stress in the inner lining of the gut promotes production of a type of immune cell linked to chronic inflammatory diseases. The inner lining of the gastrointestinal tract, called the intestinal epithelium, absorbs nutrients into the body and acts as a barrier restricting entry of harmful factors. Damage to the intestinal epithelium plays a role in chronic inflammation and development of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Understanding how a healthy intestinal epithelium is maintained and what leads to damage is critical to broadening knowledge about inflammatory bowel diseases and developing prevention and treatment strategies.

*Scientists discovered a link between cellular stress and production of a type of immune cell implicated in development of inflammatory bowel diseases.*

In this study, scientists explored how the intestinal epithelium promotes production of Th17 cells—immune system cells that produce a protein called IL-17 and

contribute to both the protective barrier of the intestinal epithelium and to chronic inflammatory conditions. Th17 cell production is triggered by microbes adhering to the epithelium, but it is unclear how the epithelium orchestrates this response. Knowing that epithelial cells are susceptible to a cellular state known as endoplasmic reticulum (ER) stress, where the capacity of a cell to properly shape newly generated proteins becomes overwhelmed, they sought to determine if ER stress in the intestinal epithelium influenced production of Th17 cells. To do so, they utilized two mouse models of ER stress and found an increased number of Th17 cells in both models. Interestingly, this increase in Th17 cells occurred in the mouse model even in the absence of gut microbes. This suggests that ER stress is a key player in Th17 production, and that, in wild-type mice, microbes may boost Th17 cell production by invoking ER stress in the epithelium. Additional experiments revealed that this response required production of a family of molecules called purine metabolites, most notably the small molecule xanthine.

To explore whether ER stress was linked to Th17 cell production in humans, the researchers looked at genes with increased activity in biosamples from people with ulcerative colitis and people with Crohn's disease. They noted that Th17-, ER stress-, and purine metabolism-associated genes were increased in the samples, suggesting that the response observed in mice is also associated with inflammatory bowel diseases in humans. These studies revealed how ER stress in the mouse intestinal epithelium leads to increased production of Th17 cells, generating new knowledge of intestinal epithelium biology. Additional research will be needed to elucidate what causes Th17 cells to promote chronic inflammation and lead to the development of inflammatory bowel diseases.

Duan J, Matute JD, Unger LW,...Blumberg RS. *Endoplasmic reticulum stress in the intestinal epithelium initiates purine metabolite synthesis and promotes Th17 cell differentiation in the gut.* *Immunity* 56: 1115-1131. e9, 2023.

**The Complex Interplay of Diet and the Gut Microbiome Influences Human Health:** In a controlled feeding study in people, researchers found that a diet designed to nourish the gut microbiome led to altered microbial composition, diversity, and function; changes in people's hormones; and improved energy balance (*i.e.*, the relation of calorie intake to calories used or excreted). Gut microbes have long been associated with body weight and metabolism through their ability to harvest energy

from food. However, prior studies in people have lacked the precision necessary for a comprehensive evaluation of the contributions of the gut microbiome to energy balance. Thus, in this randomized study, the researchers developed a diet intervention to address these critical knowledge gaps.

Employing a microbiome enhancer diet (MBD) designed to deliver more fiber and other dietary sustenance to the gut, the researchers gave 17 healthy, weight-stable men and women either the MBD or a standard, Western diet (WD) with less fiber and more processed foods for approximately 3 weeks. This was followed by the other diet for the same amount of time. Using specialized laboratory techniques in a metabolic ward, the researchers measured energy intake, energy expenditure, and energy output (fecal and urinary) in each participant on each diet and made "within-participant" comparisons. They found that, compared to the WD, the MBD led to an additional 116 calories lost in feces daily, meaning less energy available for the person to metabolize and improved energy balance. When they explored compositional and functional changes in the microbiome, they discovered that the MBD led to an altered diversity of microbes and to an increase in microbes with an ability to break down nutrients, such as fiber, more efficiently to produce beneficial molecules compared to the WD. In addition, the researchers uncovered a small, but measurable, decrease in body fat stores on the MBD. Lastly, the MBD was associated with a notable increase in circulating hormones that are known to promote a feeling of fullness.

Taken together, these results suggest that an intentional remodeling of the gut microbiome through provision of adequate dietary fiber and minimally processed foods can modulate human energy balance. Future research on the complex interplay of diet and the gut microbiome could lead to personalized nutrition approaches.

Corbin KD, Carnero EA, Dirks B,...Smith SR. *Host-diet-gut microbiome interactions influence human energy balance: a randomized clinical trial.* *Nat Commun* 14: 3161, 2023.

## UNDERSTANDING INFLAMMATORY BOWEL DISEASE

**Uncovering Biological Links Between Stress and Inflammatory Bowel Disease Flare-Ups:** Researchers have identified biological pathways that link stress to worsening inflammatory bowel disease (IBD) symptoms,

suggesting that strategies to reduce stress could be an important component of IBD treatment. IBD, such as Crohn's disease and ulcerative colitis, is marked by chronic inflammation in the intestines that causes debilitating symptoms. Stress is known to significantly impact inflammatory processes in the body and has been associated with triggering IBD flare-ups. The biological processes that link stress to the severity of IBD flare-ups, however, are not well understood.

In new research, scientists found that stress exacerbated intestinal inflammation in different IBD mouse models. Comparing immune cells from colon tissue of stressed and control mice with IBD, the scientists found that stressed mice had higher levels of monocytes (a type of white blood cell) that promoted inflammation. The scientists next asked: how are stress signals transmitted from the brain to the gut to cause accumulation of monocytes? Surprisingly, they found that glucocorticoids—steroid hormones historically associated with reducing inflammation—were critical for triggering the observed stress-induced gut inflammation. They found that the glucocorticoids have two effects on the enteric nervous system (ENS, the gut's nervous system). First, they activate inflammatory pathways in a subset of glial cells in the ENS. (Glia and neurons are the two main cell types in the ENS.) The glial cells in turn recruit monocytes to the gut, thereby exacerbating inflammation in the colon. Second, glucocorticoids result in more undifferentiated, or immature, neurons in the ENS. The larger proportion of undifferentiated neurons means there are less of the signals (neurotransmitters) that mature neurons release, resulting in abnormal intestinal motility (movement of content through the gut). Finally, by studying three different cohorts of people with IBD, the scientists found evidence that these pathways likely played a role in mediating the effect of stress on IBD flare-ups in people.

*Researchers have identified biological pathways that link stress to worsening inflammatory bowel disease (IBD) symptoms, suggesting that strategies to reduce stress could be an important component of IBD treatment.*

This study sheds light on underlying mechanisms that link stress to IBD flare-ups, identifying a key role for glucocorticoids interacting with glia in the ENS to increase the susceptibility of the gut to inflammatory triggers. It also suggests the importance of considering

people's mental health in the clinical management of IBD. Furthermore, the knowledge gained from this research may not only benefit people with IBD, but also those with other gut inflammatory diseases and other diseases that are worsened by stress.

*Schneider KM, Blank N, Alvarez Y,...Thaiss CA. The enteric nervous system relays psychological stress to intestinal inflammation. Cell 186: 2823-2838.e20, 2023.*

### **Expanded Study Diversity Uncovers New Genetic Risk Factors for Inflammatory Bowel Disease:**

Researchers recently identified new genetic risk factors for inflammatory bowel disease (IBD) by analyzing the genomes of tens of thousands of people from countries in East Asia alongside the genomes of people with ancestry from European countries. The inclusion of people from East Asia significantly expands the diversity of IBD genetic studies and provides insights that will help to understand and predict the disease.

Finding effective treatments for IBD, an umbrella term for Crohn's disease and ulcerative colitis, has been challenging because it arises from a complicated interaction between genetic and environmental factors, resulting in a disease that varies from person to person. Researchers in the International IBD Genetics Consortium, of which NIDDK's IBD Genetics Consortium is a member, have been combing through the human genome to find genetic variations (variations in DNA) that increase risk of IBD. By 2022, genetic variations associated with IBD risk had been identified in close to 250 regions of the genome, providing insight into the biology of IBD and opening the door to the development of new treatments. Most of these studies, however, had been with participants from (or with ancestry primarily from) European countries, which limited genetic diversity and likely missed many genetic variations that could play important roles in IBD. (While everyone shares the same genes, and many genetic variations are also shared across ancestries, some genetic variations are more common in specific ancestries than others.)

Recently, researchers expanded the diversity of IBD genetics research by analyzing the genomes of close to 30,000 men and women from China, Japan, and Korea, including people with and without IBD, undertaking the largest IBD genetic analysis of participants from countries in East Asia to date. When the East Asian data were analyzed together with previous studies that included about 370,000 participants with ancestry from European countries, also including people with and without IBD, the researchers identified 81 new regions

of the genome associated with the disease, raising the total number of IBD-associated regions to 320. The researchers found that, in general, the amount of IBD risk contributed by genetics was similar between the East Asian and European populations; however, the genetic risk for Crohn's disease was more influenced by ancestry than that for ulcerative colitis. They also tested whether the combined East Asian and European data would enable a more accurate prediction of IBD risk than the European data alone. Looking at IBD risk in Chinese individuals, the researchers found that the new data improved risk prediction significantly, underscoring the importance of including diverse study participants to improve ways of predicting the probability that any given individual might develop IBD.

*By analyzing the genomes of tens of thousands of people from regions in East Asia, researchers identified new risk factors for inflammatory bowel disease (IBD), helping to understand and predict the disease.*

In addition to improving risk prediction, increasing the diversity of participants in IBD genetic studies also deepened the understanding of IBD by enabling identification of specific genetic variations that could drive the disease in all people. NIDDK's IBD Genetics Consortium is currently expanding the diversity of its cohorts further; additional studies could determine exactly how genetic variations may affect IBD development across individuals and whether they could potentially serve as targets for new IBD therapies.

Liu Z, Liu R, Gao H,...Huang H. Genetic architecture of the inflammatory bowel diseases across East Asian and European ancestries. *Nat Genet* 55: 796-806, 2023.

## IMPACTS OF PANCREATITIS PAIN

**Pain Linked to Lower Physical and Mental Health in People With Chronic Pancreatitis:** Researchers have shown that people who experience severe or constant abdominal pain due to chronic pancreatitis also have significant loss of physical and mental health, suggesting that they may benefit from ways to detect and manage pain-related conditions.

While researchers continue to search for effective ways to treat—and ultimately cure—chronic pancreatitis, other

important efforts have focused on ways to manage the most commonly reported symptom: pain, which can be debilitating. In other chronic diseases, pain has been shown to affect several aspects of health, causing anxiety and depression, for example. Knowing the effects of pain on the quality of life for people with chronic pancreatitis is important because it could guide treatment approaches that would help manage the disease.

To determine how pain might shape the lives of people with chronic pancreatitis, researchers gathered information from men and women (488 with pancreatitis and 254 without) participating in the Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED). PROCEED is one of many clinical studies being conducted by the NIDDK- and NCI-sponsored Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, and is the first study in the United States to track chronic pancreatitis symptoms and progression in people over time. The researchers used a state-of-the-art assessment system for self-reported health called PROMIS (Patient-Reported Outcomes Measurement Information Systems), which was developed previously with NIH support. This assessment consists of questionnaires that provide highly reliable, precise measures of self-reported pain, along with measures of physical, mental, and social well-being. Applying PROMIS, the researchers found that the pain from chronic pancreatitis varies from person to person, ranging from no pain to severe pain, and from intermittent to constant pain. Most study participants, however, reported pain that was severe or constant, resulting in lower scores for overall physical and mental health. Severe or constant pain was also linked to declines in several specific health-related quality of life areas, including higher anxiety, depression, fatigue, and sleep disturbance. Participants with these categories of pain also had lower physical function, such as the inability to do everyday chores, and compromised ability to fulfill social roles.

This study provides strong evidence that, in addition to the life-threatening organ and tissue damage caused by chronic pancreatitis, the associated pain can have profound effects upon an individual's mental and physical well-being. This suggests that people with chronic pancreatitis may benefit from additional screening and treatment to manage pain and pain-related conditions.

Yadav D, Askew RL, Palermo T,...Conwell DL; on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). Association of chronic pancreatitis pain features with physical, mental, and social health. *Clin Gastroenterol Hepatol* 21: 1781-1791, 2023.

## PREVENTING AND TREATING LIVER DISEASE

### Limits on Acetaminophen in Acetaminophen-Opioid Combination Medications Affected Causes of Acute Liver Failure:

Researchers found that a U.S. Food and Drug Administration (FDA) mandate limiting the amount of acetaminophen in combination opioid-acetaminophen pain relievers was associated with lower rates of acetaminophen and opioid-induced liver failure, although rates of liver failure from acetaminophen alone increased. The harms stemming from the opioid addiction crisis in the United States are well recognized, but pain relievers used in combination with (or instead of) opioids can also present safety hazards. Acetaminophen (or paracetamol) is a pain reliever and fever reducer commonly available over the counter and in prescription formulations combined with opioids. However, too much acetaminophen can cause liver injury or failure, and consumers can unintentionally ingest a dangerously high dose, especially if taking multiple acetaminophen-containing medications together. Combination acetaminophen-opioid medications can provide pain relief with lower doses of the two drugs, but previous research found that these combination medications might contribute disproportionately to acetaminophen overdoses. In January 2011, the FDA mandated that by March 2014 prescription combination acetaminophen-opioid products could only contain up to 325 mg of acetaminophen, reduced from the previous maximum of 750 mg. Manufacturers were also required to add a warning about the risk of liver injury to these medications' labels. (This mandate did not affect over-the-counter acetaminophen products.)

To study the potential effects of this change, researchers used two large independent data sources, one on hospitalizations in the United States and the other on men and women with acute liver failure. By comparing hospitalization and acute liver failure rates, scientists concluded that after the FDA mandate went into effect, there was a significant reduction in the rate of hospitalizations associated with a combination of both acetaminophen and opioids, and in the rate of acute liver failure associated with this combination of medications. However, the rate of acute liver failure attributed to acetaminophen alone increased in the same time frame. Thus, the FDA rule on limiting the acetaminophen dose in combination acetaminophen and opioid preparations correlated with a decrease in the rate of acute liver failure and hospitalization associated with these medications. More research will be required

to determine if this specific reduction in acetaminophen dosages caused these changes or if they were due to other factors, such as changes in labeling, prescribing patterns, or usage of either opioids or acetaminophen alone. Overall, these results illustrate the complexities of how acetaminophen is used and of balancing pain management and drug safety in real-world situations.

*Orandi BJ, McLeod MC, MacLennan PA, ... Locke JE; US Acute Liver Failure Study Group. Association of FDA mandate limiting acetaminophen (paracetamol) in prescription combination opioid products and subsequent hospitalizations and acute liver failure. JAMA 329: 735-744, 2023.*

### Disrupting “Talk” Amongst Liver Cells Yields Therapeutic Targets for Nonalcoholic Fatty Liver Disease:

Researchers “listening in” on how liver cells chemically “talk” amongst themselves have uncovered a host of new targets for therapies against a common and advanced stage of nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease and its more severe form of nonalcoholic steatohepatitis (NASH) are common in both adults and children in the United States and around the world. No approved therapy exists for NASH, which is among the leading causes of liver transplantation and liver cancer. NASH is marked not only by excess fat accumulation in the liver, but also by liver inflammation and fibrosis, or scar tissue formation, mostly driven by overactivity of a type of liver cell called a hepatic stellate cell (HSC). Mechanisms driving this activation, or how to halt or even reverse it, are not fully understood.

One potential way HSCs can become activated is by talking amongst themselves and with other cells nearby. As part of this “conversation,” the activated HSCs also send their own signals, creating self-perpetuating feedback loops or circuits. Scientists wondered if, by zeroing in on these signaling circuits, they could interrupt them, breaking the cycle that keeps the liver cells activated and causes disease. They used a new technology capable of analyzing genetic products of single cells—simultaneously for millions of cells—to provide a unique signature for each cell based on its signaling components. Examining liver samples from women and men with NASH and from male and female mice with diet- and chemical-induced NASH, they identified some common circuits, composed of 68 unique proteins and their receptors, that emerge in the activated liver cells only during the late stage of NASH. The researchers then visualized these circuits using technologies that map contacts among neighboring cells. In this way, they showed the liver cells physically reaching out and becoming increasingly well-connected

to each other over the disease course, enabling exchange of short-range signals to sustain their collective activation and drive disease progression. To explore the therapeutic applications of this finding, the team blocked one of the protein-receptor signaling circuits in cultured human liver cells and in the animal model and found that blocking this circuit led to inactivation of disease-causing liver cells.

In this study, the research team applied cutting-edge technologies in single-cell sequencing and imaging to uncover new insights into how to interrupt the “vicious cycle” of cellular signals underlying fibrosis in late-stage nonalcoholic fatty liver disease. This work offers a basis for developing what could be the first dedicated therapy for this common and severe form of liver disease.

Wang S, Li K, Pickholz E,...Friedman SL. An autocrine signaling circuit in hepatic stellate cells underlies advanced fibrosis in nonalcoholic steatohepatitis. *Sci Transl Med* 15: eadd3949, 2023.

**Optimizing Treatment Regimens for Adults With Chronic Hepatitis B:** In adults with chronic hepatitis B participating in NIDDK-funded Hepatitis B Research Network (HBRN) studies across North America, investigators tested whether a combination treatment regimen could increase long-term clearance of the virus. Chronic hepatitis B, a form of viral hepatitis, is a global problem that disproportionately affects people living in or originating from certain geographic areas, such as Asia and sub-Saharan Africa. If not appropriately treated, the disease can lead to cirrhosis, liver failure, and liver cancer. Effective treatments for chronic hepatitis B include interferon-based therapy, which targets immune cell function, and a class of drugs called nucleoside analogues that inhibit viral enzyme activity. However, these drugs’ effectiveness varies across individuals, in terms of reliably clearing the virus and ultimately preventing development of severe liver disease. In addition, these drugs often must be taken lifelong to prevent recurrence of disease; therefore, better treatments that clear the virus long-term are needed.

The NIDDK-funded HBRN conducted clinical trials of treatment approaches for chronic hepatitis B in a study population that was primarily men, women, and children of Asian descent. Though the Network studies concluded in 2022, data analysis and publication of results have continued, with study samples available for additional research through the NIDDK Central

Repository. One HBRN clinical trial in adults, results of which were recently published, assessed the safety and efficacy of combining two treatments—a long-lasting form of interferon called peginterferon and the nucleoside analogue tenofovir—to increase the currently low or variable rates of viral clearance. Two hundred people with hepatitis B were treated, all of whom had active disease with high levels of viral DNA and elevations in serum liver enzymes, which indicate liver inflammation or disease. Half of the study participants’ samples contained the hepatitis B e antigen (HBeAg), a protein produced by the hepatitis B virus that signals an active infection. All study participants were treated with tenofovir for approximately 4 years; half also received peginterferon, but only for the first 6 months. After 4 years, those individuals who had received combination therapy had a higher rate of clearing the viral proteins and viral DNA, though nearly all study participants had an excellent clinical and biochemical response. An overall complete response with clearance of all hepatitis B proteins, however, was uncommon. Furthermore, almost all responses occurred in people with HBeAg and a single type of hepatitis B virus called genotype A2, found mostly in White and Black populations and rarely among those of Asian ancestry. At the 4-year point, study participants were eligible to continue or to stop tenofovir therapy, based on withdrawal of therapy being one approach to increasing the rate of complete viral clearance. One year after withdrawal of tenofovir therapy, slightly more of the participants who stopped treatment had complete clearance than those who continued therapy. Furthermore, a proportion of the study participants who elected to withdraw from further tenofovir therapy had a severe flare of hepatitis and had to be restarted on treatment.

These results indicate that the addition of peginterferon to tenofovir therapy for hepatitis B leads to an increased rate of response, but only in people with the viral protein HBeAg. Withdrawal of therapy after 4 years did not seem to increase the rate of complete response and could be followed by worsening of the hepatitis, requiring restarting of therapy. Future studies will continue to build on these findings to develop more effective, individualized approaches to treating people with hepatitis B.

Terrault NA, Lok AS, Wahed AS,...Janssen HLA; for the Hepatitis B Research Network. Randomized trial of tenofovir with or without peginterferon alfa followed by protocolized treatment withdrawal in adults with chronic hepatitis B. *Am J Gastroenterol* 118: 1214-1225, 2022.

## CONNECTING THE MICROBIOME AND LIVER DISEASES

### Complex Interplay Among Gut, Liver, and Microbes Underlies Metabolic Changes in Chronic Hepatitis C:

A team including researchers from NIDDK's Intramural Research Program uncovered how complex metabolic changes in the gut, its microbes, and the liver mirror the state of diseases such as chronic hepatitis C, which could lead to the development of new treatments for liver disease. The gut, the microbes it houses, and the liver all play central roles in the body's metabolism of nutrients and their by-products. Nutrients and microbial products absorbed in the gut travel directly to the liver through the portal vein before they are further metabolized and distributed throughout the body. Liver disease, such as that resulting from chronic infection with the hepatitis C virus, not only damages the liver through inflammation and fibrosis (scar tissue formation), termed cirrhosis in severe cases, but also disrupts metabolic processing by human cells and microbes.

*Researchers studying adults with chronic hepatitis C have uncovered how complex metabolic changes in the gut, its microbes, and the liver mirror disease state, offering clues to counteracting disease progression.*

Scientists selected chronic hepatitis C as a disease model in which to study how these complex metabolic and microbial changes correlate with the degree of liver disease. They recruited 23 men and women with chronic hepatitis C, either with or without cirrhosis present, to participate in a study at the NIH Clinical Center. Assessments included measures of human- and microbe-produced metabolites in blood samples from the portal vein and arm, liver biopsies, and fecal samples, taken initially and then 6 months after treatment with antiviral drugs to eliminate the viral infection. Over time, they found an anticipated uptick in immune activity and inflammation in these individuals, but also dampened gut-liver metabolism, particularly in utilizing fat for energy. Within the liver, these metabolic changes were localized to cellular structures called peroxisomes and mitochondria that handle inflammation-fighting antioxidants and energy production, and the changes persisted in cases of severe liver fibrosis even after the viral infection was cleared. Gut microbial activity was also altered with worsening liver disease, as microbes boosted fat production, reduced methane

metabolism, and degraded the protective mucus lining the intestine, changing the mix of metabolites feeding into the liver and leaving both organs more vulnerable to inflammation.

These findings illustrate how the fates of gut and liver are intimately linked, and that multiple disruptions in cellular and microbial metabolism in these organs are associated with inflammation and disease severity in the setting of chronic liver disease, in this case due to hepatitis C infection. They offer clues for future exploration into disease processes and therapeutic remedies to counter these metabolic changes and slow disease progression.

*Ali RO, Quinn GM, Umarova R,...Heller T. Longitudinal multi-omics analyses of the gut-liver axis reveals metabolic dysregulation in hepatitis C infection and cirrhosis. [Nat Microbiol](#) 8: 12-27, 2023.*

### The Yin and Yang of Microbial Influences on the Liver Disease Primary Sclerosing Cholangitis:

Studies in an animal model of primary sclerosing cholangitis (PSC), and in samples from adults with the disease, reveal gut microbes' vital role in both countering and fueling this form of chronic liver disease. PSC results from autoimmune-driven inflammation and fibrosis (scarring) that block the ducts that carry bile out of the liver. These blockages cause bile to accumulate, leading to further damage and possibly liver failure. Males are more likely to develop PSC, which often occurs together with other autoimmune conditions. Factors influencing disease development and progression are unclear, and available treatments are limited to surgeries to re-open the bile ducts. Past research in people with PSC suggested that gut microbes might play a role, though exactly which species were protective or detrimental was unknown.

To probe this important question, scientists studied an animal model of PSC: male and female mice that were genetically altered to develop features of the disease. They raised some of the mice under germ-free conditions and inoculated other mice with specific microbes, then tracked their overall survival, weight, liver enzymes and fibrosis, gut microbes, and genetic and metabolic products. Overall, the presence of gut microbes was beneficial—mice that had been raised in sterile conditions gained lower than normal amounts of weight as they grew and had elevated liver enzymes and bile, bile duct damage resembling PSC, and shortened lifespans, compared to similar mice with gut microbes. The fates of each group could be switched by changing their microbes—either by giving germ-free mice a fecal



microbial transplant from the other group, or by giving antibiotics to the mice with microbes. By studying these mice and the effects of different antibiotics, the researchers were able to identify bacteria that exerted protective or pathogenic effects. Bacteria in the *Lachnospiraceae* family protected against liver damage while those in the *Escherichia* genus promoted it. Relevance to human PSC was tested through analyses of the bacteria in stool samples from Norwegian and German studies of men and women with PSC.

*Studies on the chronic liver disease primary sclerosing cholangitis revealed how the balance of different gut microbes can both counter and fuel disease, knowledge that could lead to more individualized therapies.*

These human PSC samples supported the mouse findings, with the presence of *Lachnospiraceae* bacteria correlating with better disease outcomes and some *Escherichia* bacteria correlating with more severe disease. Antibiotic use in people with PSC also appeared to shift the balance of these bacteria toward species associated with worse disease.

Results from this study of PSC help form the knowledge base needed to enable more individualized predictions of disease progression based on the balance of beneficial and harmful microbes present. These results may also inform the development of personalized, microbe-based approaches to therapy for this liver disease.

Awoniyi M, Wang J, Ngo B,...Sartor RB. Protective and aggressive bacterial subsets and metabolites modify hepatobiliary inflammation and fibrosis in a murine model of PSC. *Gut* 72: 671–685, 2023.

## Research Aims to “Triumph” Against Childhood Liver Disease

The impacts of liver disease can be devastating for children and their families. NIDDK and its partners support a wide range of research on liver diseases that affect children, with studies focusing on the early identification of disease resulting from multiple causes, preservation of liver function, and development of new treatment options. Much of this work is initiated by individual investigators supported by NIDDK, but the Institute also funds large networks of researchers focusing on specific types of liver disease in children.



**Childhood Liver Disease Research Network**

### RARE LIVER AND BILIARY DISEASES

Since 2008, NIDDK has sponsored studies through its Childhood Liver Disease Research Network (ChiLDRen). The Network’s goals are to facilitate the understanding of many rare biliary diseases in which the liver is damaged due to impaired bile flow in children, to discover new diagnostic and treatment options, and to help train the next generation of investigators specializing in pediatric liver diseases. ChiLDRen consists of sites across the United States and Canada, with additional support provided through partnerships with the Cystic Fibrosis Foundation and the Alpha-1 Foundation. The Network conducts studies on a variety of liver diseases affecting children,

including Alagille syndrome, alpha-1-antitrypsin deficiency, biliary atresia, cystic fibrosis liver disease, progressive familial intrahepatic cholestasis, and others. Several important advances have come from the Network’s research, such as important insights into the genetics, pathogenesis, and treatment of biliary atresia and Alagille syndrome. For example, one Network study helped to provide the data necessary for the U.S. Food and Drug Administration to approve the first dedicated treatment for severe itching associated with Alagille syndrome in children.

Porphyrias are rare, often inherited diseases that can affect the liver and other organs from a young age. NIDDK has provided support for studies on porphyrias through the Porphyrias Consortium, part of NIH’s Rare Diseases Clinical Research Network. The Consortium is supported by NIDDK and NIH’s National Center for Advancing Translational Sciences. The Consortium’s studies aim to understand disease mechanisms and progression of multiple forms of porphyria and develop new approaches to diagnosis, treatment, and prevention, with children currently participating in some of these studies.

### NONALCOHOLIC FATTY LIVER DISEASE

In addition, NIDDK has supported pediatric research on the relatively common disease of nonalcoholic fatty liver disease (NAFLD) and its more severe form of nonalcoholic steatohepatitis (NASH). For example, the Nonalcoholic Steatohepatitis Clinical Research Network conducts clinical studies of nonalcoholic fatty liver disease in children. Recent studies by the Network have linked genetic risk factors to outcomes in children with NAFLD that can inform clinical care, and the Network has partnered with pharmaceutical

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companies and the Eunice Kennedy Shriver National Institute of Child Health and Human Development on clinical trials testing the safety and efficacy of new treatments for pediatric NAFLD.



## ACUTE LIVER FAILURE

Acute liver failure in children can result from damage due to viruses, metabolic disorders, drugs and toxins, or other causes. It is one of the most common reasons for children to need a liver transplant. The Institute has sponsored studies in children on severe liver injury caused by drugs, herbs, and dietary supplements through its Drug-Induced Liver Injury Network, which aims to develop better tools for diagnosis and prevention, and to enhance knowledge of disease processes. Recently, Network investigators found that antimicrobial and anti-epileptic drugs are leading causes of this form of liver injury in children, which can lead to acute liver failure requiring a liver transplant.

The newest of NIDDK's pediatric liver disease research initiatives is also geared toward aiding children with acute liver failure. Launched in 2021, the Treatment for Immune Mediated Pathophysiology, or TRIUMPH study, is testing immunosuppressive therapy for children with acute liver failure of unknown cause. NIDDK has supported past studies on this topic through the Pediatric Acute Liver Failure Study Group,

which paved the way for efforts such as TRIUMPH. The goal of the current study, which is currently enrolling participants at 20 sites across the country, is to test the safety and efficacy of two different treatments for improving survival of children with the rare and potentially life-threatening condition of acute liver failure for which no cause can be identified. Recent research supports the theory that many of these patients have liver injury related to heightened inflammation caused by an immune response to everyday infections or environmental exposures. Treatments to reduce inflammation may improve recovery in children with acute liver failure linked to immune disorders, increasing their chance of surviving and avoiding a liver transplant.

## LIVER TRANSPLANT

Related to this work, NIDDK supports the Improving Medication Adherence in Adolescents who Had a Liver Transplant Network (iMALT) study, which is testing an intervention in young people who have had a liver transplant due to multiple causes, including liver diseases and acute liver failure. The study involves monitoring of blood medication levels and remote communications from study staff, in order to boost adherence to taking the immunosuppressive medications needed to prevent rejection of the transplanted organ.

Through the collective efforts of these multi-center networks and investigator-initiated studies, NIDDK aims to help children and their families "triumph" over liver disease.

*For additional information on the ChiLDReN and TRIUMPH studies see: [childrennetwork.org/Clinical-Studies](https://childrennetwork.org/Clinical-Studies) and [www.pedsalf.com](http://www.pedsalf.com).*

## Making New Connections to Address the Silent Epidemic of Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease, or NAFLD, is one of the most common and growing types of chronic liver disease in adults and children, marked by excess fat storage in the liver. An estimated quarter of people in the United States have NAFLD, and up to 70 percent of people with type 2 diabetes also have NAFLD, though it often goes undetected. The disease often accompanies obesity and type 2 diabetes as part of a cluster of conditions called metabolic syndrome, though NAFLD can occur even in people who are lean and do not have diabetes, including those who carry some genetic factors and/or whose ancestors are from regions of the world with higher risk. Its more severe form of nonalcoholic steatohepatitis, or NASH, includes additional features of inflammation and scarring (fibrosis) that can lead, over many years, to compromised liver function; permanent damage, termed cirrhosis; liver cancer; and liver failure requiring a transplantation. There are currently no dedicated therapies approved by the U.S. Food and Drug Administration (FDA) for NAFLD and NASH. The current standard of care is weight loss through diet and exercise, which is challenging to achieve. Additionally, diagnosing these diseases is difficult because it relies on an invasive liver biopsy. New approaches are needed to prevent and treat NAFLD and NASH and to develop noninvasive means to identify people who could benefit from therapies as they become available.

NIDDK supports a long-standing, multifaceted, and highly collaborative research program to improve understanding of NAFLD/NASH disease processes and identify new treatment approaches. The progress achieved through these efforts is made possible through the collective efforts of research teams and study participants at institutions across the country, at NIH, and internationally.

### EARLY STUDIES OF DISEASE DEVELOPMENT

NIDDK sponsored early research on NAFLD and NASH to identify the biologic processes involved and chart the course of disease development and progression. In the 1990s, studies of liver biopsies from patients with obesity (with or without diabetes) identified some of the key morphologic changes that take place in NASH. They also tracked disease progression in these patients, some of whom developed fibrosis, which can progress to cirrhosis. Furthermore, these studies pointed to a link between NASH and insulin resistance, a condition that is also associated with type 2 diabetes. Additional studies in the early 2000s confirmed the link between NASH and insulin resistance, as well as other metabolic abnormalities, such as increased fatty acid breakdown and oxidative stress in the liver. NIDDK also sponsored population-level studies in the United States documenting the prevalence and risk factors for these diseases in people of different ages, genders, and ancestry. For example, disease risk at the time was found to be higher in people with ancestry from Hispanic and South Asian countries than in people with ancestry from African or European countries.

### CONNECTING RESEARCHERS TO ACCELERATE NEW APPROACHES

In 2002, NIDDK dramatically ramped up these efforts by establishing the NASH Clinical Research Network (NASH CRN), which supports a collaborative group of clinical researchers at centers across the country focusing on adult and pediatric forms of NAFLD

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and NASH. Currently made up of teams and study participants at 17 participating clinical centers and a data coordinating center, the Network aims to advance understanding of disease causes and processes, and to also develop new approaches to diagnosing, treating, and managing these diseases. During the Network's history, NIDDK has partnered with the National Cancer Institute and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at NIH, and with the pharmaceutical industry, on clinical trials testing the safety and efficacy of new treatments for NAFLD/NASH. Over the past two decades, the Network has made many important contributions to the field, including developing a scoring system for diagnosing the disease and its progression, assessing genetic and other risk factors, and testing multiple candidate therapies.

To date, the Network has enrolled thousands of adults and children who have participated in its many observational studies and clinical trials. These include trials showing that a daily dose of the natural form of vitamin E improved NASH in adult study participants and in some children. Network trials tested other possible therapeutic approaches, including the diabetes drug pioglitazone in non-diabetic adults with NASH and the kidney disease drug cysteamine bitartrate in children with NAFLD, both of which improved some features, but did not reduce overall disease. In 2015, Network investigators released results of a trial finding that a small molecule drug called obeticholic acid improved liver health in people with NASH, though the drug was associated with some increases in itching and total cholesterol. These findings helped fuel an explosion of industry-sponsored NASH clinical trials of this drug and others. The NASH CRN collaborates with and complements industry partners by testing existing, low-cost agents that industry is unlikely to pursue, as well as conducting early phase studies of agents with novel mechanisms of action.

Recent findings flowing from Network studies have shown a direct link between disease stage and outcomes in adults, with severe, later-stage disease associated not only with a higher risk of liver-related

complications and death, but also with complications in other organ systems. And Network studies have uncovered new knowledge about the underlying biology of this disease, such as new genetic factors associated with responsiveness to vitamin E treatment in adults with NASH. Network research on genetic factors in children with NAFLD showed that some gene variants increase risk of the disease, particularly its more severe form. Because the majority of study participants were children with ancestry from Hispanic countries, these findings are particularly valuable for this at-risk population. These findings add to the evidence base for determining prognosis and informing clinical care for both adults and children with NAFLD.

The goal of the Network's current phase is to continue database-driven studies of disease processes and to conduct new trials of NASH therapies for children and adults, with a constant emphasis on low-cost agents that could be implemented across the population. In recent years, a Network study found that the anti-hypertension drug losartan did not reduce signs of liver disease in children with NAFLD. Another study is determining the minimum effective dose of vitamin E in adults with NAFLD needed to improve liver enzyme levels. And the Network's impacts are further amplified through availability of its databases and vast repository of samples for additional studies by other scientists. For example, a current ancillary study is characterizing and testing treatments for the disease in people living with HIV, a population in which NAFLD is projected to become the leading cause of liver disease.

The Network also continues to develop and validate less invasive ways to diagnose NASH, such as by identifying biological markers of the disease and using imaging technologies. A recent ancillary study builds upon the NASH CRN to identify biomarkers in the blood that could be used in noninvasive tests related to NASH and NAFLD. Using data and samples from participants in four Network studies, the researchers provided evidence that these biomarkers could be used for noninvasive diagnosis of people at risk for NASH and for assessing the degree of fibrosis severity. This study was conducted through a collaborative

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project called Noninvasive Biomarkers of Metabolic Liver Disease, or NIMBLE, overseen by the Foundation for the NIH with participation from the FDA, academia, and industry partners, with partial funding provided by NIDDK and NIH's National Center for Advancing Translational Sciences. If approved by the FDA, these markers could be used instead of biopsies to more easily screen and diagnose people with NAFLD and NASH as early as possible in their disease course—an important milestone in clinical care.

## INVESTIGATOR-GENERATED RESEARCH ADVANCES

In addition to the highly productive NASH CRN, a wealth of investigator-initiated research efforts supported by NIDDK have made important, complementary contributions to advancing knowledge in this area.

For example, NIDDK-sponsored investigators have performed clinical studies to identify genetic factors that could predispose some individuals to developing NAFLD. A 2008 study scanned the genomes of participants in a large population-based study to show that a variant in a gene called *PNPLA3* was strongly associated with NAFLD and was more common among study participants of Hispanic ancestry with higher liver fat and inflammation. This was followed by a 2010 study conducted by NIDDK scientists working at the NIH Clinical Center to further analyze genomic data from participants in the NASH CRN, as well as from people with NASH who participated in non-Network studies at the Clinical Center. This study found that the *PNPLA3* variant was associated with earlier disease development in children. Other studies, including international ones, are identifying additional regions of the genome associated with NAFLD and are determining their functional significance as prospective treatment targets across diverse populations.

Basic research in animal and cell models conducted by NIDDK-supported scientists has revealed new

insights into disease development and possible treatment approaches. For example, a team of researchers supported by NIDDK and other NIH Institutes used mice and human liver cells to investigate how high amounts of fructose, a common ingredient in processed foods in the American diet, may promote NAFLD. They reported in 2020 that fructose can damage the intestinal barrier, which leads to inflammation and effects on the liver. Two teams of NIDDK-supported scientists tested lipid nanoparticles—used to deliver messenger RNA-based vaccines such as those developed against COVID-19—in mouse models to improve delivery of treatments for liver fibrosis and NAFLD. Researchers “eavesdropping” on how liver cells chemically talk amongst themselves in animal and cell models uncovered a host of new potential therapeutic targets for advanced-stage NAFLD. NIDDK is supporting ongoing research to develop innovative models for fostering new discoveries, such as stem cells, genetically altered cells in culture, and three-dimensional organoids (“mini-livers” grown in the lab) derived from people with NAFLD/NASH to develop personalized diagnostic biomarkers and treatments.

## IMAGINING THE FUTURE OF NAFLD/ NASH TREATMENT: PAST PROGRESS FUELING NEW STRATEGIES

Recent years have witnessed the most rapid expansion yet of new treatment options under development for NAFLD and NASH. Many studies have focused on a new class of hormone-based drugs approved by the FDA for treating type 2 diabetes and obesity, such as semaglutide. These drugs work through a protein called the glucagon-like peptide 1 (GLP-1) receptor, and the development of these drugs stemmed from NIDDK-supported foundational research on GLP-1 and related factors. This class of drugs causes delayed stomach emptying, reduced appetite, increased satiety, and enhanced insulin release and lower blood glucose levels, in addition to significant weight loss. In 2021, an industry-sponsored clinical trial featuring participation by NIDDK-supported scientists found

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that daily semaglutide treatment over a year and a half did improve disease resolution, based on the absence of inflammation or worsened liver fibrosis, but did not improve fibrosis stage in people with NASH but no cirrhosis. A 2023 study partially supported by NIDDK reported no improvement in disease, including resolution, in people with NASH and early cirrhosis who were treated weekly for a year with semaglutide, though the treatment did appear to be safe and have positive impacts on liver enzymes and liver fat. Researchers are conducting trials to determine whether longer-term treatment is required in people with cirrhosis resulting from NASH. NIDDK-supported researchers are currently conducting a clinical trial of semaglutide at the NIH Clinical Center in people with NAFLD/NASH to understand the mechanisms by which it may prove beneficial in treating the disease and identify predictors of clinical response. Additionally, NIDDK is supporting a new study testing another GLP-1 drug called liraglutide in young people with obesity, prediabetes or new onset type 2 diabetes, and NAFLD. And industry-sponsored trials are showing promising results in adults with obesity, type 2 diabetes, and fatty liver disease treated with similar drugs such as tirzepatide and testing other agents that target more than one receptor related to proteins like GLP-1.

Other novel treatment approaches are being investigated in parallel, including a study supported by NIDDK examining the impacts of intermittent fasting and aerobic exercise on NAFLD, which in combination were found to reduce liver fat more than either intervention alone. Another clinical trial is currently testing a low dose of the diabetes drug pioglitazone for improving signs of liver disease in people with both type 2 diabetes and NASH. NIDDK also supports many research projects overseen by industry scientists through the Small Business Innovation Research

program that are testing new approaches to NAFLD/NASH therapy.

## ONGOING “NETWORKING” TO FACILITATE TREATMENTS

NIDDK continues to seek new opportunities to connect scientists studying NAFLD and catalyze research progress in this area, in addition to the ongoing NASH Clinical Research Network. In 2021, the Institute established the Liver Cirrhosis Network to conduct clinical and translational research toward expanding treatment options and transforming clinical care for cirrhosis caused by NAFLD and other forms of chronic liver disease. Network scientists are working in collaboration with a diverse population of adult study participants, some of whom have been underrepresented in past studies despite carrying a higher disease risk and burden. The Network is conducting an observational study, including on risk factors across racial and ethnic groups, to determine what drives cirrhosis progression and point to possible treatments. Current Network studies are also testing whether statins, which are drugs commonly taken for high cholesterol, can protect against cirrhosis progression. The goal of the Network’s studies is to usher in a new era of cirrhosis management, with a wider array of effective treatment options beyond liver transplantation, for NAFLD and other causes of severe liver disease.

*For more information on NIDDK-sponsored research on NAFLD/NASH, such as the NASH Clinical Research Network, please see: [www.niddk.nih.gov/health-information/liver-disease/nafl-d-nash/clinical-trials](http://www.niddk.nih.gov/health-information/liver-disease/nafl-d-nash/clinical-trials).*

*For more information on the NIDDK’s Liver Cirrhosis Network, please see: [www.lcnstudy.org](http://www.lcnstudy.org).*

## Advancing Research to Improve the Health of People With Pancreatitis

People who have pancreatitis experience extreme, radiating pain caused by inflammation in the pancreas, a flat and oblong gland located behind the stomach. Aside from making hormones such as insulin needed to control blood sugar (glucose), the pancreas also performs another vital function: producing powerful enzymes for secretion into the small intestine, where they become activated and help break down food. But if these digestive enzymes are activated before leaving the pancreas—due to a blockage that prevents their flow into the intestine, for example—they can irritate or damage the pancreas, leading to painful inflammation that is often accompanied by other symptoms like nausea, vomiting, and fever.

### THE VALUE OF RESEARCH

Pancreatitis is typically classified as acute (coming on suddenly and typically resolving over several days), or chronic (long-lasting), although there appears to be no clear boundary between these two types. Brief, acute episodes of pancreatitis can progress to the chronic form. It is possible, for example, to experience multiple unpredictable acute episodes (a condition called “recurrent acute pancreatitis”), stretching out the disease over years. Currently, there is no certain way to predict whether someone will progress from acute to chronic pancreatitis, which, if unchecked, can lead to serious life-threatening complications like kidney failure, breathing difficulty, and malnutrition. Additionally, the long-term inflammation and damage to the pancreas can impair insulin production, leading to diabetes. It also significantly raises the risk for pancreatic cancer.

There is no specific treatment for pancreatitis. The causes and course of the disease vary from person to person, making it difficult to find suitable

targets for therapy. Several different factors can cause pancreatitis in different people; for example, some people have genetic variants that cause or contribute to the disease, though for many people with the disease, the cause remains unknown. (More information about pancreatitis is available on NIDDK’s website.) The search for treatments has also been hampered by the lack of large, long-term studies to understand the host of factors that influence how the disease develops and progresses. In addition, researchers have yet to identify early disease biomarkers—proteins or other chemicals in the body that could signal whether someone may eventually develop chronic pancreatitis. To address these needs, NIDDK, along with the National Cancer Institute (NCI), launched the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer in 2015. The Consortium’s goal is to design and conduct clinical studies to understand pancreatitis and its complications, including diabetes and pancreatic cancer. (See inset for the story of a participant in one of the Consortium’s studies.)

### GAINING A BETTER UNDERSTANDING OF PANCREATITIS

Since its inception, the Consortium has overseen several major clinical studies. PROCEED (Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies) has thus far enrolled close to 2,000 adult volunteers to understand disease progression, test potential biomarkers, and pave the way for clinical trials to test new therapies. Study participants are categorized into one of three groups: people with no pancreatic disease, people with suspected chronic pancreatitis (including those who have had one or more episodes of acute pancreatitis), and people with definite chronic pancreatitis.



# PERSONAL PERSPECTIVE

By collecting data and biological samples over time from all three groups, researchers can identify biomarkers and gain a better understanding of how pancreatitis progresses. For example, researchers in PROCEED recently found molecular markers in the immune system that are different between people with acute pancreatitis and people with the chronic form, suggesting these markers could serve as indicators for different stages of the disease. The researchers also identified inflammation signals that gradually increased as the disease progressed. These results provide a potential way to distinguish between someone experiencing pancreatitis or someone having unrelated abdominal pain. And, importantly, the study identified components of the immune system that could represent targets for new treatments.

Consortium researchers are also investigating complications that result from pancreatitis. Both chronic pancreatitis and pancreatic cancer could cause a form of diabetes called type 3c diabetes, which can be challenging to distinguish in the clinic from the more widespread type 2 diabetes. This is important because people with type 3c diabetes would likely require different treatment approaches from those with type 2 diabetes—they typically require insulin treatments earlier, for example. Recent results from the DETECT study (Evaluation of a Mixed Meal Test for Diagnosis and Characterization of Pancreatogenic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis) have found that, compared to people with type 2 diabetes, people with type 3c diabetes have lower levels of a substance called pancreatic polypeptide in their blood after consuming a test meal. This means measurement of pancreatic polypeptide levels could be used to differentiate type 3c from type 2 diabetes. Also, because type 3c diabetes often precedes other signs of pancreatic cancer,

measurements such as this could potentially serve as tools to help detect pancreatic cancer in its early stages when treatment is more likely to be successful.

While both PROCEED and DETECT are studying pancreatitis in adults, the Consortium's INSPPIRE 2 study (International Study Group of Pediatric Pancreatitis: In Search for a Cure) is characterizing acute recurrent and chronic forms of pancreatitis in over 800 children and adolescents. (INSPPIRE 2 is an expansion of INSPPIRE, an earlier pediatric pancreatitis study that predates the Consortium.) Similar to PROCEED, INSPPIRE 2 is gathering information from children with pancreatitis to help researchers determine the prevalence, causes, and progression of the disease. INSPPIRE 2 researchers have shown that the risk factors and course of the disease are different in children than in adults, a finding that could help researchers and clinicians develop better approaches to diagnose and treat children with pancreatitis.

Along with these large clinical studies, the Consortium is continuing to engage in other research that focuses on the diagnosis and treatment of pancreatitis, including new ways to treat pain, with the goal of improving the lives of people living with the disease. The Consortium's researchers—with the invaluable collaboration of the thousands of people participating in studies—are making great strides in understanding pancreatic disease, paving the way toward new treatments and bringing hope to those with pancreatitis.

*For additional information on the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, please visit its website at:*

[www.dmscro.org/cpdpc](http://www.dmscro.org/cpdpc).

## Dianna's Story



Dianna is participating in the PROCEED study, which aims to better understand pancreatitis

On a winter night in Western Pennsylvania 20 years ago, Dianna was at a friend's house when her stomach suddenly began to hurt. Only a minute later, she was vomiting uncontrollably in the bathroom and experiencing the most excruciating abdominal pain she had ever felt in her life. Her friend's mother drove her to a local emergency room, where she was told she had the flu.

Looking back, Dianna, now a working mother of two in her mid-forties, knows the symptoms she had been experiencing were her first encounter with recurrent acute pancreatitis, which would continue to barrage her pancreas with repeated bouts of painful inflammation. But she had little reason to suspect she had the disease

at the time—no one in her family had it, and she had no risk factors that she had been aware of. So, a week and a half after that emergency room visit and with the vomiting under control, she started her new job. She would still feel sore for weeks. "I just pushed through it," she says with a casual grin and a shrug.

***"I get zero warning," Dianna says of her pancreatitis attacks. "I could be talking to someone, and by the end of our conversation I could be on the way to the emergency room because the pain comes sharp, and I just start vomiting... and off we go."***

Dianna speaks with an entertaining, witty, and wry sense of humor. She has always been good at math and problem solving, talents she uses to design simulators—life-sized replicas of control stations that provide hands-on training for students. They have all the switches, gauges, and warning lights that the real equipment has. "You want [the students] to be trained so they know what to do when a component fails, and how to rectify it," she says.

But pancreatitis episodes do not come with warning lights, and there is no way to prepare for the debilitating pain. If untreated, pancreatitis could lead to organ failure and death. "I get zero warning," she says. "I could be talking to someone, and by the end of our conversation I could be on the way to the emergency room, because the pain comes sharp, and I just start vomiting... and off we go."

### CLOSE CALLS

In August of that same year when Dianna had her first episode, she was visiting her parents when, out of the blue, she began vomiting every hour

# PERSONAL PERSPECTIVE

on the hour, like clockwork. Still unaware of her pancreatitis—and suspecting something less serious like the stomach flu—she decided to wait until the next day to see a doctor. The doctor immediately sent her to a hospital where she waited for 12 hours in a backed-up emergency room. She was severely dehydrated by the time she was admitted, and her kidneys were starting to fail. “They had no idea what was wrong,” she says. “They pulled my mother outside and told her I was dying.”

Eventually the medical staff were able to stabilize her. She was diagnosed with pancreatitis and stayed in the hospital for 11 days while the doctors searched for a cause. An important clue had come in her bloodwork: it was normal except for her triglycerides, which were “sky-high,” she says. A healthy triglyceride level is under 150 milligrams per deciliter (mg/dL); Dianna’s would regularly be well over 1,000 mg/dL—and at times much higher.

Like so many aspects of the disease, the role triglycerides play in pancreatitis is not completely understood. One possibility is that high levels of triglycerides could cause the pancreas to over-produce digestive enzymes. The resulting buildup of these powerful enzymes in the pancreas could lead to permanent damage and other life-threatening complications—including a higher risk for pancreatic cancer—all the while causing painful inflammation in the abdomen.

Dianna’s pancreatitis, she later learned, is caused by three genetic variations in her DNA: one that raises the overall risk of the disease and two that cause high triglycerides. Keeping her triglycerides lower has been a challenge. She tries to limit her diet to low-fat and low-carb foods, and some triglyceride-lowering medicines she’s taken had very serious side effects, including severe depression.

Dianna describes the pain caused by pancreatitis as like a very bad friction burn, but on the inside of the body, and it can last for weeks. “It becomes so severe that you just want to double over, and nothing you do

makes it feel any better,” she says. Given the choice, she would prefer the pain from natural childbirth—which she experienced when each of her two sons were born—over the pain from pancreatitis.

The August trip to the hospital was the first time Dianna came close to dying. The second came several years later. This time the hospital was full, and she was directed to a smaller hospital that struggled to get her symptoms under control. While she slipped into unconsciousness, “they worked feverishly to keep me alive,” she says. “As soon I was conscious again, they told my husband and me to say a last word to each other because they weren’t sure if they were going to pull me through.”

She remembers her husband refusing to say goodbye: “He said, ‘I’m not saying it, because you’re making it through this. Because we’re not done. This is not the end.’” With those words, she says, “he really gave me strength.”

The small hospital airlifted Dianna by helicopter to the University of Pittsburgh Medical Center (UPMC), where, luckily, she was able to recover.

## PROCEEDING THROUGH LIFE WITH PANCREATITIS

At UPMC, Dianna met Dr. Dhiraj Yadav, a gastroenterologist and investigator in NIDDK’s Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, who took her on as a patient. He also encouraged her to participate in one of the Consortium’s major research efforts, Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED), which has thus far collected data on close to 2,000 volunteers to better understand pancreatitis. The study’s ultimate goals are to develop new therapeutic options and create tools to predict how the disease might progress in any individual, which would also help to guide treatment approaches.

# PERSONAL PERSPECTIVE

***Says Dianna about the PROCEED study, which aims to better understand pancreatitis: “I feel like it’s a two-way thing. If something can be learned from me, maybe it’ll turn around and benefit me as well.”***

Dianna says her participation in PROCEED is simple: it involves completing an annual questionnaire and giving blood and stool samples. “I found it easy,” she says. “And I feel like it’s a two-way thing. If something can be learned from me, maybe it’ll turn around and benefit me as well.” And, she says, one of her worst fears is that her sons may have inherited the disease. “So, even if it takes 10 years to figure out, maybe it’ll help my kids.”

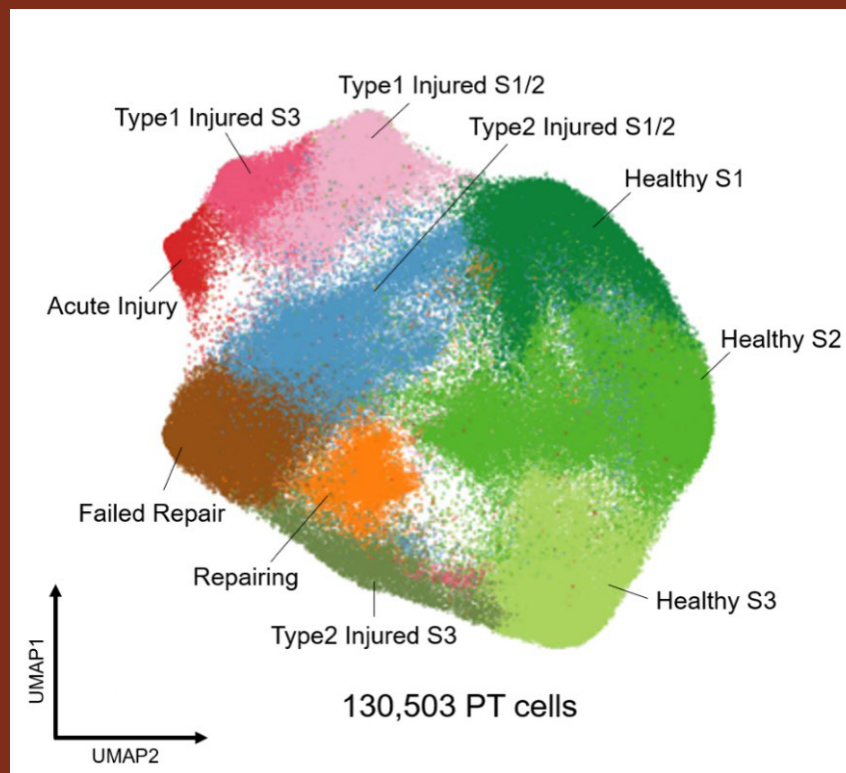
Dianna’s harrowing experiences with pancreatitis attacks—she’s had 16 of them over the years—have given her a new perspective in life. Her motto has become “laugh, don’t cry,” partly because she always looks for the silver lining in bad situations, and partly because she spent a lot of time in the hospital connected to a feeding tube that went through her nose, which she says can be especially

uncomfortable with stuffy sinuses from crying. (She likes to make hospital staff laugh by referring to the medical tubes clinging to her neck as “her jewelry.”) “There are times when crying is very much needed,” she says. “But if you can find something to laugh about first, no matter how small, then you can tap into that feeling of ‘Yes, I can do this!’”

Her friends share her sense of humor. Once, wishing they could give her a new, disease-free pancreas, they presented her with a stuffed plush version instead. “It’s those kinds of things that help,” Dianna says. “Laughter is the better medicine.”

Still, she draws much of her resiliency from within. “Even though it can get depressing, and I’m spending a week or two in the hospital at a time, I bounce back,” she says. “I keep going.”

***“There are times when crying is very much needed,” Dianna says of her many hospital stays due to pancreatitis. “But if you can find something to laugh about first, no matter how small, then you can tap into that moment of ‘Yes, I can do this!’”***



Acute kidney injury can cause long term damage by promoting fibrosis, which is the formation of scar tissue. This scarring process modifies genetic activity by turning genes on or off in cells. These changes can affect the kidney's ability to function properly but do not happen uniformly across all cells. Described within this chapter, researchers recently examined how two types of acute injury change the array of activated genes in cells across the kidney. In the above constructed image, cells of the injured kidney are sorted via a technique called UMAP plotting into clusters based on similar gene expression, indicated by the different colors. Cells from structures in the kidney known as proximal tubules (PT), which have three segments known as S1, S2, and S3, were found to exist in a healthy state (green clusters) or to have genetic activity consistent with injury (red), active repair (orange), or failed repair (brown). The research also identified two novel states of injury (type 1 and type 2) with distinct activation profiles that had not been previously characterized. These two subsets had metabolic changes that could differentially affect the cells' ability to repair and recover. Recognizing and understanding this heterogeneity in genetic activity following injury allows for a better understanding of specific repair mechanisms that promote healing and limit damage from fibrosis. Ultimately, this could lead to new treatments to help prevent chronic kidney disease.

Reprinted from *Cell Metabolism* 34, Li, H., Dixon, E. E., Wu, H. & Humphreys, B. D. Comprehensive single-cell transcriptional profiling defines shared and unique epithelial injury responses during kidney fibrosis, 1977-1998.e9, Copyright 2022, with permission from Elsevier.

# Kidney, Urologic, and Hematologic Diseases

***Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the United States. They affect millions of Americans, and their impact is felt across the lifespan. To improve our understanding of the causes of these diseases, and to identify potential new prevention and treatment strategies, NIDDK supports basic and clinical research studies of the kidney and urinary tract and of the blood and blood-forming organs. The overall goal of NIDDK's research programs is to improve the health of people who have or are at risk for kidney, urologic, and hematologic (blood) diseases.***

Normal, healthy kidneys filter about 200 quarts of blood each day, generating about 2 quarts of excess fluid, salts, and waste products that are excreted as urine. Loss of function of these organs, either for a short period of time or as a consequence of a gradual, long-term decline in kidney function, is a life-threatening condition.

An estimated 35.5 million American adults have impaired kidney function—also called chronic kidney disease (CKD).<sup>1</sup> However, up to 9 of every 10 adults with CKD are not aware that they have the disease.<sup>1</sup> CKD has two main causes: high blood pressure and diabetes. The increases in obesity and type 2 diabetes in the United States in recent years—especially among children and adolescents—have grave implications for the Nation's health, as young people with these conditions are more likely to face serious health complications at an earlier age than people who historically have developed these conditions later in life. CKD can also result from other factors, as noted below.

***An estimated 35.5 million American adults have chronic kidney disease.***

CKD, especially if undetected, can progress to irreversible kidney failure, a condition known as end-stage kidney disease (ESKD). People with ESKD require dialysis or a kidney transplant to live. In 2021, over 808,000 patients in the United States and its territories were living with ESKD.<sup>2</sup> Over 541,000 had previously received either hemodialysis or peritoneal dialysis, and over 251,000 were living with a kidney transplant.<sup>2</sup> Racial and ethnic minority

populations in the United States, particularly African Americans, Hispanic and Latino Americans, and American Indians and Alaska Natives, bear a disproportionate burden of CKD and ESKD. ESKD prevalence in 2021 was about four times greater in African Americans; over twice as high in American Indians, Alaska Natives, and Hispanic Americans; and 1.6 times greater in Asian Americans, compared to Whites.<sup>2</sup> NIDDK supports a significant body of research aimed at understanding the biology underlying CKD and developing treatment strategies.

In addition to research on kidney disease related to diabetes and high blood pressure, NIDDK also supports studies of inherited diseases—such as polycystic kidney disease, congenital kidney disorders, and focal segmental glomerulosclerosis—and immune-related kidney diseases, such as IgA nephropathy and hemolytic uremic syndrome. One feature common to kidney diseases arising from varying causes is the deposition of fibrotic scar tissue in the kidney. Research supported by NIDDK has enhanced our understanding of the origin of this scar tissue, how it can impair kidney function, and how it might be prevented or treated.

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<sup>1</sup> Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2023*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2023.

<sup>2</sup> United States Renal Data System. *2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

*Racial and ethnic minority populations in the United States, particularly African Americans, Hispanic and Latino Americans, and American Indians and Alaska Natives, bear a disproportionate burden of chronic kidney disease and end-stage kidney disease.*

Urologic diseases and conditions affect people of all ages, result in significant health care expenditures, and can lead to substantial disability and impaired quality of life. Areas of NIDDK-supported research include the causes of and treatments for urologic diseases and disorders, such as urinary tract infections and urinary stone disease, two of the most common and costly urologic conditions affecting people in the United States. Urinary incontinence (UI) is another prevalent problem. Based on U.S. medical insurance claims over several years, the annual prevalence of UI among individuals 65 and older ranged from 7.0 to 7.8 percent for women and from 3.6 to 4.0 percent for men. Among those aged 18 to 64, UI prevalence ranged from 0.9 to 1.2 percent for women while the prevalence was 0.2 percent for men.<sup>3</sup> These estimates may be lower than the actual prevalence of UI due to stigma surrounding the condition. Many suffer in silence due to embarrassment and lack of knowledge about treatment options available.

Many people are also living with one of a cluster of disorders collectively called urologic chronic pelvic pain syndrome (UCPPS). The two most common examples of UCPPS are interstitial cystitis/bladder pain syndrome (IC/BPS)—also known as IC/painful bladder syndrome (PBS)—and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). IC/BPS is a debilitating, chronic, and painful urologic disorder. Based on a large, national interview survey, it is estimated that among U.S. women 18 years or older, three to eight million have pelvic pain and other symptoms, such as urinary urgency or frequency, that are associated with IC/BPS.<sup>4</sup> Using a community-based epidemiologic survey, researchers have estimated that among U.S. men ages 30 to 79 years old, 1.3 percent have persistent urologic symptoms, such as pain with bladder filling and/or pain relieved by bladder emptying, that are associated with IC/BPS.<sup>5</sup> NIDDK-supported basic and clinical research on IC/BPS and on CP/CPPS is focused on elucidating the causes of these conditions, identifying important subsets of patients to aid diagnostic stratification, and improving treatment and interventions.

Research on UCPPS is one example of how NIDDK is seeking a broad-based understanding of symptoms affecting the lower urinary tract (LUTS), including pain, bladder leakage, and problems urinating. For the wide range of LUTS, we still need to learn more about causes and contributing factors to improve management and treatment of symptoms. NIDDK is supporting research to better understand factors that contribute to bladder health over the lifespan, with the ultimate goal of preventing LUTS.

*Among U.S. women 18 years or older, three to eight million have pelvic pain and other symptoms, such as urinary urgency or frequency, associated with interstitial cystitis/bladder pain syndrome.*

NIDDK's hematology research program uses a broad approach to enhance understanding of the normal and abnormal function of blood cells and the blood-forming (hematopoietic) system in order to develop effective treatment strategies. Blood diseases and disorders—some of which cause severe, debilitating pain, and premature death—affect millions of Americans. These inherited and acquired diseases can affect red and white blood cells, platelets, bone marrow, or blood vessels. Research efforts include studies of a number of nonmalignant blood diseases, including sickle cell disease, the thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, thrombocytopenia, the anemia of inflammation and of chronic diseases, hemochromatosis, HIV-associated blood-related dysfunction, and bone marrow failure. NIDDK also supports research on the basic biology of adult blood (hematopoietic) stem cells, which are used clinically in bone marrow transplants and may have broader application in gene therapy research.

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<sup>3</sup> *Urologic Diseases in America. 2023. Urologic Diseases in America: Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.*

<sup>4</sup> *Berry SH, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 186: 540-544, 2011.*

<sup>5</sup> *Link CL, et al. Prevalence and psychosocial correlates of symptoms suggestive of painful bladder syndrome: results from the Boston Area Community Health (BACH) survey. J Urol 180: 599-606, 2008.*

## UNDERSTANDING THE MOLECULAR PATHWAYS TO KIDNEY INJURY

**“Kidney Atlas” Helps Illustrate Changes That Occur With Kidney Injury:** Researchers have compared healthy and diseased kidney tissue at the cellular and molecular level to create the most comprehensive “kidney atlas” to date. The work, supported in part by NIDDK’s Kidney Precision Medicine Project (KPMP), will help researchers delve into the mechanisms of kidney injury and healing. The kidney is a complex organ composed of multiple cell types, each of which has a specific role. Acute kidney injury (AKI) occurs when the kidney is damaged by factors such as low blood flow, certain medications, or infection. While the kidney typically continues to function following injury, some people with AKI progress to chronic kidney disease (CKD). In CKD the kidneys gradually lose their ability to excrete excess salt, eliminate waste, and balance water levels. This can lead to end-stage kidney disease, which must be treated with dialysis or may even require a kidney transplant. The atlas helps investigators understand the changes that occur in specific kidney cell populations due to different stresses and further differentiates distinct disease states to identify optimal treatment approaches.

*In a breakthrough toward understanding and treating kidney injury, researchers have compared healthy and diseased kidney tissue at the cellular and molecular level to create the most comprehensive “kidney atlas” to date.*

In the study, kidney samples provided by male and female donors who were healthy or had AKI or CKD were analyzed for the types of cells present, what region of the kidney these cells were in, and how the cells adapted to their local environment. Damaged tissue was analyzed for which molecular repair pathways were turned on, what types of immune cells were present, and what cell types were communicating with each other through chemical signals. Additionally, the research distinguished pathways that led to injury resolution versus those that became “maladaptive,” causing long-lasting inflammation and irreversible damage (called fibrosis). The data, available to investigators through the KPMP Kidney Tissue Atlas at [www.kpmp.org](http://www.kpmp.org), represent a collection of three-dimensional renderings and kidney maps that can help scientists from around the globe understand the kidney in health, injury, and disease.

This work could significantly improve our understanding of why some people overcome AKI while others experience a progressive loss of kidney function that develops into CKD. Furthermore, it helps distinguish distinct disease states that we now collectively treat as AKI or CKD, which could allow for more targeted therapeutics that not only halt disease progression but reverse kidney damage as well. Ultimately, KPMP research aspires to form the basis for new treatments for kidney diseases that are personalized, effective, and safe.

*Lake BB, Menon R, Winfree S,...Jain S. An atlas of healthy and injured cell states and niches in the human kidney. Nature 619: 585–594, 2023.*

**Probing the Molecular Events Linking Kidney Injury to Fibrosis:** New research has utilized cutting-edge methods to analyze the way different types of cells respond to kidney injuries that lead to fibrosis in two mouse models of kidney injury. Acute kidney injury (AKI) often leads to chronic kidney disease—and sometimes to kidney failure—by triggering events that lead to kidney fibrosis, or scarring. Clarifying the molecular links between injury and fibrosis in the kidney might therefore suggest new and better ways to treat people with AKI to prevent long-term kidney damage.

To identify the processes involved, scientists used male mice in which one kidney was injured either by a temporary blockage of blood flow or by a temporary block of the path for urine to drain from the kidney. Using 24 kidneys from mice with one injury type or the other, they used high-throughput methods that allowed them to record details of genetic activity in over 300,000 cells, including 50 different cell types. These experiments revealed a wide variety of cellular responses in the different types of kidney injury. The animals with AKI caused by blood flow restriction were more likely to recover their kidney function than those with AKI from temporary urinary obstruction, and researchers found differences in genetic activity in various cell types that might help explain the unequal outcomes. Comparing these changes to cellular responses from other mouse models as well as human kidney disease states allowed the researchers to verify that many were relevant to human disease. Study scientists assembled their data into an atlas of genetic activity profiles of various cell types from the two injury states, which is available on the web as a useful resource for future research. This atlas is improving our understanding of the pathways that lead to kidney fibrosis and could one day lead to



treatments that help prevent chronic kidney disease from developing in people who experience AKI.

Li H, Dixon EE, Wu H, and Humphreys BD. *Comprehensive single-cell transcriptional profiling defines shared and unique epithelial injury responses during kidney fibrosis. Cell Metab 34: 1977-1998.e9, 2022.*

## INVESTIGATING POLYCYSTIC KIDNEY DISEASE

### Resolving Key Details of Polycystic Kidney Disease

**Genetics:** Researchers helped clarify what genetic variations can cause polycystic kidney disease (PKD) by examining specific gene sequences in more than 170,000 people in a regional health care system who agreed to participate. In PKD, numerous kidney cysts form that interfere with the organ's function. As the disease progresses it often leads to kidney failure and complications such as high blood pressure, cysts in the liver, and problems with blood vessels in the brain and heart. The most common form of PKD—autosomal dominant PKD, or ADPKD—usually occurs when someone has a disease-causing variant in either the gene *PKD1* or the gene *PKD2*. However, although some specific variations in these genes are known to cause disease, many other *PKD1* and *PKD2* variants are of uncertain significance. Importantly, a significant number of people with ADPKD have been found to have only normal versions of *PKD1* and *PKD2*, and previous research has implicated rare variants in at least 10 other genes as potentially being able to cause the disease.

*New research potentially improves on scientists' ability to predict who will develop polycystic kidney disease, and who might benefit from treatments currently in development.*

To shed more light on the genetic causes of ADPKD, scientists used a technique that allowed them to zero in on the key portions of each gene previously suggested to have a role in causing the disease. They examined the gene sequences in consenting participants—more than 170,000 people—among whom 235 had a diagnosis of ADPKD. This allowed them to identify genetic variants in *PKD1* and *PKD2* that truly are likely to cause ADPKD—including previously unknown variations—while ruling out some of the previous suspects. Variations in *PKD1* turned out to be causing the disease in a bit more than half of those with ADPKD, while *PKD2* variations

accounted for 14 percent, and variations in other genes accounted for an additional 8 percent. Importantly, it was not possible to identify the genetic cause of ADPKD in almost a quarter of the participants with the disease, suggesting there is much more to discover about its causes. Because 93 percent of the study participants were of European ancestry, it will be important to extend this research in a study with a more diverse group of participants. These findings potentially improve on scientists' ability to predict who will develop ADPKD, and who might benefit from treatments currently in development.

Chang AR, Moore BS, Luo JZ,....Mirshahi T. *Exome sequencing of a clinical population for autosomal dominant polycystic kidney disease. JAMA 328: 2412-2421, 2022.*

### New Technologies Help Uncover an Unexpected Role of Glucose in Polycystic Kidney Disease:

Using an innovative new method to simulate a micro-environment within the kidney, scientists have discovered that glucose (sugar) absorption contributes to the growth of cysts in polycystic kidney disease (PKD). PKD is a genetic disorder that causes many fluid-filled cysts to grow in a person's kidneys, leading to chronic kidney disease, high blood pressure, and often kidney failure. When waste products are initially filtered out of the blood in the kidney, water and important nutrients go along for the ride. These valuable materials are largely reabsorbed as they pass through tiny structures called tubules. It is within these tubules that cysts form in PKD. Because tubules are enclosed within the kidney, it is difficult to research the mechanisms behind PKD cyst formation in humans or using animal models. Previous studies have led to the development of microscopic structures outside of a living organism, called kidney organoids, which contain not only the tubules, but the other components of the blood filtration system. Importantly, kidney organoids from cells with PKD-causing mutations develop tubular cysts, just as they would in a person. Organoids are typically grown in static fluid conditions, but because of the constant exchange of fluid within the kidney, an understanding of the impact of liquid flow on PKD organoids is needed. This understanding could provide needed insight into the mechanisms of cyst formation in the kidney.

For this research study, scientists grew organoids and attached them to special microscope slides called chips that contain small channels to provide a fluid-flow environment similar to that of a living kidney. They observed via microscope that the PKD organoid cysts grew twice as fast in fluid-flow conditions as they did

when the liquid around them was motionless. The researchers discovered that cyst growth rate was closely linked to their exposure to glucose, a nutrient normally reabsorbed by the tubules. They found that the PKD cysts absorbed and expanded in response to glucose and subsequently showed that this expansion could be reversed with the use of a drug that inhibits tubular reabsorption of glucose. Equipped with the insight gained from the PKD organoid-on-chip model, the researchers were then able to confirm the uptake of fluorescent glucose in PKD cysts within the kidneys of a PKD mouse model, suggesting that the same phenomenon occurs in living PKD kidneys.

The novel organoid-on-chip PKD model used in this study provided new insight into the impact of fluid flow and glucose uptake on the formation of PKD cysts within the kidney. With further research, safety studies, and clinical trials, these findings suggest that glucose uptake-inhibiting drugs might one day help prevent the progression of PKD in people with the disease.

*Li SR, Gulieva RE, Helms L,...Freedman BS. Glucose absorption drives cystogenesis in a human organoid-on-chip model of polycystic kidney disease. Nat Commun 13: 7918, 2022.*

## EXPANDING KNOWLEDGE OF KIDNEY TRANSPLANTATION

### **Kidneys From Deceased Organ Donors With or Without Acute Kidney Injury Show Similar Transplant Outcomes:**

Findings from a national cohort study showed that kidneys from deceased donors with acute kidney injury (AKI) were not clinically different than kidneys from donors with no or resolved AKI, in terms of graft survival and function. Kidney transplantation significantly improves quality of life and eliminates costs associated with chronic dialysis, but innovative approaches are urgently needed to expand the donor pool because many people are on a waitlist and often never make it to transplant. To fill this gap, this study provides evidence for the benefits of transplanting kidneys from deceased donors with AKI, suggesting they are an underutilized resource that could help improve long-term health outcomes for those in dire need of new kidneys.

AKI is an often-reversible condition in which one's kidneys suddenly stop functioning properly. AKI can lead to thickening and scarring of the kidney tissue and increases risk of chronic kidney disease, but whether kidneys transplanted from donors with AKI can go on to function as well as those from donors without AKI needs further

*Kidneys from donors with acute kidney injury often get discarded, but there may be an opportunity for these organs to serve as safe and effective organ transplants and expand the donor pool.*

research. In this study, researchers analyzed data from over 7,000 donors with ongoing AKI and over 13,000 adults who received kidney transplants from the donors from 2007 to 2016. When they compared the results to outcomes from people who received kidneys with no or resolved AKI, they did not find any clinically meaningful differences in either kidney function over 12 months or in failure rates of transplanted kidneys within 3 years. The data also showed that kidneys from donors with AKI and diabetes had slightly worse transplant outcomes, compared to kidneys with AKI but without diabetes. The researchers also found that during the study period, nearly 3,000 kidneys were discarded from donors with ongoing AKI who were under age 65 and had neither hypertension nor diabetes, suggesting that more widespread use of kidneys from potential donors with AKI could help expand the donor pool.

These findings show that even severe, ongoing AKI that persisted at the time of kidney donation does not have a significant adverse effect on transplant outcomes, and that kidneys from donors with AKI are too often discarded, needlessly limiting the pool of kidneys that could be safely and effectively transplanted into people awaiting the procedure. Continued research will be important to confirm the long-term outcomes and to increase the clinical practice of transplanting kidneys from deceased donors with AKI for those who are waiting for kidney transplants.

*Sonnenberg EM, Hsu JY, Cohen JB,...Reese PP. Acute kidney injury in deceased organ donors and kidney transplant outcomes. Ann Surg 276: e982-e990, 2022.*

## DISCOVERING GENETIC RISK FACTORS FOR DIABETIC KIDNEY DISEASE

### **A Potential Explanation for Differences in Susceptibility to Kidney Complications of Diabetes:**

New research in mice has identified a genetic factor that might help explain why some people with diabetes are more prone than others to kidney complications of the disease. Between 10 and 30 percent of people with either type 1 or type 2 diabetes develop diabetic kidney disease

(DKD), making diabetes a major risk factor for loss of kidney function. But because most people with diabetes do not develop DKD, there is considerable interest in understanding what puts some people at higher risk than others. One of the early events in development of DKD is loss of a type of kidney cells called podocytes, which act as the first filter for blood. These cells permit water, salts, and other small molecules in the blood to exit the bloodstream, while blocking larger compounds like proteins from coming along for the ride. When podocytes disappear, protein levels start to fall in the blood, and rise in the urine—hallmarks of kidney disease.

Podocytes also disappear in a strain of mice that are susceptible to DKD, but they remain present in a different strain of mice with kidneys that stay healthy even when the animals have diabetes. Looking for differences between the two strains, researchers noticed that the mice that lose their podocytes after developing diabetes were producing more of a protein called xanthine oxidoreductase (Xor). They found that this was due to a difference in a region of DNA that helps regulate how much of the protein is produced when glucose levels rise (as in diabetes). To see if this difference was important, the scientists created a mouse strain that had the genetic predisposition to create excess Xor but was otherwise identical to the DKD-resistant animals. When experimentally given diabetes, these mice rapidly lost their podocytes, suggesting that elevated Xor might be an important factor in contributing to DKD. If levels of Xor turn out to have a similar impact on podocytes and kidney health in people with diabetes, future work might focus on trying to develop a medication that can safely inhibit Xor's effects in hopes of one day preventing DKD or slowing its progression in those at risk for the disease.

Wang Q, Qi H, Wu Y,...Daehn I. Genetic susceptibility to diabetic kidney disease is linked to promoter variants of XOR. *Nat Metab* 5: 607-625, 2023.

## UNDERSTANDING THE SPECTRUM OF UROLOGIC DISEASE SYMPTOMS AND TREATMENT RESPONSES

### New Insights Into Overactive Bladder Urinary

**Symptoms:** Recent findings suggest that two manifestations of overactive bladder (OAB) may reflect a spectrum of symptom severity rather than two distinct subtypes. People with OAB may experience a variety of symptoms including increased urge to urinate (urinary urgency or UU), frequent urination,

urine leakage (urgency urinary incontinence or UUI), and nocturia (nighttime frequent urination). Some hypothesize that UU and UUI represent different degrees of OAB symptoms (i.e., they are the same condition), while others hypothesize that they are two separate subtypes of OAB. Though OAB is a relatively common condition, there is limited understanding of the characteristics that distinguish people with UU from those with UUI, making the clinical management of these burdensome and painful conditions challenging. Increased knowledge about these conditions could help identify if some people respond better to certain treatments, enabling a more personalized and targeted approach to treatment.

In this observational study, people with lower urinary tract symptoms who were enrolled in the Symptoms of Lower Urinary Tract Dysfunction Research Network study were characterized as experiencing either UU-only or UUI based on their answers to a questionnaire about their urinary symptoms. Of the 683 participants who reported urinary urgency at their initial visit, one-third were characterized with UU alone and two-thirds were characterized with UUI. At their initial appointment and at 3- and 12-month follow-ups, participants also answered questions to assess their urological pain, other urological symptoms, and quality of life. Individuals experiencing UU-only reported fewer symptoms like severe urgency and urinary frequency; lower levels of anxiety, depression, and stress; and better sleep and higher physical activity than those with UUI. Additionally, individuals with UUI reported a lower quality of life than those with UU alone. Interestingly, the researchers did not observe differences in urological pain between people with UU-only and people with UUI. The study investigators also observed that some people transitioned between UU-only and UUI after 12 months, whereas some improved to the point of having no urgency at all. These results suggested that UUI may be a more severe form of UU, rather than two different subtypes of OAB.

While this study provides new information about the symptoms of UU and UUI, further research is needed to definitively characterize the relationship between these conditions. A limitation of this study is that participants were followed for only 12 months. Longer observations of people with UU and UUI will provide better insight into their long-term impact on health and well-being. Further, since the population included was predominantly White, observations of more diverse

groups will help determine whether these findings apply to all people living with OAB.

Lai HH, Wiseman JB, Helmuth ME, ...Kenton K; for the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN). Phenotyping of urinary urgency patients without urgency incontinence, and their comparison to urgency incontinence patients: findings from the LURN study. *J Urol* 209: 233-242, 2023.

**Discovering the Risks of Developing Symptoms Due to Ureteral Stent Placement:** Kidney stones are small, hard structures that are sometimes found in the kidneys or in the tubes known as ureters that move urine from the kidney to the bladder. When stones are too large to pass through, they can cause blockages. Physicians often recommend a surgery called a ureteroscopy (URS) in which a small tube containing a camera is used to look inside the ureters and kidneys to find, and in some cases remove, the cause of the blockage. Sometimes the surgeon may temporarily leave a tiny tube called a stent inserted in the ureters to assist in holding them open to facilitate urine flow and passage of any stones after surgery, promoting healing. Unfortunately, these stents often cause discomfort and may themselves lead to urinary difficulties in some people. However, identifying individuals who are most at risk of experiencing severe stent-related symptoms has been difficult. The NIDDK-supported Urinary Stone Disease Research Network, therefore, conducted and published the findings of the Study to Enhance Understanding of Stent-Associated Symptoms, or STENTS, with the goal of improving understanding of stent-related symptoms and risk factors for developing them.

STENTS researchers enrolled 424 people who underwent a URS and stent placement at four hospitals across the United States. Before surgery, participants filled out four short questionnaires to report pain intensity, level of pain interference on daily activities, urinary symptoms such as incontinence, increased frequency and difficulty urinating, and the level of bother due to those symptoms. These questionnaires were repeated 1, 3, and 5 days after the URS, on the day of stent removal, and 30 days after stent removal. The study researchers found that while they observed a peak in pain and urinary symptoms 1 day post-surgery with a steady decline until day 5, the level of daily interference and bother due to pain and urinary symptoms persisted longer. Surprisingly, no specific surgical factors, such as surgery length or method, were associated with higher pain and urinary symptoms or their impact. Instead,

they found that painful past stent experiences were associated with higher pain intensity and interference, higher body mass index was associated with higher urinary symptoms and bother, and younger age and history of depression were associated with higher levels of all symptoms and their impact. A month after stent removal, however, all reported symptoms were below pre-surgery levels.

*Researchers gained more insight into individual risk factors for pain and urinary symptoms among people with stents placed after surgery for urinary stones.*

Further investigation of stent-related symptoms is needed since these results may not be broadly representative, as the study population was primarily White, and the surgeries were performed at academic medical centers. However, the knowledge gained from this study can lead to new strategies, such as options for stent-less ureteroscopies, more informed patient counseling, and new potential therapies to improve experiences of patients with kidney stones.

Harper JD, Desai AC, Maalouf NM, ...Scales CD Jr; for the Urinary Stone Disease Research Network (USDRN). Risk factors for increased stent-associated symptoms following ureteroscopy for urinary stones: results from STENTS. *J Urol* 209: 971-980, 2023.

## EXPLORING THE BIOLOGY OF BLOOD DISORDERS TO FIND NEW AVENUES FOR TREATMENT

**Identification of a New Potential Therapeutic Approach to Blood Disorders:** Scientists detailed a novel way to restart production of fetal hemoglobin (HbF), suggesting a new potential therapeutic approach for some blood disorders. Thalassemias and sickle cell disease are inherited blood disorders that affect hemoglobin, a protein that carries oxygen through the body. Around birth, production of HbF is turned off and shifts to production of “adult” hemoglobin (HbA). In this research, investigators studied hemoglobin genes and their regulation and identified how HbF is turned on in response to high-altitude conditions of low oxygen (hypoxia), an example of a condition in which more red blood cells are needed rapidly. This research identifies a new therapeutic approach to blood disorders of hemoglobin.

The scientists found that a protein called hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) can turn on production of HbF in an adult human blood cell line. Using cutting-edge molecular and genetic strategies, they found that HIF1 $\alpha$  binds specific sequences of DNA in regions known to regulate hemoglobin genes and recruits additional proteins to stimulate production of HbF. They uncovered molecular changes in HIF1 $\alpha$ , as well as changes in how it interacts with other proteins, that occur in the developmental switch from production of HbF to HbA. They hypothesized that reversing these changes might re-induce HbF production. To test whether this approach could be a potential therapeutic strategy, the scientists treated cells with a drug known to boost red blood cell levels. They found that treating healthy adult donor cells or cells from donors with sickle cell disease with this drug increased production of HbF

to levels similar to those induced by treatment with hydroxyurea, which is used to treat sickle cell disease. Treatment of the cells from a donor with sickle cell with the drug also reduced the sickling characteristic of the disease.

The exciting finding that stabilization of HIF1 $\alpha$  can induce production of HbF in human blood cells provides important new knowledge in understanding the regulation of hemoglobin production and indicates a potential therapeutic strategy to restart HbF production in people affected by blood disorders. Additional research will be needed to test whether this strategy can be translated from the bench to the clinic.

*Feng R, Mayuranathan T, Huang P, ... Weiss MJ. Activation of  $\gamma$ -globin expression by hypoxia-inducible factor 1 $\alpha$ . Nature 610: 783–790, 2022.*

## Lower Urinary Tract Symptoms Network (LURN): Development and Use of Improved Assessments of Urinary Symptoms

Symptoms affecting the lower urinary tract, such as urinary incontinence, frequent urination, and bladder pain, are common among adults and often have negative impacts on a person's quality of life. Gaining a comprehensive understanding of the full spectrum of lower urinary tract symptoms (LUTS) and their impact on people dealing with them will allow for better diagnoses and development of improved treatment options.

LUTS are typically assessed using questionnaires that allow individuals to self-report and rank their symptoms, and sometimes their quality of life, via a point scale to determine their symptom severity scores. When used alongside other clinical tests and physical examinations, these assessments can help guide clinicians in their recommendations. Several questionnaires have been developed to assess LUTS, however many of them are either limited in their scope, focusing on specific disorders, or were originally developed to assess sex and/or gender-specific symptoms. For example, the American Urological Association Symptom Index was initially designed to assess symptoms of benign prostatic hyperplasia in men, while the Pelvic Floor Distress Inventory evaluates the impact of LUTS and other symptoms on the quality of life of women with pelvic floor disorders. Additionally, many of the available questionnaires do not assess the full range of LUTS.

In 2012, NIDDK established the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) with the long-term goals of better understanding



different LUTS subtypes and improving measurement of patient experiences of LUTS. To achieve these aims, LURN researchers first developed the Comprehensive Assessment of Self-Reported Urinary Symptoms (CASUS), which is a 93-question survey measuring a broad variety of symptoms in both men and women with LUTS.

For use in a clinical or research setting, an optimal questionnaire must be simple and brief enough to ensure that people can fully understand and complete it, yet comprehensive enough to gather meaningful information. Therefore, using the CASUS as a starting point, LURN researchers along with a panel of clinicians used a multi-step process to develop two shorter-form questionnaires: the LURN Symptom Index 10 (SI-10) and the LURN Symptom Index 29 (SI-29). The SI-10 is primarily intended for clinical use and is composed of 10 core questions, while the SI-29, which consists of 29 core questions, is primarily designed for research. Both questionnaires cover five key symptom areas of LUTS: urinary urgency, incontinence, urination difficulty, night-time frequent

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urination (referred to as nocturia), and pain. When tested for validity against commonly used LUTS measurement questionnaires, both SI-10 and SI-29 provided scores that were comparable to those of the established surveys while also providing assessment of a broader range of symptom areas.

The LURN questionnaires have already proven to be valuable resources in both research and clinical settings, facilitating assessment of LUTS symptoms and their impact on people's lives. Several hospitals have integrated the SI-10 questionnaire into their electronic health record systems, providing clinicians with more insight into the symptoms that their patients experience.

Recognizing that addressing disparities in urological health requires ensuring these tools are accessible to diverse patient populations, LURN researchers optimized each question during questionnaire development to promote easy translation into other languages. In fact, the NIDDK-supported Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium developed a Spanish translation of the

SI-10 for inclusion in its RISE FOR HEALTH study of women's bladder health. In addition, Turkish translations of both questionnaires and a Hindi version of the SI-29 are available for download on the LURN website, and more translations are planned for the future. By making the questionnaires available in multiple languages, LURN scientists are helping ensure that their research will be both broadly applicable and widely available, thus improving comprehensive LUTS assessment in diverse communities.

More research will be necessary to fully understand and optimally treat the complex array of diseases and conditions that contribute to LUTS. Through development of the CASUS, SI-29, and SI-10 questionnaires, LURN has laid a key foundation for that work by providing comprehensive tools that are yielding new insights that may one day improve diagnostic and treatment approaches for LUTS.

*For more information, visit*  
<https://nih-lurn.org/Resources/Questionnaires>.

# Alternatives to Race-Based Kidney Function Calculations

Race has long been used as a biological variable in health research, under the mistaken belief that racial categories correlate with genetic traits that account for population-level biological differences. However, we now know that more genetic variation exists within race categories than between them, and that race correlates poorly with the spectrum of biological variability that exists among human beings.

Accordingly, NIDDK-supported research is leading to a change in the way kidney disease is diagnosed and monitored by removing race as a variable from the equations used to estimate glomerular filtration rate (GFR). Estimated GFR remains a primary tool to assess kidney function and to classify the severity of kidney disease. Estimated GFR also helps determine prognosis and treatment, such as when hemodialysis or a transplant may be needed and how to optimize the dosage of certain drugs.

Because measuring someone's GFR directly is expensive, difficult, and burdensome on the person being tested, GFR is normally estimated by using an inexpensive blood test to determine the concentration of a compound called creatinine. Because creatinine is synthesized at a constant rate by one's muscles and filtered out of the blood by the kidneys, its concentration in the blood is strongly linked to kidney function. For several reasons, however, creatinine is not a perfect biomarker of a person's actual kidney function. For example, its synthesis rate is determined by how much muscle a person has, and its blood concentration is also affected to a degree by how much meat they eat. As a result, a person's real GFR might be a bit higher or lower than their estimated GFR, but the estimates are generally close.

However, the original study data used to develop estimated GFR calculations came overwhelmingly from participants of European descent. Subsequent work showed that the relationship between creatinine level and real GFR, on average, was the same for people from most other groups. Researchers discovered, though, that for unknown reasons creatinine levels tend to be slightly higher in Black study participants than in participants from other populations, at any given directly measured GFR. As a result, for many years estimated GFR calculations have taken into consideration whether the person being tested is "Black" or "non-Black."

This practice is problematic. Race was created for social and political reasons, and thus has no biological basis. Indeed, race categories do not align with the continuum of human genetic and biological variability. For example, many individuals who identify as Black do not, in fact, have a higher creatinine to GFR ratio than is found in other groups. Therefore, applying the "correction factor" for Black race sometimes leads to overestimation of GFR, potentially aggravating the significant health disparities that exist in kidney health outcomes. For example, a person who identifies as Black could be erroneously excluded from receiving a kidney transplant because the equation overestimates their GFR, making it appear that their kidneys are more functional than they are. Further, the physiological reason why some Black people have a higher creatinine to true GFR ratio remains unknown, so there is no way to test for it. Thus, it is unclear who, exactly, does have a higher creatinine to true GFR ratio and thus should receive a correction factor for determination of estimated GFR.

Recent NIDDK-supported research from the Chronic Renal Insufficiency Cohort Study and the Chronic



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Kidney Disease Epidemiology Collaboration has sought to address these issues by identifying new, better methods for assessing kidney function. For example, one group investigated whether genetic ancestry analysis might be useful for helping determine who the correction factor should apply to. While the use of ancestry did improve accuracy at the population level, it is both impractical and not always applicable at the individual level. Other approaches that considered body composition (e.g., how muscular a person is) or urinary creatinine excretion rates marginally improved accuracy. Another group tested an alternative formula for estimating GFR from creatinine that corrects somewhat for age and sex, but that does not use race as a modifier. On average, this approach slightly underestimated GFR for participants who identified as Black, and slightly overestimated GFR for people who considered themselves non-Black.

Encouragingly, both studies also found that estimating GFR based on blood levels of a compound called cystatin C, which does not vary by a person's race, could help improve the accuracy of kidney function tests. One of the studies found that the most accurate, least biased results were obtained using equations that utilize both markers—creatinine and cystatin C. Thus, NIDDK-supported research has

informed recent recommendations to use both serum creatinine and cystatin C to estimate GFR in adults, when cystatin C is available. Using the combined serum creatinine-cystatin C equation is particularly important when the estimated GFR value is close to a critical decision point, such as when determining drug dosing or kidney transplant eligibility.

At present, however, laboratory and reimbursement infrastructure are not yet adequate to support routine ordering of cystatin C tests in clinical settings for all people for whom GFR should be more accurately assessed. Therefore, two leading kidney health advocacy groups—the American Society of Nephrology and the National Kidney Foundation—have called for measures to improve the availability of cystatin C testing, as well as more research to find still better approaches for assessing kidney health. In the meantime, they have called for adoption of the improved creatinine-only based GFR estimation method that uses age and sex—but not race—as modifiers.

Thus, NIDDK-supported research is improving the equitable and accurate assessment of kidney function. NIDDK remains committed to research that builds on that improvement and to the overarching goal of reducing disparities in kidney disease.

## Improving Kidney Stone Measurements With Automated Systems

Urinary stones, also called kidney stones, are pebble-like structures that form due to buildup of minerals from urine in the kidneys. About 11 percent of men and 6 percent of women in the United States have kidney stones at least once during their lifetime. If small enough, kidney stones can pass through the urinary tract freely, while larger stones can cause symptoms such as severe pain, bleeding, and urinary blockage. Treatment courses for kidney stones are informed by the size and location of stones and can involve simply monitoring for their passage, using methods to break them into smaller pieces, or surgically removing the stones. Reliable and precise measurement methods are therefore crucial for accurate diagnosis and treatment of kidney stones.

Multiple tests are used collectively to diagnose kidney stones, including lab tests like blood and urinary analyses to measure levels of certain minerals, and imaging tests like x-rays and computed tomography (CT) scans to visualize the location of the stones. Some stones can be missed by x-rays depending on their size and location. Therefore, CT scans, which consist of x-rays taken at multiple angles that are computer processed to produce detailed images, are more commonly used to visualize kidney stones. While CT scans are better able to detect stones, they require manual input to determine the size and other characteristics of kidney stones and to measure the anatomy surrounding them. This need for human input introduces variability and less precise measurements, as the same stone may be characterized differently from one person to the next. This variability can make it difficult to assess factors such as the likelihood of a stone passing

and the measurement of changes in stone size over time. A more automated measurement process could help to ensure reliable kidney stone measurements and reduce the need for the tedious, more variable manual process.

NIDDK supports research to develop automated, more reliable measurement tools for kidney stone detection. For example, the Center for Machine Learning in Urology (CMLU), which is a joint venture of Children’s Hospital of Pennsylvania and University of Pennsylvania, aims to use machine learning with CT imaging to improve prediction of kidney stone passage. In a recent advance from the CMLU, scientists described the ability of their machine-learning algorithm to accurately measure kidney stones and compared it to the manual measurements of three different researchers. Of the 94 children and adults included in the study, both manual measurers and the algorithm were able to detect that 42 of the patients had kidney stones. However, the algorithm was shown to provide more reliable measurements of stones and regions of the urinary tract than manual input. The algorithm also had a quicker average measuring time of 12 seconds—regardless of the number of stones—compared to increased manual input times with the presence of more stones. Another NIDDK-funded program, the O’Brien Urology Research Center at Mayo Clinic, has supported the development of a semi-automated software system called qSAS. The system, which is currently in use for CT research at the Mayo Clinic and is freely available to other research groups, provides standardized stone characterization with minimal manual input.

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Automated CT scan image measurement processes can lessen, and in some cases remove, the variability that comes from manual measuring, while providing more accurate assessments. Machine-learning CT imaging tools like the one developed by CMLU researchers have an added advantage of automatic continued refinement as more data points are entered. With further validation and optimization, the quicker and more reliable measurements offered by these new technologies have the potential to ensure more precise research and diagnosis of kidney stones.

# PERSONAL PERSPECTIVE

## Contributing to Research Toward Achieving Equity in African American Kidney Transplant Outcomes

Chronic kidney disease (CKD) is characterized by a long-term decrease in the ability of a person's kidneys to effectively filter toxins from the blood. CKD can often lead to end-stage kidney disease (ESKD), also known as kidney failure. Treatment options for ESKD are either dialysis, which typically involves filtration of toxins from the blood by a machine, or kidney transplantation. Though beneficial, dialysis can be burdensome and draining, typically requiring 4-hour visits to a dialysis center 3 days per week. However, transplantation, if available, can provide better quality of life and enhanced survival to recipients.

African Americans experience disproportionately higher rates of ESKD compared to other racial groups in the United States. NIDDK-supported research contributed to the discovery that one factor impacting this disparity is a greater presence of specific high-risk genetic variations in the *APOL1* gene among people with recent African ancestry. Two variants of this gene have been shown to account for nearly all the additional risk of ESKD in African Americans who do not have diabetes. However, it is not completely clear whether donated kidneys with two of these high-risk *APOL1* variants have worse outcomes after transplantation.

To address this, NIDDK, with additional support from the National Institute of Allergy and Infectious Diseases and the National Institute on Minority Health and Health Disparities, started the APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO) in 2017. APOLLO is an observational study that involves extensive collaboration of many organizations, including the United Network for Organ Sharing, organ

procurement organizations, and kidney transplant centers across the United States. The aim of the study is to determine the impact of *APOL1* gene variations on outcomes of transplants with kidneys from both living and deceased African American donors. (See inset for the story of a kidney donor and kidney transplant recipient participating in APOLLO.)

### THE LINK BETWEEN AFRICAN ANCESTRY AND *APOL1*-RELATED KIDNEY DISEASE RISK

Like many other sustained genetic mutations, the variations found in the *APOL1* gene likely aid in human adaptation to a specific environment. Studies have shown that the proteins of the same two *APOL1* variants that result in increased risk of kidney disease likely protect people against infection with the parasites that cause a disease called sleeping sickness in humans. Scientists believe that the predominance of these parasites in sub-Saharan Africa has contributed to the high prevalence of the *APOL1* variants in people with recent African ancestry.

Only people who inherit the high-risk variants from both parents appear to have increased risk of ESKD associated with *APOL1*. However, most people who inherit two high-risk variants will never experience ESKD or even develop kidney disease. The mechanism by which the variant *APOL1* genes lead to development of kidney disease is not fully understood, but other factors – including certain immune responses or infection with HIV (human immunodeficiency virus) might play a role.

# PERSONAL PERSPECTIVE

## **APOLLO: ASSESSING THE INTERSECTION OF *APOL1* AND AFRICAN AMERICAN DONOR KIDNEY TRANSPLANTATION**

Because of the burden of dialysis treatment, kidney transplants provide people with ESKD greater quality of life. However, there are many more people who need a kidney than there are donor organs available. Unfortunately, many African American donor kidneys are not used. This occurs for a variety of reasons, including observations that kidneys transplanted from African American donors typically function for shorter periods of time and may have viral infections that kidneys from donors of other groups do not. Kidneys from African American donors are also more likely to be transplanted into African American recipients, meaning that these potential recipients are disproportionately impacted by the decreased pool of viable kidneys. If *APOL1* high-risk variants among African Americans contribute to the lower rates of available kidneys, a genetic test of the donor could be used to determine the risk of kidney transplant failure instead of race. In that case, more kidneys could become available for donation, and there may be better outcomes for the recipients.

The ongoing APOLLO long-term observational study is the first forward-looking study of *APOL1* and kidney transplant risk, meaning that participant outcomes and health will be observed over time instead of assessed retroactively. In APOLLO, kidney donors and recipients will be genetically tested to determine their *APOL1* gene type. The outcomes of kidney transplant recipients, primarily the length of time to transplant failure, will be observed over a span of several years and assessed according to the number of donor and/or recipient *APOL1* high-risk variants involved.

Although most of the kidney transplant recipients participating in APOLLO receive organs from deceased donors, some of the donors are living. As such, the study will also observe the health outcomes of these donors. Some evidence suggests that living kidney donors who have two high-risk *APOL1* variants may have a higher risk of developing kidney disease at some point, long after donation. While the outcomes of living kidney donors will be observed throughout the main APOLLO study, the supplemental Living-donor Extended Time Outcome (LETO) study will assess donor outcomes as well. The LETO arm of APOLLO will look back at the kidney health outcomes of kidney donors from 15 to 20 years ago to assess any risk of *APOL1* high-risk variants to living kidney donors.

Working alongside the researchers to develop and steer the study is APOLLO's Community Advisory Council, which is made up of African American living kidney donors, kidney recipients, and their family members. An important goal of the Community Advisory Council and the researchers alike is to provide understandable education to the broad patient community. They have, therefore, collaborated to develop many videos, pamphlets, and other resources explaining the link between *APOL1* gene variants and kidney disease, as well as the purpose, plans, and hopes of APOLLO. (For more information, please see: [www.apollocommunity.net/community-education](http://www.apollocommunity.net/community-education).) Findings from APOLLO have the potential to lead to a nationwide reworking of the current assessments for kidney donations, which could provide a second chance at life for many more people awaiting kidneys.

## Deryl's and Tanya's Story



Cousins Deryl and Tanya are participating in the APOLLO study, which aims to improve African American kidney donation and transplant outcomes

Deryl didn't learn that he had chronic kidney disease (CKD) until he was in his forties, but knowing what he knows now, he believes that there were hints of it throughout his life. Since he was a child, he says, "I knew something was wrong.... I believed my kidneys were not functioning properly based on personal frequent occurrences. I remember my mom asking if I wanted to go to the doctor. I always said no because of the embarrassment of the situation." His life completely changed in 2020, after a severe case of COVID-19 when he developed end-stage kidney disease (ESKD) and needed a kidney transplant. Hope soon came from his cousin, Tanya, who was ready and willing to donate one of her kidneys. Remembering when she learned of her cousin's need for a kidney, she says, "I think that it was just kind of a no-brainer for me to say, 'Oh, OK, well I'll get tested.'" The subsequent journey, including their participation in NIDDK's APOL1 Long-term Kidney

Transplantation Outcomes Network (APOLLO), resulted in a new beginning and a family's passion to advance health equity in kidney transplantation.

### LEARNING ABOUT AND LIVING WITH CKD

Having played basketball for most of his life and now coaching a high school basketball team in Highland, Illinois, Deryl has always lived an athletic lifestyle without any other major health issues. He remembers receiving his first bit of insight into his kidney disease as a transfer student athlete at Kansas State University. "The only thing I knew was when I was in college the doctor said, 'You have protein in your urine,'" he remembers. "The doctor said that I could have a more serious problem down the line. I was told I had [high] blood pressure also," he says. "I was told to try and eat certain food items in moderation. It was difficult...." Overall, though, he says, "I didn't know what it really meant and the effects that it could cause. There was no cure." Detection of protein in a person's urine can be an early sign of kidney disease. However, Deryl did not let that stop him. He recalls telling himself, "You're an 18-year-old young man and student athlete. Only thing that I know is all my coaches told me to play hard, and I believed playing and working hard was a cure-all."

And that is exactly how Deryl lived a lot of his life. After college he went on to have a successful professional basketball career for over 10 years. In fact, it wasn't until he went to his doctor for a routine exam as an Indiana State University basketball coach in his forties that he learned he had kidney damage and was diagnosed with CKD. The diagnosis was important to Deryl: "When you have a condition, it's important to have knowledge and, if possible, treat it. In my case, I was affected by CKD on and off the court."

# PERSONAL PERSPECTIVE

While kidney damage due to CKD can be slowed through lifestyle changes like blood pressure management, weight loss, and diet changes, there are currently no known ways to reverse CKD-related damage. Deryl made many adjustments to manage his CKD, although he says that it wasn't easy. His hard work changing his diet paid off, though, and he managed to avoid needing dialysis. All of that changed when, in 2020 at the height of the COVID-19 pandemic, Deryl contracted the illness, which resulted in his ESKD.

## THE LONG ROAD TO A NEW KIDNEY

Tanya, Deryl's cousin, works as a lawyer and has dedicated her life to providing justice to her community as the head of a civil legal aid clinic in Chicago. Tanya says that as her parents' only child, she, Deryl, and his sister "grew up more like siblings than cousins." So, she sprang into action when she received a call from his sister saying that Deryl needed a kidney transplant. Deryl's sister already knew then that she wasn't a match to donate a kidney to her brother, so Tanya decided to get tested.

***When Tanya learned of her cousin's need for a kidney, she says, "I think that it was just kind of a no-brainer for me to say, 'Oh, OK, well I'll get tested.'"***

Matching a living donor to a transplant recipient is a complex, multi-step process. It involves tests to assess the health of both donor and recipient, determine blood type compatibility, and, most critically, to predict the chance of the recipient's body rejecting the donor organ. Once Tanya learned she was a match, she and Deryl's sister waited to tell him, not wanting to get his hopes up prematurely. "We just wanted to make sure that there was a plan, that I had gone through all of the education, that I had passed all the things that I needed to pass," Tanya says.

Despite finding a donor fairly quickly, it would take over a year before Deryl could receive his cousin's kidney. Deryl's medical team found that his parathyroid hormone levels were elevated—a complication that can commonly occur in people with ESKD—and wanted his levels to decrease before they could safely perform the surgery. In the interim, he had to begin dialysis. "I was on dialysis for 14 months," says Deryl. "We were not expecting me to be on dialysis that long." He remembers the challenges of maintaining a normal life during this time: "I did dialysis from 5:00 a.m. to 9:00 a.m., and then I went to work, coached my high school team, and ran my DJ business with bookings on the weekends. And there were days that I was super weak at work and barely making it, so it was very difficult."

In 2021, Deryl finally got the OK to undergo surgery. To Tanya and Deryl, even the date of the surgery was a good sign. "They give us a surgery date of December 1, which happens to be our maternal grandmother's birthday," Tanya says. "We all see this as a positive sign from God—it's all going to go well." Both of their surgeries did, indeed, go well. When speaking of his medical team who performed the transplant, Deryl says, "You ever seen the 'Dream Team' in basketball? They became my Dream Team."

## APOLLO: GAINING INSIGHT AND "CLOSURE" THROUGH KNOWLEDGE

It was in the time leading up to his kidney transplant surgery that Deryl and Tanya first learned about APOLLO. The Transplant Center at SSM Health Saint Louis University Hospital where Deryl received his transplant was a Clinical Center participating in APOLLO. He spoke to the Principal Investigator at the Center, Dr. Krista Lentine, who provided information about enrolling in the study. Speaking about his decision to enroll, Deryl recalls thinking, "Maybe I can help someone else. Maybe someone else with kidney disease." He also says that he "started to want to know even more" regarding his kidney health.

# PERSONAL PERSPECTIVE

The primary outcome measured for APOLLO is the success or failure of participant kidney transplants—as tracked by electronic medical records and the United Network for Organ Sharing—over a span of up to 4.5 years. Participant visits are infrequent and consist of an initial visit and an additional visit to collect blood and urine samples, all of which are saved in the APOLLO Central Laboratory. These samples will allow APOLLO researchers to assess secondary study measurements of kidney health, such as the presence of protein in the urine and changes in participants' estimated kidney function.

***Speaking about his decision to enroll in the APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO), Deryl recalls thinking, "Maybe I can help someone else. Maybe someone else with kidney disease."***

Another important component of APOLLO is providing information and health education to the patient community about APOL1 variants and the risk for kidney disease. Though study participants have the opportunity to learn their—or in the case of deceased donors, their family member's—APOL1 genetic results 3 to 4 years after their enrollment, they are not prevented from getting tested themselves sooner outside of APOLLO. It was through this outside testing that Deryl learned that he had received a high-risk APOL1 variant from both of his parents. "It gave me closure," he says, referring to now having a better understanding of the medical issues with his kidneys that he'd experienced throughout his life.

Speaking about her thoughts on the impact that APOLLO could have on outcomes for African Americans with kidney disease, Tanya says, "For me,

it's huge, because of the work that I do." She views her participation in APOLLO and her and Deryl sharing their story as a type of justice for the African American community, saying, "Justice gets construed as what we see in the criminal justice system or in a court of law, but justice takes many forms." She continues by saying that African Americans "have generations of not trusting our health care professionals, so I'm hoping that studies like this will give people some more agency." The advice that she would give anyone considering donating a kidney: "Get information. Be educated about it and not so quick to assume that you know everything there is to know about donating."

Throughout his journey with CKD and ESKD, Deryl saw the value of learning all he could about his own health. Providing his advice to anyone living with kidney disease, he says that people should learn and be informed about their own health, as it is important "to be front and center on your medical situation." Since his transplant, he now has much more energy to do the things he loves, like spending time with his family, playing and coaching basketball, and sharing his love of music through his side job as a DJ. His days look a lot different now. "This morning," he says, "I got up at 4:45 a.m. I played basketball from 5:30 a.m. to 7:00 a.m. I came back home... showered, went to work, got in by 7:45 a.m., worked a full day, got on the phone with you, will talk to a couple clients tonight, [my son's] got football later today.... I'm able to power right through the day."

The participation of Deryl, Tanya, and many others in APOLLO may one day lead to more organs for transplants, improve the health of people with ESKD, and advance health equity in kidney transplantation.



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