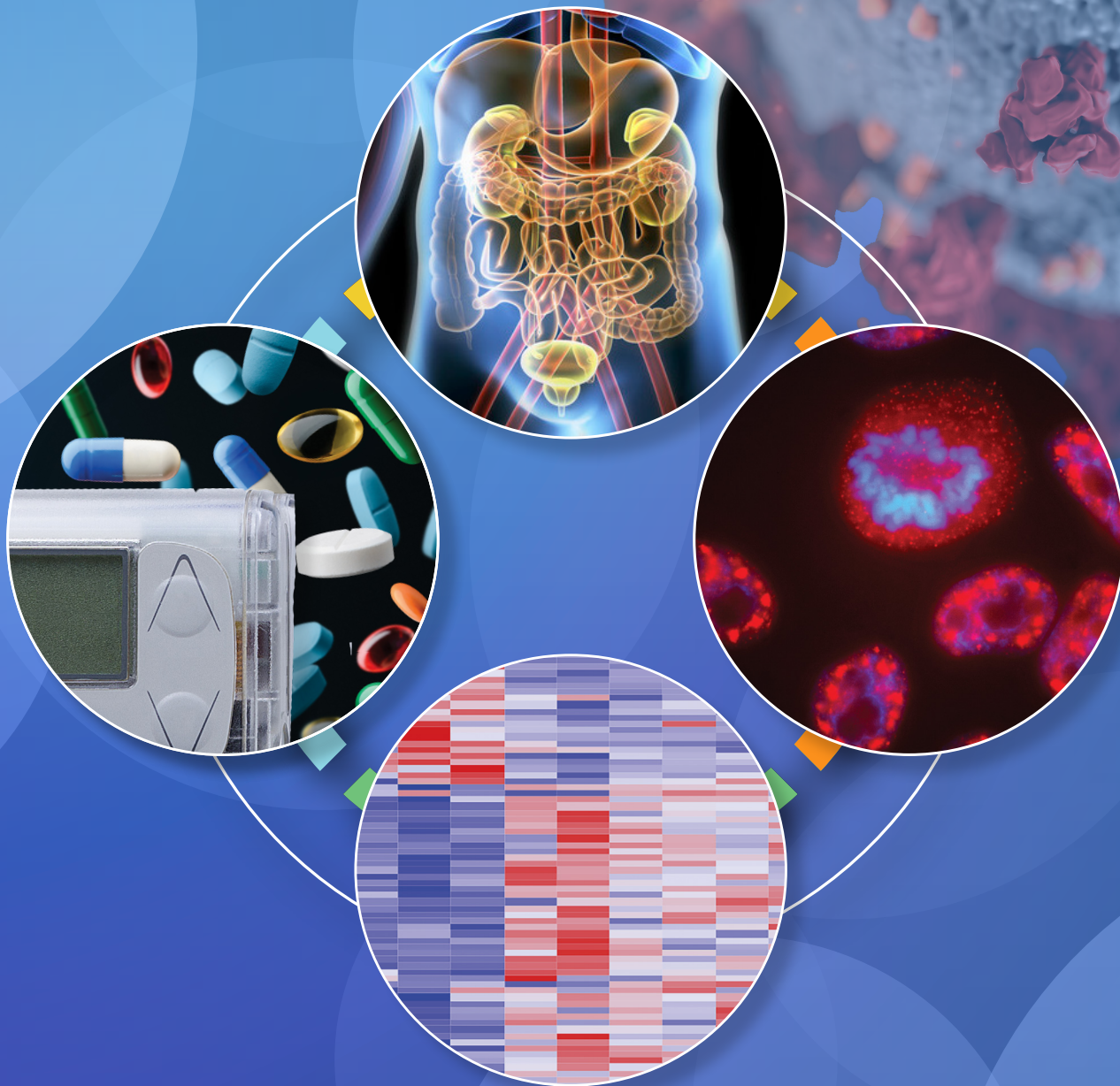


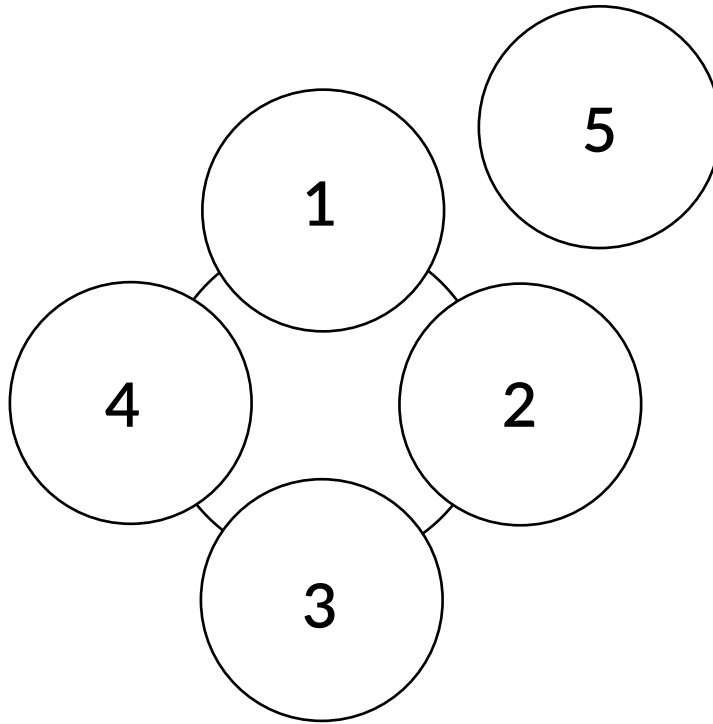
# NIDDK

## Recent Advances & Emerging Opportunities

January 2021



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



The NIDDK supports research to understand how the body’s organs and tissues—such as the pancreas, gut, liver, kidney, and bladder **(1)**—function in health and disease. Organs and tissues are made up of cells that work together to carry out the body’s functions. In the past, changes at the level of a single cell have been difficult to tease out because of experimental limitations. Now, scientists are using new and sophisticated technologies to analyze characteristics of individual cells **(2)**, such as the proteins and metabolites that each cell produces. The large amounts of data stemming from these analyses **(3)** are giving us unprecedented new scientific insights and showing that the behavior and function of individual cells can vary greatly, even between cells that are in close proximity to one another. This new knowledge is illustrating how differences among individual cells can play a role in determining health and disease. It is also helping to inform the development of new therapies, such as medicines and devices **(4)**, to improve the health and quality of life of people with diseases and disorders within the NIDDK mission, giving them hope for a healthier future. Many of these diseases and disorders put people at high risk of severe illness from SARS-CoV-2 **(5)**, the virus that causes COVID-19, so the NIDDK is also pursuing research to combat COVID-19 and find ways to reduce the additional dangers it poses for those with underlying health conditions. In parallel, as the virus disrupted research earlier in 2020, the NIDDK sought input from the scientific community and has taken action to reinvigorate research across the Institute’s mission.

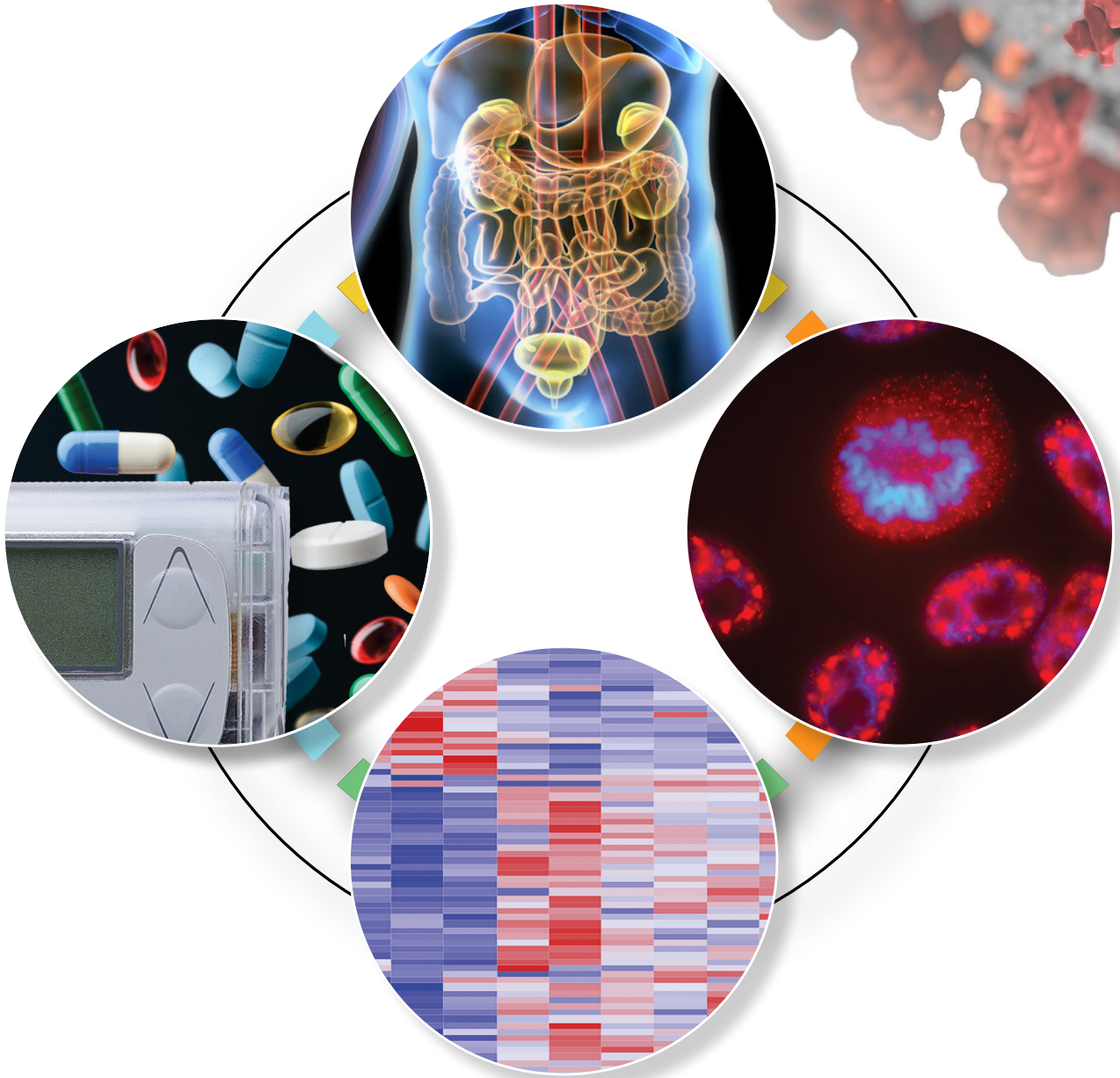
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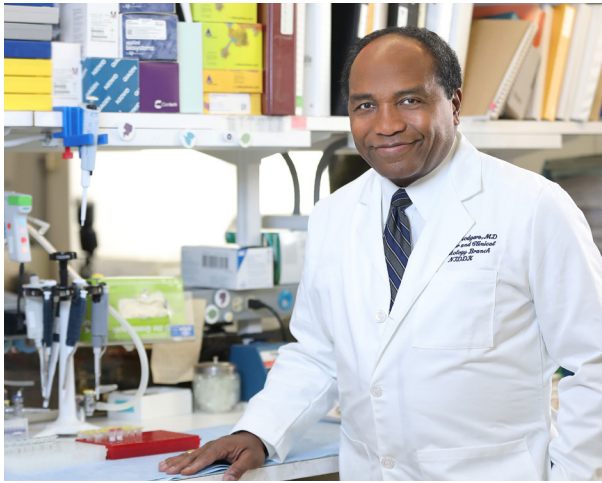
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**ACKNOWLEDGMENTS**

# Message from the Director



As the Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I am pleased to present this annual report highlighting the research efforts and programs supported by the Institute. The 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/painful bladder syndrome, prostatitis, and urinary tract infection; and blood diseases.

In view of the profound effects that COVID-19 (Coronavirus Disease 2019) has had on our Nation and the world, and the ways in which the disease has exacerbated some of the existing health disparities in the NIDDK's mission diseases, the "Cross-Cutting Science" chapter of the 21st edition of this report highlights our Institute's multi-pronged efforts toward the goal of health equity. In addition, the report describes recent NIDDK-supported scientific advances on topics such as:

- An innovative approach from NIDDK intramural researchers shows the potential importance of speech in transmitting the virus responsible for COVID-19;
- Lab-generated cell clusters that can produce insulin in mice while avoiding destruction by the immune system, a step toward a possible long-term treatment for type 1 diabetes;
- A dramatic increase in knowledge of type 2 diabetes genetics from combining analyses of studies in people of East Asian descent;
- Finding that community barbershops are promising venues for screening Black men for type 2 diabetes;
- Demonstration of health benefits in people from a treatment that converts energy-storing fat cells into an energy-burning form of fat;
- Testing of medications that now make it possible to partly restore the function of the protein missing in 90 percent of people with cystic fibrosis;
- The weight-loss and metabolic effects of bariatric surgery compared to non-surgical weight-loss approaches;
- The physiological effects of exercise;
- The role of the microbiome, including its regulation of circadian rhythms and its effects on nutrient absorption;
- Development of a new mouse model that mimics the immune system features and gluten-dependent intestinal damage seen in people with celiac disease;
- Insights into the way high fructose consumption may promote nonalcoholic fatty liver disease;
- Kidney development and function, as novel insights bring us closer to new strategies to address kidney diseases;
- Development of a noninvasive technique with potential application to treat urinary stones; and



- Identification of a compound that may one day lead to improved treatment for dyskeratosis congenita, a rare blood disease.

In addition to reporting on recent advances, this publication traces the multi-step path to research achievements through several “Stories of Discovery.” These essays illustrate how major new discoveries that have greatly advanced biomedical science and are benefitting human health often emerge from incremental insights gained from research investments spanning many years and even multiple research disciplines.

This report also includes personal perspectives of those who have given time and effort to participate in NIDDK-sponsored clinical research. A woman describes how an artificial pancreas device she tested as part of a clinical trial helped her manage her type 1 diabetes and improved her mental well-being during some challenging personal times. Parents share their experience raising a daughter born with a life-threatening liver disease called biliary atresia and their participation in clinical research to find better ways to detect and manage the disease. A woman tells of her decades-long

participation in a landmark study demonstrating that type 2 diabetes can be prevented with lifestyle modifications. A retired chemist describes how her participation in clinical research revealed that she has a rare type of kidney disease—a diagnosis that for years had eluded her physicians.

The 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 distribute it through our information and outreach programs and our website. I invite you to visit us at [www.niddk.nih.gov](http://www.niddk.nih.gov). Health information, news, and scientific advances related to NIDDK research are also available on our Twitter feed: [@NIDDKgov](https://twitter.com/NIDDKgov).

This report reflects only a fraction of the immense body of NIDDK-funded research across the country, performed by basic scientists, clinical investigators, and patient 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.

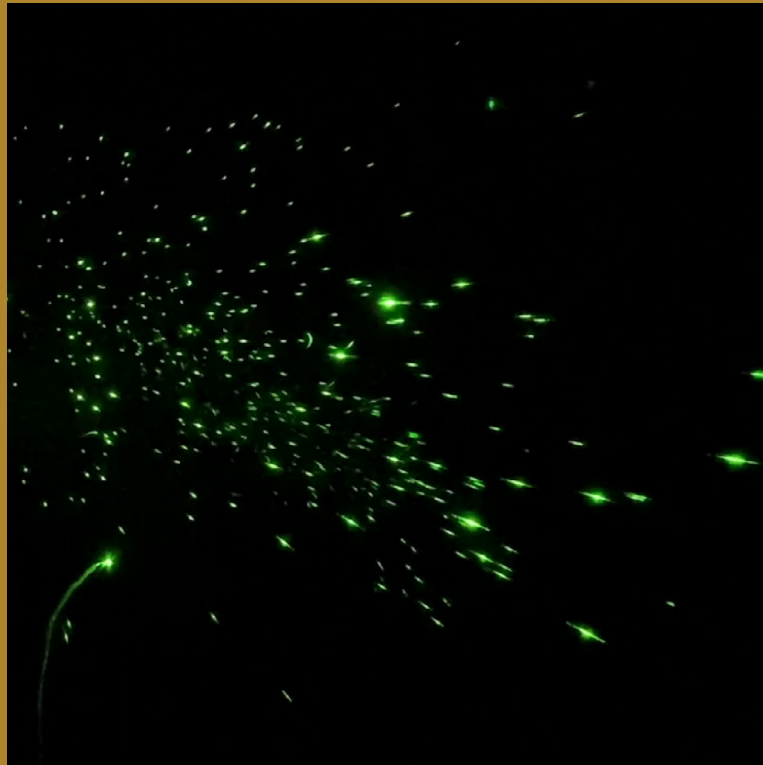
The efforts featured in this publication reflect the core mission of the NIDDK, including the Director’s guiding principles:

- 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 the NIDDK’s activities support these guiding principles can be found in the “NIDDK Extramural Funding Trends and Support of Guiding Principles” section at the end of this report and on our website at: [www.niddk.nih.gov](http://www.niddk.nih.gov).

## **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



As scientific findings began to accumulate during the spring of 2020 about SARS-CoV-2, the virus that causes COVID-19, two facts became increasingly apparent: that it can be transmitted even by people who are asymptomatic, and that transmission occurs primarily through the air. What was less clear was how a person who is neither coughing nor sneezing might still be able to put virus particles into the air for others to inhale, and what could be done about the problem. NIDDK intramural scientists used an innovative approach to answer both questions. A person spoke into an opening in one side of a box, and a camera was placed on the opposite side. The researchers projected a sheet of laser light into the box through a slit in one of the other sides, so that droplets of fluid coming from a person's mouth would be visible as they passed through the light, so they could be recorded by the camera. A researcher spoke the words "stay healthy" into the box, and video from the camera captured the results: droplets generated in the act of speaking showed up as bright flashes of light as they passed through the laser sheet. Those two words alone were enough to generate hundreds of "speech droplets." When the researchers covered the speaker's mouth with a damp cloth, simulating use of a mask, the number of speech-generated droplets dropped virtually to zero. These experiments showed that speech is an important potential means of transmitting the virus and showed one way that the use of masks can be valuable for helping limit viral transmission. The image shown is from one of the videos at the moment when the highest number of speech droplets (shown in green) were visible in a single frame. The spots of light vary in brightness because of the differences in the size of the droplets, with the largest causing the brightest flashes. (The bright spot at the end of a curving line near the bottom left of the image is not a speech droplet: it corresponds to the tip of a very thin wire positioned near the light sheet and used as a reference for focusing the camera.) The complete video is available at: [www.nejm.org/doi/full/10.1056/nejmc2007800](http://www.nejm.org/doi/full/10.1056/nejmc2007800).

*Image provided by Dr. Adriaan Bax, NIDDK. Reprinted from N Engl J of Med; Anfinrud P, Stadnytskyi V, Bax CE, and Bax A; Visualizing speech-generated oral fluid droplets with laser light scattering; Volume 382, Pages 2061-2063. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.*

# 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 the fundamental biologic building blocks and processes of an organism—its 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 knowledge of disease and disease treatment can be traced to laboratory studies whose relevance to health could not have been fully known or appreciated at the time they were conducted.*

There are also moments when the biomedical research enterprise is called upon to rapidly harness knowledge, resources, and expertise across many fields to meet extraordinary and urgent challenges that threaten the public health. This past year has seen the emergence of a pandemic new viral disease, COVID-19, whose short- and long-term impacts on human health are still being discovered as the NIH and others strive to develop effective vaccines and treatments as quickly as possible. At the same time, events highlighting racial injustice in this country have drawn fresh and much-needed attention to the burden of health disparities on communities that are also most heavily affected by COVID-19 and by chronic diseases within the NIDDK mission.

Described in this chapter are NIDDK research-related efforts to overcome these critical challenges, as well as a feature celebrating 70 years of NIDDK-supported accomplishments and continued research for the betterment of public health today and into the future.

## COVID-19

The COVID-19 pandemic has brought illness, disability, and death for many in the United States and around the world, while upending lives and normal activities. COVID-19 is caused by a novel respiratory virus, SARS-coronavirus-2, or SARS-CoV-2, that uses a cell surface receptor, called angiotensin-converting enzyme 2 (ACE2), to enter and replicate within cells in the body. Disease symptoms range from mild to severe. While the majority of people with severe COVID-19 disease suffer respiratory symptoms, the virus can cause damage throughout the body, with many other serious and life-threatening effects.<sup>1</sup>

Although people of any age or state of health can contract the virus, those with chronic diseases such

as type 2 diabetes, obesity, and chronic kidney disease are at higher risk of developing severe disease leading to hospitalization and death,<sup>2</sup> as are older adults and people with depressed immune systems. Alarming, many people who become infected with SARS-CoV-2 do not develop obvious symptoms themselves but can still spread the disease to others—including those at high risk. Researchers have just recently begun to gain insights into genetic and other factors that could help explain and hopefully help predict the observed variability in COVID-19 disease severity.<sup>3</sup> At the same time, as researchers are examining people in recovery from COVID-19, they are finding evidence of damage to the heart and other organs even in people with mild or asymptomatic infections, suggesting that the

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<sup>1</sup> Gupta A, et al. *Nat Med* 26: 1017-1032, 2020.

<sup>2</sup> Centers for Disease Control and Prevention: [www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html). Accessed October 29, 2020.

<sup>3</sup> Zhang Q, et al. *Science* 370: eabd4570, 2020; Bastard P, et al. *Science* 370: eabd4585, 2020.

virus can cause silent damage to the body whose permanence is yet unknown as the disease is so new.<sup>4</sup>

### Multifaceted Research Response

The NIH has undertaken a multi-pronged approach to rapidly establish studies aimed at vaccine development and testing, improved COVID-19 testing strategies, more effective treatments, and better understanding of COVID-19 disease and the virus that causes it. These efforts are detailed on the NIH website at: [www.nih.gov/coronavirus](http://www.nih.gov/coronavirus). The NIDDK and other NIH components have also undertaken specific efforts to support research that can address the many facets of this novel disease. For example, the NIDDK has provided funding supplements to grantees who proposed revisions to ongoing projects aimed at achieving insights into the relationship between COVID-19 and preexisting or new-onset kidney, metabolic, and gastrointestinal diseases and that may lead to rapid translation and impact in the COVID-19 emergency. The NIDDK has also solicited new applications for research funding that would support projects focused on basic and clinical mechanistic studies of SARS-CoV-2 and COVID-19 susceptibility, routes of infection, course of disease, morbidity and mortality in people with preexisting diseases, or adverse acute or chronic outcomes in organs, tissues, and biological systems within the Institute's purview.

Another key aspect of the NIDDK's response has been to work toward alleviating the burden imposed by the COVID-19 pandemic on the biomedical research enterprise: as businesses, government and community agencies, and academic institutions shuttered to protect staff and employees and prevent spread of SARS-CoV-2 in the early days of the pandemic, many biomedical research efforts not directly involved in COVID-19 studies mostly ground to a halt. Many NIDDK clinical studies were halted due to concerns regarding face-to-face clinic visits and closures of academic clinical research facilities, and thousands of NIDDK-supported researchers suspended laboratory-based investigations. Subsequent efforts by institutions to begin conducting research activities anew underscored novel challenges and hurdles posed by COVID-19. As the timeline for a return to "normal" is unknown, this disruption to research has had tremendous ripple effects on scientific progress, careers, and prospects

for funding, especially for younger investigators. To obtain greater insight on the challenges "on the ground" and possible solutions, the NIDDK solicited input from its National Advisory Council—whose members include scientific luminaries, academic leaders, and representatives from health advocacy groups and professional societies—on the scope of the pandemic's impact on Institute-supported research. Both NIH-wide policy changes and NIDDK efforts have enabled the Institute to implement several of the Council's recommendations, including strategies for "re-starting" research activities that were affected by the pandemic.

NIDDK intramural researchers were also affected by the disruptions to onsite laboratory research. However, as part of a nimble public health response, the NIH asked its scientists to propose studies germane to COVID-19, which could be pursued within careful parameters at NIH research campuses as local caseloads, conditions, and safety measures allowed. Numerous NIDDK investigators proposed such studies and many are under way, ranging from fundamental studies of the virus and potential vaccine targets to clinical studies of viral detection, organ impact, and possible symptom prevention. For example, NIDDK investigators published findings from one set of studies early in the pandemic that have proven critical in establishing an evidence base for measures to prevent viral spread, as detailed below.

Through all of these efforts, as the Nation continues its struggle with COVID-19, the NIDDK continues to strive toward ensuring the health and safety of researchers, study volunteers, and patients while also helping to maintain research progress and a robust scientific workforce across all of the areas within its research mission.

More details and updates on the NIDDK response to COVID-19 can be found at: [www.niddk.nih.gov/research-funding/research-programs/niddk-covid-19-research-response](http://www.niddk.nih.gov/research-funding/research-programs/niddk-covid-19-research-response).

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<sup>4</sup> Puntmann VO, et al. *JAMA Cardiol* 5: 1265-1273, 2020; Oran DP and Topol EJ. *Ann Intern Med* 173: 362-367, 2020.

### Speaking of COVID-19...

A series of experiments by NIDDK intramural investigators shows how speech might promote the spread of the virus that causes COVID-19 even from people who have no apparent symptoms of the disease—results that underscore the importance of mask-wearing to stem the pandemic. Any of a wide variety of respiratory infections are known to spread from person to person through sneezing and coughing, both of which generate a mist of potentially pathogen-containing small droplets of saliva and mucous that can be inhaled by people nearby. This is one important way that the virus that causes COVID-19 is transmitted. However, a growing body of evidence suggests that the virus may also spread easily from infected people who feel well and are neither coughing nor sneezing—but how? Some suggestive evidence has raised the possibility that normal speech might play a role. Speaking is also known to generate droplets that can harbor viruses; moreover, many of these droplets are smaller than those produced by coughing and sneezing, which means they have the potential to remain airborne for longer. But how many such droplets are produced during speech, how long they last, and how far they travel have been open questions.

To provide answers, NIDDK intramural researchers developed a clever tool for quantifying speech-generated droplets and following their fates. They used a specially designed lens to spread the narrow beam of a laser into a thin sheet of light, which they projected through a slit in a cardboard box of about 18x20x25 inches in size, painted black inside to prevent the light from reflecting off the sides. Droplets generated by speaking the words “stay healthy” through a hole in the box caused visible flashes when they passed through the light sheet. Using the video camera feature of a mobile phone to record these flashes allowed the scientists to determine not only how many droplets were created—about 2,600 per second of speech—but also to estimate their size (from the intensity of the flash) and to find out how long they continued to circulate within the enclosed box. The louder the words were spoken, the more droplets they generated; also, certain sounds, particularly the “th” sound in “healthy,” produced more droplets than others. While the largest droplets disappeared quickly, likely falling to the bottom of the box, thousands of smaller droplets persisted far longer,

often continuing to circulate within the enclosed box for 14 minutes or more. In fact, many of the tiniest droplets rapidly dried out to form particles that were still circulating in the box over an hour later. Importantly, one set of experiments showed that covering the mouth with a damp cloth—analogue to wearing a mask—virtually eliminated movement of speech-generated droplets into the box. As a high proportion of people with COVID-19 harbor potentially transmissible virus yet initially have no symptoms—and indeed may never develop a severe form of the illness—this experiment highlights one way that using masks in public spaces is important for limiting the spread of COVID-19.

*Anfinrud P, Stadnytskyi V, Bax CE, and Bax A. Visualizing speech-generated oral fluid droplets with laser light scattering. N Engl J Med 382: 2061-2063, 2020.*

*Stadnytskyi V, Bax CE, Bax A, and Anfinrud P. The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission. Proc Natl Acad Sci USA 117: 11875-11877, 2020.*

### NIDDK EFFORTS TOWARD ACHIEVING HEALTH EQUITY

As the United States has grappled with the impact of the COVID-19 pandemic, heartbreaking events have been highlighting racial injustice in the Nation. This injustice falls heavily on people who are simultaneously burdened by health disparities. In fact, disparities in COVID-19 outcomes are exacerbated by chronic diseases, such as obesity, diabetes, and kidney disease, that disproportionately affect U.S. minority groups. Because combating these conditions is central to the NIDDK mission, the Institute is firmly committed to research programs aimed at reducing COVID-19 disparities. For example, the NIDDK is participating in an NIH-wide program called Rapid Acceleration of Diagnostics-Underserved Populations, which is working to understand the factors associated with disparities in COVID-19 morbidity and mortality and to lay the foundation to reduce disparities for those underserved and vulnerable populations who are disproportionately affected by, have the highest infection rates of, and/or are most at risk for complications or poor outcomes from the COVID-19 pandemic. Moreover, because many NIDDK mission diseases and disorders place disparate burdens on

minority groups and people with limited resources, and because the Institute believes health equity is integral to social justice, the NIDDK has reaffirmed its commitment to combating health disparities—whether pandemic related or not—through basic, translational, and clinical research.

### **NIDDK Approaches Toward Advancing Health Equity In Its Mission Diseases**

The NIDDK is pursuing four main strategies to help advance the cause of health equity:

- *Continue vigorous efforts to recruit diverse study cohorts inclusive of those most affected, which often means reaching out to underserved segments of the population.*
- Because having people from disproportionately affected backgrounds conduct and guide research helps address health disparities most effectively, the NIDDK seeks to *open doors for young people from underrepresented groups* through training, support, and inspiration to pursue research careers.
- Engaging clinical trial participants more broadly in the research enterprise can help advance scientific inquiry; thus, the NIDDK is now implementing strategies to *promote participant engagement*, not only as study volunteers, but also in study design, recruitment, and consent.
- The Institute is *supporting research to identify the causes of health disparities*, fueling clinical research by yielding testable hypotheses. Disparities may stem partly from biological differences, such as genetic risk factors more prevalent in one population than in another. Disparities that stem from systematic differences in access to care, environmental exposures, and other external factors are of equal interest; for this reason, the NIDDK also supports research on social determinants of health, which are conditions in the places where people learn, live, play, and work that affect health risks and outcomes. Research on social determinants of health is crucial for lighting a path toward health equity and is a vital complement to studying biological factors that contribute to health disparities.

### **Mutually Reinforcing Approaches Toward Health Equity**

The four approaches outlined above can interact and bolster one another, as illustrated by the NIDDK-supported APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO). Groundbreaking NIDDK research demonstrated a key biological factor contributing to the elevated rates of end-stage renal disease (ESRD), sometimes known as kidney failure, in people of African descent: specific variants of a gene called *APOL1*, found almost exclusively in people of recent African ancestry, are associated with significantly elevated ESRD risk. Based on this discovery, the NIDDK led the development of the APOLLO research network to determine the impact of *APOL1* genetic variants on kidney transplant outcomes for 2,614 pairs of living African American donors and the recipients of their kidneys. APOLLO is also pioneering the Institute's approach to participant engagement via its Community Advisory Council (CAC). Composed of African American transplant recipients, kidney donors, and individuals on dialysis, the CAC provides input and guidance on study design, including recruitment, retention, implementation of protocols, and return of results. Thus, APOLLO integrates three approaches to overcoming disparities: it proceeds from a seminal discovery about a health disparity's cause, is composed of a large and representative group of those most affected, and is demonstrating the value of engaging participants in research.

### **Promoting Diversity in the Scientific Workforce**

While NIDDK researchers from every race and ethnicity are striving to reduce health disparities, the NIDDK recognizes that these vital efforts would benefit substantially from having a scientific workforce that better reflects the diverse backgrounds and experiences of the U.S. population. Indeed, the overall biomedical research enterprise would be greatly strengthened by the scientific ideas and talent of people currently underrepresented in research. While scientific talent is surely well represented across all groups, opportunity is not. Therefore, it is important to ensure that young people are exposed to the challenges, joys, and opportunities of science and are provided needed mentoring.

The NIDDK's approach to overcoming the dearth of minority scientists therefore begins in grade school and continues through support and mentorship for minority investigators early in their careers. For

example, each year the High School Short-Term Research Experience for Underrepresented Persons (STEP-UP) program provides a stimulating, rigorous summer opportunity to discover experimental science for about 100 African American, Latino/Hispanic, and American Indian or Alaska Native students, as well as students from U.S. territories. STEP-UP also supports undergraduates interested in conducting NIDDK-supported research. Complementing this effort, the NIDDK Diversity Summer Research Training Program (DSRTP) brings college students from minority groups to the NIH campus for mentored research experiences. Both DSRTP and STEP-UP are intended to help build and sustain a diverse biomedical, behavioral, clinical, and social science researcher pipeline focused on NIDDK mission areas. NIDDK support for minority investigators continues through graduate school and into faculty positions. For example, the Network of Minority Health Research Investigators (NMRI) connects postdoctoral and junior faculty investigators with more senior researchers who mentor and serve as role models for them.

Information on NIDDK programs designed to increase the number of minority investigators—and foster their success—may be found on the NIDDK website at: [www.niddk.nih.gov/research-funding/research-programs/diversity-programs](http://www.niddk.nih.gov/research-funding/research-programs/diversity-programs).

### **The NIDDK's Role in Promoting Better Health Across American Society**

Systemic changes across many U.S. sectors will be needed to achieve health equity. While many changes are beyond the missions of the NIH, the NIDDK's approaches to the problem proceed from the recognition that research can play a valuable role in advancing these goals. The programs described here are just a sample of the NIDDK's ongoing efforts toward health equity and toward ensuring that NIDDK-supported research benefits all of America—especially those most burdened by the diseases and disorders in its mission.

*(Adapted from an article by Dr. Griffin P. Rodgers, NIDDK Director, and Dr. B. Tibor Roberts, NIDDK Office of Scientific Program and Policy Analysis, J Clin Invest 130: 5036-5038, 2020.)*

# Celebrating the Past and Planning for the Future: The 70<sup>th</sup> Anniversary of the NIDDK



National Institute of  
Diabetes and Digestive  
and Kidney Diseases



In 2020, the NIDDK celebrated 70 years since its founding in August 1950 (see “History of the NIDDK” inset). Over the course of its history, the Institute that is known today as the National Institute of Diabetes and Digestive and Kidney Diseases is proud to have supported and conducted research on many of the Nation’s most serious chronic diseases. Affecting people of all ages and racial and ethnic groups, the diseases and disorders within the NIDDK research mission encompass some of the most common, costly, and disabling conditions, as well as less prevalent but nonetheless debilitating diseases affecting Americans today: endocrine and metabolic diseases and disorders such as diabetes and obesity, digestive diseases such as nonalcoholic fatty liver disease and inflammatory bowel disease, chronic kidney disease and kidney failure, urologic diseases such as interstitial cystitis/bladder pain syndrome and benign prostate enlargement, and blood diseases such as anemias.

The research advances made possible through 70 years of NIDDK support have saved lives, improved quality of life, and laid the foundation for future progress. The Institute has supported a number of winners of the world’s most prestigious scientific honors, including the Nobel Prize in Physiology or Medicine, the Nobel Prize in Chemistry, and the Lasker Awards. These honorees include extramural scientists at universities and other research institutions across the country who have been supported by the NIDDK, as well as scientists within the Institute’s Intramural Research Program.

As part of activities to mark its 70<sup>th</sup> anniversary, in the summer of 2020 the NIDDK highlighted important research accomplishments supported over the past seven decades and showcased how these advancements inform the Institute’s current activities and guide its vision for the future. These communications are highlighted on the NIDDK

*History of the NIDDK:* On August 15, 1950, President Harry S. Truman signed into law the Omnibus Medical Research Act, establishing the National Institute of Arthritis and Metabolic Diseases (NIAMD)—which would become today’s NIDDK. The new Institute incorporated the laboratories of the Experimental Biology and Medicine Institute and expanded to include clinical investigation in rheumatic diseases, diabetes, and a number of metabolic, endocrine, and gastrointestinal diseases. That same year, the NIAMD Council held its first meeting and recommended approval of NIAMD’s first grants. Over the years, the NIAMD evolved into the National Institute of Arthritis, Metabolism, and Digestive Diseases (in 1972) and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (in 1981). In 1986, the Institute’s Division of Arthritis, Musculoskeletal and Skin Diseases became the core of a new, independent Institute. The NIDDK then acquired its current name—the National Institute of Diabetes and Digestive and Kidney Diseases.



website ([www.niddk.nih.gov/about-niddk/70th-anniversary](http://www.niddk.nih.gov/about-niddk/70th-anniversary)) and in social media, and additional communications took place through such venues as the “Healthy Moments” radio broadcast featuring the NIDDK Director, Dr. Griffin P. Rodgers. During the 70<sup>th</sup> anniversary year, the NIDDK also embarked upon the development of an Institute-wide strategic plan, which will complement disease-specific planning efforts and help guide research planning across its mission. External input is key to this effort. The NIDDK invited broad external input with a public Request for Information, which was open for several months; the Institute is also gaining input from its Advisory Council and strategic plan Working

Group and will seek further external input during the planning process.

In addition to celebrating seven decades of substantial research accomplishments, 2020 brought remarkable challenges as a global pandemic upended life as we knew it. NIDDK staff, grantees, and trainees rose to those challenges, seeking ways to combat COVID-19 while keeping research operations running smoothly and safely, despite many uncertainties. With a strengthened spirit in 2021, we now embark upon the next 70 years of research with compassion and dedication to advance public health.



As described in this chapter, 2021 marks the 100<sup>th</sup> anniversary of the seminal discovery of the hormone insulin, which transformed type 1 diabetes from a fatal disease into a chronic one. The image on the left shows a commercial insulin vial from the 1930s. Although early insulin injections were lifesaving, there were many challenges to their use. Today, as a result of research supported by the NIDDK and others, people have improved formulations of insulin along with advances in technology that can more closely mimic normal physiologic delivery of insulin. These advances provide people with less burdensome disease management options that have led to a reduction in diabetes complications, and improved health, quality of life, and longevity. Examples of those options are represented by images on the right: insulin pen (boy), insulin pump (woman), and artificial pancreas technologies (drawing) that link blood glucose (sugar) sensing with insulin delivery. Although it is clear that type 1 diabetes treatment has come a long way since 1921, the NIDDK strives to continue its pursuit of research to build on advances and further improve people's health.

*Image credits: Historic insulin vial—Division of Medicine and Science, National Museum of American History, Smithsonian Institution; boy—iStock.com/dmphoto; woman—iStock.com/MarkHatfield; artificial pancreas drawing—Fang-Mei Liu, The Scientific Consulting Group, Inc.*

# Diabetes, Endocrinology, and Metabolic Diseases

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

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

Diabetes is a debilitating disease that affects an estimated 34.2 million people in the United States—or 10.5 percent of the total population—and is the seventh leading cause of death.<sup>2</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>1</sup> Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial cost for diagnosed diabetes in the United States in 2017—including costs of medical care, disability, and premature death—was \$327 billion.<sup>3</sup> Effective therapy can prevent or delay diabetic complications, but nearly one-quarter of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.<sup>2</sup>

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease

complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin, and type 2 diabetes, in which the body becomes resistant to insulin, with subsequent impaired insulin production. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that develops during pregnancy, but in many cases may resolve after pregnancy. However, women who develop gestational diabetes are at greater risk of developing type 2 diabetes later in life. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the mother and baby before, during, and after delivery.

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of diagnosed diabetes cases in adults and the majority of diagnosed cases in children and youth.<sup>2</sup> It most often develops

<sup>1</sup> *Diabetes in America, 3rd ed.* Cowie CC, et al., Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 17-1468, 2018.

<sup>2</sup> Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2020.* Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2020.

<sup>3</sup> American Diabetes Association. *Diabetes Care* 41: 917-928, 2018.

during childhood but may appear at any age.

Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the insulin-producing  $\beta$  (beta) cells of the pancreas. If left untreated, type 1 diabetes results in death: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed, and body metabolism is significantly disrupted, resulting in a severely decompensated and catabolic (a breakdown of molecules such as proteins or lipids) state. This disruption of the body's metabolism causes a biochemical chain reaction that can result in a life-threatening condition called diabetic ketoacidosis (DKA). DKA can be deadly if it is not aggressively treated with insulin. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—to regulate their blood glucose levels.

The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated with type 1 diabetes. However, despite vigilance in disease management and current technologies to test blood glucose levels and administer insulin, it is still not possible for people with type 1 diabetes to manage blood glucose levels as well as functional, insulin-producing  $\beta$  cells do. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery. In this regard, NIDDK-supported research has contributed to the development or testing of new diabetes management technologies recently approved by the U.S. Food and Drug Administration, including the first commercial "hybrid artificial pancreas" device that automatically links glucose monitoring and insulin delivery, and next-generation continuous glucose monitors, including the first fully implantable device. Researchers are also working to further develop and enhance  $\beta$  cell replacement therapies, such as islet transplantation, to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases in U.S. adults.<sup>2</sup> The risk for developing type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.<sup>3</sup>

Type 2 diabetes occurs at higher rates among racial and ethnic minority populations in the United States, including African Americans, Hispanic and Latino Americans, American Indians, some Asian Americans, and Native Hawaiians and Pacific Islanders.<sup>2</sup>

Gestational diabetes is also a risk factor: about half of women with gestational diabetes will develop type 2 diabetes within 5 to 10 years after giving birth.<sup>4</sup>

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic  $\beta$  cells lose their ability to secrete enough insulin to restore balance, and the reduction of insulin secretion, relative to the body's needs, results 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. There are also an estimated 88 million U.S. adults who have a condition called "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.<sup>2</sup> This population is at elevated risk of developing type 2 diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that people with prediabetes can dramatically reduce their risk of developing type 2 diabetes with diet and exercise changes designed to achieve a 7 percent reduction in body weight. To a more limited degree, the safe and well-tolerated drug metformin can also help prevent or delay type 2 diabetes. Moreover, follow-up research has shown that the benefits of reduced diabetes risk from weight loss or metformin can persist for at least 15 years.

Type 2 diabetes was previously called "adult onset" diabetes because it is predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and in this population it disproportionately affects youth from racial and ethnic minority populations in the United States. Believed to be related to increasing rates of pediatric obesity, this trend is alarming for many reasons. For example, results from the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents

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<sup>4</sup> Kim C, et al. *Diabetes Care* 25: 1862-1868, 2002.

and Youth (TODAY) clinical trial and the Restoring Insulin Secretion (RISE) Pediatric Medication Study showed that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because the onset and severity of disease complications correlate with diabetes duration and management of blood glucose levels, so those with early disease onset are at especially high risk for developing complications. In addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes in young women could contribute to a cycle of ever-growing rates of diabetes. Therefore, the advent of type 2 diabetes in youth has the potential to worsen the enormous health burden that diabetes already places on the United States.

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

## ASSESSING DIABETES RATES IN YOUTH

### Diabetes Continues To Rise Among American Youth:

Scientists demonstrated that rates of both type 1 and type 2 diabetes continue to increase in people under the age of 20 in the United States, with higher rates of increase among racial/ethnic minority youth. Diabetes is a common chronic disease and results in increased risk for serious complications of the heart, kidneys, and eyes, among others. Efforts to understand the burden of this disease among different populations are essential to development of targeted public health efforts to help people at risk for or diagnosed with diabetes. The SEARCH for Diabetes in Youth study, a joint effort supported by the NIDDK and the Centers for Disease Control and Prevention, was established in 2000 to produce

data on the scope of and trends in the disease. This research continues to highlight important and concerning information.

In this report, SEARCH researchers compared the rates of development (incidence) of type 1 and type 2 diabetes from 2002 to 2015 to determine whether the annual rates were changing. For type 1 diabetes, the scientists determined an overall rate of increase of 1.9 percent per year. They observed the steepest increases among racial/ethnic minority populations: Asian and Pacific Islanders (4.4 percent per year), Hispanics (4.0 percent per year), and Blacks (2.7 percent per year). In contrast, incidence among Whites rose 0.7 percent per year, and an increase was not observed among American Indians.

Among youth with type 2 diabetes, the annual rate of increase in incidence was determined to be 4.8 percent per year. Again, the researchers observed the highest increases among racial/ethnic minority populations: Asian and Pacific Islanders (7.7 percent), Hispanics (6.5 percent), Blacks (6.0 percent), and American Indians (3.7 percent). These trends are worrisome as research supported by the NIDDK has demonstrated that type 2 diabetes is more difficult to treat in youth than adults as youth may not respond as well to medications used in adults, and that many youth with type 2 diabetes develop complications early in their lives. These data highlight the continued need for research to prevent and treat both type 1 and type 2 diabetes.

*Divers J, Mayer-Davis EJ, Lawrence JM, ... Wagenknecht LE. Trends in incidence of type 1 and type 2 diabetes among youths—selected counties and Indian reservations, United States, 2002-2015. MMWR Morb Mortal Wkly Rep 69: 161-165, 2020.*

## RESEARCH ON TYPE 1 DIABETES

### New Artificial Pancreas System Outperforms Sensor-augmented Pump Therapy for Managing

**Type 1 Diabetes:** A clinical trial has found that a new artificial pancreas system is more effective than sensor-augmented pump (SAP) therapy at increasing the time people with type 1 diabetes spend with blood glucose (sugar) levels in a healthy range, knowledge that led to U.S. Food and Drug Administration (FDA) approval of the new system in 2019. Artificial pancreas technology, or a closed-loop system, aims to automate type 1 diabetes

management by measuring blood glucose levels using a continuous glucose monitor (CGM) and automatically delivering insulin when needed using an insulin pump. By contrast, SAP therapy—the control treatment used in the trial—couples CGM use with an insulin pump but does not adjust insulin levels automatically. Thus, by automating diabetes management, artificial pancreas technology holds promise to help people with type 1 diabetes achieve recommended blood glucose levels day and night, as well as alleviate the enormous burden associated with managing the disease. A first-generation closed-loop system was approved by the FDA in 2016, and researchers have continued working to develop new and improved systems.

Researchers in the NIDDK-supported, multi-center International Diabetes Closed-Loop (iDCL) Study enrolled 168 female and male participants ages 14 to 71 years with type 1 diabetes. Participants were randomly assigned to use either SAP therapy or an artificial pancreas system called Control-IQ™. Some unique features of the artificial pancreas system include a dedicated safety module to prevent hypoglycemia (dangerously low blood glucose levels), and gradually intensified blood glucose control overnight to target near-normal blood glucose levels every morning. During the 6-month trial, participants lived their normal day-to-day lives and only had contact with study staff every 2 to 4 weeks to download and review device data. Results showed that artificial pancreas users significantly increased the amount of time with their blood glucose levels in the recommended target range (percent increase in time in range) by an average of 2.6 hours per day, while the time in range in the control SAP group remained unchanged. Compared to the SAP group, artificial pancreas users also showed improvements in their average blood glucose control (HbA1c levels) and had less high and low blood glucose. There were no severe episodes of hypoglycemia in either group.

These positive trial data—showing that the artificial pancreas system outperformed SAP therapy—were used by the FDA to approve marketing of the Control-IQ technology. The Control-IQ technology itself was derived from a system originally developed with NIDDK support. This success story demonstrates how the sustained and long-term NIDDK investment in research—from technology development to supporting

clinical trials testing the technology and the clinical trial demonstrating the efficacy of the system—culminated in a new commercially available device to improve type 1 diabetes management.

*Brown SA, Kovatchev BP, Raghinaru D, ...Beck RW; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 381: 1707-1717, 2019.*

### **Researchers Develop First Functional, Lab-generated Islets That Evade Immune System Attack:**

Scientists have developed functional human islet-like organoids (HILOs) that can be shielded from immune system attack, an advance that allowed these HILOs to treat a mouse model of type 1 diabetes for weeks without immunosuppressive drugs. Pancreatic islet dysfunction can compromise the body's ability to maintain healthy blood glucose (sugar) levels. In type 1 diabetes, the immune system plays a key role in this dysfunction, destroying insulin-producing  $\beta$  (beta) cells in the islets. Transplanting healthy, insulin-producing islets into people with diabetes can help manage blood glucose levels without the need for insulin injections, but several major issues keep this procedure from being routinely used. One hurdle is that limited amounts of cadaveric islets of transplantable quality are available. Another issue is that immunosuppressant drugs that can cause serious side effects must be used to prevent transplant rejection. However, making human islet-like cell clusters in the lab that both mimic healthy islets and evade the immune system has proven to be challenging.

Now, a group of scientists has identified physical and biological factors needed to produce functional, immune-evading HILOs. Building on previous research, they grew  $\beta$ -like cells derived from human induced pluripotent stem cells in a gel-like, three-dimensional scaffold that more closely mimics the human pancreas. These growing conditions produced mature cell clusters that had many of the characteristics of healthy islets, including producing insulin in response to glucose and reducing blood glucose levels in a mouse model of type 1 diabetes. But how could these HILOs be protected from immune attack? Previous work had suggested that a protein called PD-L1 helps shield islets from the immune system. When the scientists treated HILOs to induce PD-L1 production, these HILOs were protected from immune attack when transplanted into a mouse model of type 1 diabetes. Even when

transplanted into a mouse model engineered to have a human-like immune system, the HILOs provided steady blood glucose control for over 50 days without the need for immunosuppression.

More research is needed to clarify how long the HILOs' immune protection can last and how long they can remain functional when transplanted. These issues and others are key to determining whether HILOs can be used to manage blood glucose levels in people with diabetes. Overall, these findings give hope that it may one day be possible to protect transplanted islets in the human body from immune attack. Such advances could lead to improved treatments that free people with type 1 diabetes from the need for insulin injections without incurring the risks of immunosuppression.

Yoshihara E, O'Connor C, Gasser E, ... Evans RM. Immune-evasive human islet-like organoids ameliorate diabetes. *Nature* 586: 606-611, 2020.

**Insights into the Autoimmune Process in Type 1 Diabetes:** Using a systematic approach, researchers identified and characterized the protein fragments (peptides) associated with  $\beta$  (beta) cell autoimmunity, a misguided immune attack on the  $\beta$  cells of the pancreas that leads to type 1 diabetes. Normally, the immune system defends the body against foreign invaders or pathogens. Immune molecules known as major histocompatibility complex (MHC) molecules bind peptides from the pathogens and display them for recognition by immune cells called T cells. This prompts the T cells to "activate," leading them to attack the pathogen. In many people with type 1 diabetes, however, variants of class II MHC molecules (MHC-II) inappropriately bind and display peptides from the insulin-producing  $\beta$  cells. When this happens, the T cells can be activated by these peptides, leading them to target the  $\beta$  cells. While decades of research have added knowledge about this process, much remains unknown, including identification of all the peptides that drive the autoimmune process in type 1 diabetes. Understanding the molecular components involved in triggering the attack and its progression could lead to earlier and improved detection of the disease, a better understanding of disease progression, and new prevention and treatment approaches.

To understand further what triggers the autoimmune attack, researchers sought to catalog the "immunopeptidome" of  $\beta$  cell-derived peptides

displayed by MHC-II in a mouse model of type 1 diabetes. By examining the  $\beta$  cells, pancreatic lymph nodes, and spleens of female mice, they found that the most prominent peptide families bound to MHC-II in those sites were those derived from insulin B-chain (InsB) and C-peptide (InsC). To determine whether these peptides induced an autoimmune response, the researchers characterized the peptides both on their ability to induce a reaction from a specific type of T cell and on how well they bound MHC-II. They confirmed that most of the T cell reactivity was directed to InsB and InsC. Further experiments allowed the researchers to determine additional features of these peptides that affect reactivity and enhance binding to MHC-II, such as chemical modifications and segments that were particularly immunogenic. These findings identified what parts of the insulin protein trigger the autoimmune attack on  $\beta$  cells in this mouse model of type 1 diabetes. Additional research will be necessary to determine whether these findings extend to humans.

Wan X, Vomund AN, Peterson OJ, Chervovsky AV, Lichti CF, and Unanue ER. The MHC-II peptidome of pancreatic islets identifies key features of autoimmune peptides. *Nat Immunol* 21: 455-463, 2020.

**Identification of Risk Factors for Heart Disease in Type 1 Diabetes:** Researchers determined that blood glucose (sugar) levels and age are the strongest risk factors for total cardiovascular disease (heart disease and stroke) burden in people with type 1 diabetes. Cardiovascular disease remains a leading cause of death for people with type 1 diabetes, despite improvements in the control of blood glucose, blood pressure, and lipid (fat) levels. Insights into type 1 diabetes and cardiovascular health previously came from the NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. DCCT/EDIC demonstrated that higher levels of hemoglobin A1c (HbA1c; a measure of average blood glucose levels over 3 months) were a strong risk factor for cardiovascular disease. These findings, however, were limited to analyzing the risk of a first cardiovascular event. Because subsequent cardiovascular events are associated with significant morbidity and mortality, understanding their risk factors could improve prevention strategies.

To extend their previous analyses, the researchers evaluated potential risk factors for their association

with first and subsequent cardiovascular events after 29 years of follow-up of DCCT/EDIC participants. They found that older age was associated with an increased risk of cardiovascular death and with other first and subsequent events including heart attack, stroke, and congestive heart failure. Additionally, they found that higher levels of HbA1c were associated with increased risk of both the first and subsequent events. These findings confirm the importance of intensive glucose control to reduce the risk of a first cardiovascular event. They also suggest that after the first event, it is still important for people with type 1 diabetes to practice intensive blood glucose control to reduce their risk of a subsequent event. Importantly, blood glucose levels can be managed for many people with technologies like continuous glucose monitors and improved insulin delivery devices, making intensive blood glucose control more achievable. Continued research is needed to understand how blood glucose levels affect cardiovascular disease toward improved detection, prevention, and treatment in people with type 1 diabetes.

With these new findings, it is clear that the long-term dedication of the DCCT/EDIC volunteers and the investigators continues to generate a treasure trove of data about type 1 diabetes and its complications that is identifying ways to improve the health of people with this disease.

*Bebu I, Schade D, Braffett B,...Lachin JM; DCCT/EDIC Research Group. Risk factors for first and subsequent CVD events in type 1 diabetes: The DCCT/EDIC Study. Diabetes Care 43: 867-874, 2020.*

## RESEARCH ON TYPE 2 DIABETES

### Community-based Approach To Screen

**Black Men for Type 2 Diabetes:** Researchers have found that community barbershops are promising venues for screening Black men for type 2 diabetes and identifying those with undiagnosed disease, so treatment could begin earlier. Many people with type 2 diabetes do not know they have it, and minority groups have disproportionately high rates of undiagnosed diabetes. Timely diagnosis is important so that people with the disease receive appropriate treatment to control their blood glucose (sugar) levels and prevent life-threatening complications. Black men with diabetes have high rates of diabetes complications and are less likely to live into their seventies than men from other

racial/ethnic groups. However, type 2 diabetes diagnosis is often delayed, particularly in Black men who do not receive regular primary care and thus may not ever be screened or tested for the disease. Thus, it is important to identify approaches for timely diagnosis of type 2 diabetes in this population to improve their health.

In a recent study, researchers examined whether a community-based approach using barbershops owned by Black individuals could identify Black men with undiagnosed type 2 diabetes. The researchers asked 895 Black men at 8 different barbershops in Brooklyn, New York, if they would be willing to be screened for type 2 diabetes using a type of hemoglobin A1c (HbA1c) test that can be administered onsite and that gives results in 5 minutes. About one-third of the men agreed to be screened and 290 were successfully tested. Testing showed that 26 men (9 percent) had undiagnosed type 2 diabetes and 82 (28 percent) had prediabetes—a condition of intermediate blood glucose levels that is a known risk factor for later developing type 2 diabetes. The researchers gave the men with diabetes or prediabetes follow-up information, including the names of local primary care clinics. The most common reason participants gave for declining screening was because they already knew their health status or were under a doctor's care. Some limitations of the study include the fact that it took place in only one city, so it is unknown if similar participation rates would be observed in other areas of the country. In addition, although the point-of-care HbA1c test used is very convenient and fairly accurate, follow-up laboratory tests, which were not included in the study, would be needed to confirm the initial diagnoses.

Community-based approaches at barbershops have been used successfully for addressing other health conditions, such as identifying and treating Black men with high blood pressure. Therefore, adopting strategies like the one in this study to help identify people with undiagnosed type 2 diabetes who would benefit from treatment—particularly if paired with approaches for lowering other barriers to obtaining proven therapies—hold promise to yield progress toward U.S. health equity.

*Osorio M, Ravenell JE, Sevvick MA,...Lee DC. Community-based hemoglobin A1c testing in barbershops to identify Black men with undiagnosed diabetes. JAMA Intern Med 180: 596-597, 2020.*



### **Rare Genetic Variants Protect Against Type 2 Diabetes by Promoting Insulin Processing and Secretion:**

Studying rare variations in the gene *SLC30A8* that were previously found to protect against type 2 diabetes, researchers have now discovered that these variations promote release of insulin in response to a rise of blood glucose (sugar) levels, potentially by increasing the proportion of insulin that is ready for release relative to a precursor form of the hormone. A previous genetic study of thousands of people from several parts of the world showed that very rare variants of *SLC30A8*—found in about 1 in 5,000 people—significantly reduce the risk of type 2 diabetes. The gene encodes a protein called ZnT8 that helps package insulin in a form that is compact yet can be quickly released from insulin-producing  $\beta$  (beta) cells when blood glucose levels rise, such as after a meal. Thus, ZnT8 plays an apparently key role in controlling blood glucose levels.

Results from this new study may therefore seem surprising: people with the type 2 diabetes-protective gene variant have less ZnT8 protein in their cells than people with the more common form of the gene, yet their insulin response to rising glucose levels was both faster and more robust. This super-charged insulin response is likely to be responsible for the unusual resistance to type 2 diabetes resulting from the rare mutation, raising the possibility that a medical intervention to reduce the activity of ZnT8 in  $\beta$  cells might help prevent type 2 diabetes in people at risk, or be a useful method to treat the disease in those that have developed it. Experiments in isolated human  $\beta$  cells are consistent with that idea: the scientists utilized an experimental approach to lower the amount of ZnT8 protein produced in these cells and found that this resulted in a higher rate of insulin secretion even at normal glucose levels. Notably, the procedure shifted the ratio of mature insulin relative to a precursor form of the hormone: compared to normal  $\beta$  cells, those with less ZnT8 had a higher proportion of mature, ready-to-secrete insulin. This suggests that by helping  $\beta$  cells store large quantities of tightly packed insulin precursor protein, ZnT8 might simultaneously be slowing the production and release of the mature, active hormone in times of caloric excess, when its rapid release is a higher priority. If so, and if medications can be developed

that safely lower ZnT8 activity in  $\beta$  cells, such medicines may one day be clinically valuable for treating or preventing type 2 diabetes.

*Dwivedi OP, Lehtovirta M, Hastoy B,...Groop L. Loss of ZnT8 function protects against diabetes by enhanced insulin secretion. Nat Genet 51: 1596-1606, 2019.*

### **Combined Analysis of Studies with East Asian Participants Yields a Dramatic Increase in Knowledge of Type 2 Diabetes Genetics:**

Bringing together information from multiple genetic studies of type 2 diabetes in people of East Asian descent has yielded a wealth of new information about the disease that may one day help improve its treatment and prevention for people whether or not they have East Asian genetic heritage. Understanding genetic risk for type 2 diabetes has grown in importance in recent decades as lifestyle changes have interacted with genetic traits that might have been benign in prior generations, but now predispose a person to type 2 diabetes. This dynamic is helping fuel a worrisome rise in diabetes prevalence around the world, and East Asian countries are seeing some of the largest increases. Researchers have identified over 240 different genetic regions—mostly within the last 15 years—where variations appear to have a measurable influence on susceptibility to type 2 diabetes. Most of these advances came from genome-wide association (GWA) studies, in which scientists look for genetic features that are either more or less common in people with a disease than in people without it. By themselves, most of the known diabetes risk genes have only small effects on a person's likelihood of getting the disease, and early GWA studies often required genomic analysis of thousands of participants in order to detect them. As the field progressed, even larger studies were required to find genes with still smaller effects, or for which the variants of interest were rarer. Eventually, the only practical way to obtain a large enough sample size was to combine results from several previous studies so that hundreds of thousands of research participants were effectively included. The great majority of type 2 diabetes susceptibility genes found in this manner, however, were identified by combining GWA studies whose participants were primarily of European ancestry. As a result, less is known about unique genetic risk factors for the disease in people of East Asian and other non-White backgrounds.

Researchers have now completed a pooled analysis of numerous previous GWA studies conducted in Japan, China, Korea, and other East Asian countries, yielding a cumulative total of 433,540 participants, 77,418 of whom had type 2 diabetes. In this way they identified 183 different parts of the genome where genetic features influence predisposition to type 2 diabetes in people with ancestry from this part of the world. Most of these genetic regions had been identified in previous studies as affecting the risk for type 2 diabetes, confirming and bolstering what was known about the relationship of those gene regions to the disease. However, a remarkably large number—61—could be clearly distinguished from previously detected type 2 diabetes genetic risk factors, and were therefore new discoveries. Some of the gene regions newly linked to type 2 diabetes risk were notable for affecting susceptibility to the disease even in participants considered to have a healthy body weight. These findings may help explain an intriguing scientific mystery: although overweight and obesity are risk factors for type 2 diabetes throughout the world, people with East Asian ancestry are more likely than those from other backgrounds to develop type 2 diabetes at lower body weight. Increasing the number of known genetic risk factors for type 2 diabetes by about 25 percent, this study sheds light on aspects of type 2 diabetes genetics that are unique to those of East Asian descent and may someday make it possible to tailor diabetes prevention or care for a large fraction of the world's population. The findings have also reinforced and clarified previous discoveries in participants from other parts of the world and yielded information that could eventually lead to new therapeutic approaches with potential to benefit anyone with type 2 diabetes, regardless of where his or her ancestors come from.

*Spracklen CN, Horikoshi M, Kim YJ,...Sim X. Identification of type 2 diabetes loci in 433,540 East Asian individuals. Nature 582: 240-245, 2020.*

## **METABOLIC REGULATORS OF HEALTH AND DISEASE**

### **Fat Cell Signaling Molecules Identified as Critical for Regulating Metabolic Health in Mice:**

Researchers have identified new ways that adipocyte (fat cell) signaling can disrupt glucose (sugar) regulation in mice, with metabolic consequences throughout

the body. Adipocytes are known to mediate obesity-related disruptions in glucose metabolism, and knowing how these cells “talk” with other cells and organs in the body could lead to new targets for diabetes treatments. One major group of signaling molecules in animals is the “G proteins,” which transmit crucial information about a cell's environment to its interior and thus inform the cell's behavior. Some G proteins help to regulate adipocyte function and blood glucose levels, but the specific role of the  $G_i$  family proteins in adipocytes was unclear.

To determine  $G_i$  proteins' function in fat cells, researchers created a mouse model that lacks functional  $G_i$  proteins in adipocytes. Compared to normal male mice, male mice lacking  $G_i$  proteins in their adipocytes displayed many signs of poor metabolic health. The lack of  $G_i$  proteins in their adipocytes impaired the mice's ability to regulate their blood glucose levels. The mice also showed signs of reduced insulin sensitivity in various organs, including the liver and muscle, particularly when given a high-fat diet. Scientists found that mice on a high-fat diet that lacked  $G_i$  proteins in their adipocytes had increased fatty acid concentrations in the blood, increased fat in the liver, increased markers of inflammation in fat tissue and blood, and impaired insulin receptor signaling compared to normal mice on the same diet. The researchers then demonstrated that functional  $G_i$  proteins in adipocytes were required to prevent these poor health outcomes and to maintain metabolic health. Furthermore, work with a different mouse model showed that selectively activating  $G_i$  signaling in adipocytes improved both glucose metabolism and insulin sensitivity regardless of diet. Enhancing  $G_i$  protein signaling for longer periods of time also helped improve various aspects of metabolic health while on a high-fat diet.

Though these findings will need to be confirmed in humans, they suggest that the  $G_i$  family of proteins in adipocytes is critical to maintaining healthy glucose regulation in mice and is particularly important when the mice are given a high-fat diet. Selectively activating these proteins may also be a novel way to combat the symptoms of metabolic disorders, such as diabetes, in humans.

*Wang L, Pydi SP, Zhu L,...Wess J. Adipocyte  $G_i$  signaling is essential for maintaining whole-body glucose homeostasis and insulin sensitivity. Nat Commun 11: 2995, 2020.*

### **A Factor in Fat Tissue That Helps Preserve**

**Insulin-producing Beta Cells in Mice:** Studies of a protein involved in maintaining fat tissue and regulating metabolism have led to new discoveries about  $\beta$  (beta) cell health in mice, with possible implications for treating diabetes. During type 2 diabetes, the body becomes resistant to insulin's effects and gradually loses insulin-producing  $\beta$  cells in the pancreas. Currently, there are no therapies to stop this loss of functional  $\beta$  cells, leading researchers to study what factors are involved in maintaining  $\beta$  cell health.

Adipsin is a protein secreted by fat cells that was known to increase insulin production in the body in response to glucose (sugar), but its role in diabetes was unclear. Scientists hypothesized that adipsin might be important somehow in maintaining  $\beta$  cell numbers or  $\beta$  cell health. Researchers investigated this possibility by testing a treatment that caused increased adipsin production in a mouse model of type 2 diabetes. They saw improvements over 6 months: blood glucose levels were lower, insulin levels were higher, and fewer  $\beta$  cells had been lost in the mice that were making extra adipsin than in mice that had not received the treatment. Further experiments showed that adipsin's positive effects on  $\beta$  cell health and function stemmed at least in part from its ability to inhibit production of a protein made in  $\beta$  cells called DUSP26. The researchers found that, in a mouse model of type 2 diabetes, over-production of DUSP26 reduced insulin levels in the blood, whereas reducing DUSP26 levels improved the mice's blood glucose control. Inhibiting DUSP26 also helped preserve the health of human  $\beta$  cells in the laboratory. Taken together, these results suggested that changes in DUSP26 levels might contribute to development of type 2 diabetes by increasing susceptibility to  $\beta$  cell loss. To explore if the adipsin made by fat cells could potentially protect people from diabetes, scientists studied blood samples and body fat imaging data from a large cohort of men and women. They found that higher adipsin levels in the blood correlated with a lower risk of future diabetes in middle-aged adults with obesity. The researchers also explored the conundrum that although obesity is a risk factor for type 2 diabetes, adipsin—which is made by fat cells—seems protective. Examining different body fat tissues in people with imaging technology, they found that adipsin in the blood was associated with fat tissue mass under the skin, but not with fat tissue

deeper in the body around internal organs (visceral fat), which is linked to metabolic problems.

More research is needed to fully understand the roles adipsin and DUSP26 play in human health and disease, but these new findings suggest that boosting the effects of adipsin or inhibiting those of DUSP26 could be promising targets for future diabetes treatments.

*Gómez-Banoy N, Guseh JS, Li G, ...Lo JC. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. Nat Med 25: 1739-1747, 2019.*

### **New Tools and Surprising Results Pave the Way to More Comprehensive Understanding of Melatonin and Circadian Rhythm:**

In an important new study, scientists have combined computer modeling, chemical synthesis and refinement, and validation in animal models to identify novel compounds modulating melatonin receptor activity—advancing our ability to develop therapeutics that could help address health problems related to sleep and metabolism. Normally, the body uses a complex biological system, called the circadian rhythm or “body clock,” to help govern many physiological functions throughout the day and night. For this to work, the internal circadian rhythm needs to be synchronized to external day-night (light-dark) cycles. The hormone melatonin is key to this synchrony. In response to changing light levels, the brain produces more melatonin at night, which in people induces physiological changes that promote sleep, and less during the day, which stimulates wakefulness. Disruptions to normal circadian rhythm contribute to metabolic diseases such as diabetes and obesity, along with sleep disorders and other conditions, such as depression and increasing incidence of cardiovascular diseases. Thus, a better understanding of circadian biology and improved therapeutics are needed—and melatonin activity is a key target. Two cellular receptors for melatonin,  $MT_1$  and  $MT_2$ , are known, but it has been unclear whether these might have different functions when bound to melatonin, or whether drugs designed to target one or the other might have different effects.

To gain further insights, researchers decided to synthesize molecules that actively and selectively bind one or the other of these melatonin receptors. To do this, the research team used a virtual jigsaw puzzle piece approach. As a first step, they took

the known three-dimensional structure of human MT<sub>1</sub> and, using computer modeling, screened over 150 million virtual molecules to find ones predicted to fit well into MT<sub>1</sub>'s melatonin binding site. Based on the results, they synthesized a subset of compounds to test in the laboratory, focusing on compounds with high selectivity at a very low concentration. After synthesizing and testing 38 compounds, the scientists found 15 new chemical structures that interacted well with either MT<sub>1</sub>, the very similar MT<sub>2</sub>, or both. As a key goal was to find molecules that could selectively engage with the subtypes of melatonin receptors and thereby enable probing of each receptor's biological activities in animal models, the researchers chemically tweaked some of the 15 chemical structures and studied 3 of the resulting compounds. Two of these interacted selectively with MT<sub>1</sub>, and one interacted selectively with MT<sub>2</sub>. Among the exciting and unexpected results from circadian rhythm experiments in two different mouse models, the scientists found that the MT<sub>1</sub>-selective molecules could either block or mimic melatonin's effects, depending upon the experiment—providing new insight into how melatonin works through its receptors. For example, the researchers found that administration of the MT<sub>1</sub>-selective molecules at experimentally defined “dusk” caused the mice to change their normal behaviors in ways similar to the effect of administering melatonin itself. The study validates a powerful approach to finding novel, valuable compounds for investigating circadian biology and for potential development as therapeutics for diseases influenced by circadian rhythm—an approach that can be extended to other areas of investigation as well.

Stein RM, Kang HJ, McCorvy JD, ...Dubocovich ML. Virtual discovery of melatonin receptor ligands to modulate circadian rhythms. *Nature* 579: 609-614, 2020.

## STRIDES IN THE TREATMENT OF CYSTIC FIBROSIS

**Therapies To Treat the Molecular Cause of Cystic Fibrosis Now Approved for Ninety Percent of People with the Disease:** Researchers recently found that a combination of three drugs for cystic fibrosis (CF) has substantial benefit in people for

whom previous medical treatments did not work. CF, a rare disease resulting in childhood fatality if left untreated, is caused by mutations in the *CFTR* gene. This gene encodes the CFTR protein, a key cellular channel for chloride ions (one of the two chemical components of table salt). Everyone receives one version of *CFTR* from each parent, and if either of those copies is normal that person does not get the disease. But if neither copy produces a functional form of the CFTR protein, he or she will develop CF. There are many disease-causing variants of the *CFTR* gene known, but by far the most common is one designated *Phe508del*: 90 percent of people with CF have at least one copy of this variant, and about half received this version of the gene from both parents. Researchers previously developed a medication, ivacaftor, that restores some function to certain disease-causing forms of CFTR, so the protein can act as a channel for chloride. This was life-changing for the small number of people who have these particular variant forms of CFTR. Unfortunately, the *Phe508del* form not only lacks channel function but is also unstable and is quickly degraded by the cell. In 2018, the U.S. Food and Drug Administration (FDA) approved two different two-drug combinations of ivacaftor, the channel opening drug, along with either of two CFTR stabilizing drugs, tezacaftor or lumacaftor. These combinations made a real clinical difference for people with either two copies of *Phe508del* or one copy along with a milder *CFTR* mutation. However, even though they provided some clinical benefit, CFTR function remained too low in people with two copies of *Phe508del*. Moreover, the existing two-drug combinations were ineffective in people who have one copy of *Phe508del* plus a “minimally functioning” (MF) *CFTR*—one that effectively produces either no CFTR protein at all or a form of the protein that does not respond to any of the previously developed medications.

Scientists reasoned that an additional CFTR-stabilizing medicine might be added to one of the approved two-drug combinations to have greater benefit. In 2019, scientists found that such a three-drug combination was significantly more effective than the approved two-drug therapies at improving CFTR function in people with two copies of *Phe508del*. In a new industry-led clinical trial, with additional support from the NIDDK and others, researchers tested that three-drug combination

of tezacaftor, ivacaftor, and a newer medication—elexacaftor—in a study with 403 participants who have one *Phe508del* variant and one *MF* variant. The treatment dramatically improved lung function and quality of life while reducing serious CF complications during the 24-week study. The FDA has now approved this triple combination therapy for people ages 12 and over with CF and at least one copy of *Phe508del*. That the root cause of CF can now be treated in roughly 90 percent of those with

the disease is a tremendous achievement, yet further research will be important to develop effective therapies for those whose disease cannot be treated by any of these new methods—and to develop a cure for this life-long disease.

Middleton PG, Mall MA, Dřevínek P,...Jain R; VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single *Phe508del* allele. *N Engl J Med* 381: 1809-1819, 2019.

# Celebrating the Discovery and Development of Insulin

This year marks the 100<sup>th</sup> anniversary of the discovery, in 1921, of insulin, a hormone required for the body to absorb glucose (sugar), the main cellular fuel. The loss of insulin is the hallmark of type 1 diabetes, and, in individuals with type 2 diabetes, there is a relative lack of insulin compared to the body's needs. Without insulin the body is not able to maintain normal metabolism, resulting in high blood glucose levels and a severe catabolic (a breakdown of molecules such as proteins or lipids) state. The discovery of insulin led to its production as a commercially available lifesaving treatment for people with type 1 diabetes. Continued research to understand the insulin molecule—its structure and function—has led to new formulations and technologies that have improved the lives of people with the disease.

## DISCOVERY OF INSULIN

The discovery of insulin was built on decades of research around the world enabling scientists at the University of Toronto to extract the molecule from animal pancreata and, by injecting it into a dog model of diabetes, demonstrate its importance in the disease. More research was required, though, before the discovery could help people with type 1 diabetes; researchers needed to figure out how to purify the insulin and, eventually, how to produce sufficient quantities for the demand. It was not long, however, before this discovery would change the lives of people with type 1 diabetes, extending life expectancy considerably and improving quality of life.

In 1923, the first commercial insulin product was produced. Though this insulin was life-saving, it was far from perfect. It was extracted from animal pancreata and thus was not human insulin, was difficult to purify and produce, was unstable, and did not last long in the body. Scientists continued to study insulin to develop solutions to these problems. For example, a decade later, they discovered that the addition of the molecules protamine and zinc produced a long-acting animal insulin that required fewer injections throughout the day.

## DEVELOPMENT OF INSULIN ANALOGS

NIDDK support of research on insulin has spanned decades and made possible many advances to move the field forward. Another key milestone in insulin research occurred in the late 1970s when researchers developed the ability to produce so-called “recombinant” human insulin. Identifying and sequencing the gene that encodes insulin and determining the structure of the insulin protein were critical research feats that laid the groundwork for this improvement. Thus, based on knowledge of the human insulin gene, this recombinant insulin could be produced in large quantities in bacteria in the laboratory. This breakthrough increased production of insulin, improved purification, and eliminated the dependence on animal-derived insulin and the accompanying allergic reaction that some people had to it.

Despite its life-saving ability, insulin therapy remained a considerable burden for people with type 1 diabetes. For example, its dose needed to be calculated carefully and injected by syringe into fat in the body, limiting how quickly the body would respond. A miscalculation of too much insulin could lead to dangerously low blood glucose levels (hypoglycemia) with serious consequences, and a delay in insulin injection could lead to higher blood glucose levels (hyperglycemia) after meals. Without adequate control of blood glucose levels over time, the risk for diabetic complications increases significantly.

Armed with knowledge of the sequence and structure of insulin, scientists experimented further, modifying single amino acids (the building blocks of proteins) of the insulin protein and studying whether these modifications altered insulin's action or stability. Such studies led to the development of analogs—synthetic forms of insulin that have minor structural changes but perform the same action in the human body. Today there are many analogs on the market that provide different advantages. For example, fast-acting insulin is absorbed quickly into

the blood stream and can be used to correct high blood glucose levels and at mealtimes when blood glucose levels rise because of food intake. Long-acting insulin is absorbed more slowly, lasts longer, and is used to control blood glucose both during the day between meals and overnight. Additionally, the development of insulin pumps—small, computerized devices worn on the body that deliver insulin—have aided diabetes management. These technologies can provide people with type 1 diabetes more reliable blood glucose control, though challenges to their use remain.

## **THE FUTURE OF INSULIN AND DIABETES MANAGEMENT TECHNOLOGIES**

NIDDK-supported scientists continue to study insulin with the goal of improving its usability. On the horizon are insulins that are ultra-rapid acting or highly concentrated that could be delivered by a patch rather than a bulky insulin pump. These insulins would also improve diabetes management technologies developed with NIDDK support such as artificial pancreas technologies, which combine a continuous glucose monitor with an insulin pump and a computer algorithm to automatically control blood glucose levels. Scientists are also trying to develop thermostable formulations of insulin so that refrigeration is not

required. Not only would this generally make insulin easier to use, especially where access to refrigeration is an issue, but it would also enhance its use in technologies like the artificial pancreas. Efforts are also under way to develop a glucose-responsive insulin—an insulin that remains inactive in the body until activated in response to rising blood glucose levels—to more closely mimic the body's own regulation.

NIDDK-supported research aims to improve the technologies available, including insulin, as well as develop and test next-generation diabetes management devices that are smaller, easier to use, and could be available to all people with this disease. This could allow people with type 1 diabetes the ability to choose which device and insulin fits their needs—personalizing this treatment while reducing burden, controlling blood glucose levels, reducing risk for diabetic complications, enhancing quality of life, and improving health. One hundred years ago, a diagnosis of type 1 diabetes meant a significantly decreased life span. Today, people with type 1 diabetes are living longer and healthier lives enabled by research on insulin. Future strategies to make disease management easier for everyone will continue to improve lives and provide hope as researchers work toward the goal of a cure for type 1 diabetes.

# Seeing the Whole Picture: Two NIDDK Workshops Aim To Advance Pancreatic Imaging

The pancreas plays essential roles in converting the food we eat into fuel our cells can use. In its “exocrine” role, the pancreas makes and secretes digestive enzymes that break down the proteins, carbohydrates, fats, and other components in food. The pancreas also has “endocrine” functions, producing hormones such as insulin and glucagon that help regulate blood glucose (sugar) levels. A healthy pancreas expertly coordinates release of these enzymes and hormones with the body’s needs, while pancreatic dysfunction can lead to a variety of health problems, including diabetes, pancreatitis, and pancreatic cancer.

Detailed assessments of pancreatic function can be crucial to diagnosing pancreatic diseases, but examining a living pancreas inside the body can be challenging. The pancreas is surrounded by the stomach, small intestine, liver, and spleen, and this crowded environment limits clinicians’ ability to access the pancreas. The pancreas is also structurally delicate, and the digestive enzymes it produces can cause additional problems if the pancreas is damaged. For these reasons, inspecting the pancreas and removing and analyzing tissue samples (obtaining a biopsy) can be difficult. Thus, pancreatic imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) are especially valuable tools in monitoring pancreatic health and diagnosing issues.

In early 2020, the NIDDK held two workshops on using cutting-edge imaging tools to explore the pancreas and pancreatic diseases. These workshops brought together researchers from the endocrine and exocrine pancreas fields to identify challenges and emerging opportunities in pancreatic imaging as a whole. The presentations and panel discussions from these workshops demonstrated that though significant challenges remain, recent technological advances in pancreatic imaging are paving the way toward new methods to diagnose, monitor, and/or guide treatment of various pancreatic diseases and conditions.



**Imaging the Pancreas in Diabetes, and Benign and Malignant Exocrine Pancreatic Disease, January 13-14, 2020:** Clinicians have observed numerous connections between the exocrine pancreas and the pathogenesis of diabetes, which is considered an endocrine disease. Substantial changes in the size and probably the architecture of the exocrine pancreas can precede the onset of diabetes, for example, and both type 1 and type 2 diabetes can coincide with various exocrine pancreatic diseases. Furthermore, there are likely shared causes for some endocrine and exocrine pancreatic diseases, and their treatment could potentially have favorable or adverse effects on the function of the entire pancreas. However, the pancreas’ exocrine and endocrine functions tend to be studied by different research communities, and as such, endocrine and exocrine pancreatic diseases are generally treated by different medical specialists. There is thus a great opportunity for researchers in these different disciplines of pancreatic research to inform each other, and imaging serves as a major nexus where advances can further both the endocrine and exocrine pancreas fields.

The goal of this symposium was to showcase the use of pancreatic imaging to detect and explore the pathogenesis of diabetes, pancreatitis, pancreatic cancers, and other pancreatic diseases, with an emphasis on information that could inform various pancreatic fields. Topics included the use of clinical imaging in cancerous and non-cancerous pancreatic disease, imaging pancreatic physiology both in health and disease, and imaging’s role in examining the architecture, development, physiology, and function of pancreatic islets, structures that play a key role in diabetes. Scientific poster sessions and panel



discussions offered opportunities for attendees to share knowledge, discuss emerging technologies, and identify promising research opportunities.



**Strategies for Clinical Imaging in Diabetes, January 15, 2020:** The ability to noninvasively image the numbers and function of different cell types in the pancreatic islet (particularly the insulin-producing  $\beta$  [beta] cells) would allow researchers and clinicians to better track the development and progression of diabetes. Current data on the fate of human  $\beta$  cells comes largely from data “snapshots” gathered from donated cadaver pancreases or from studies of  $\beta$  cells cultured in the laboratory, but neither of these

approaches can give a full picture of how  $\beta$  cells develop and change in living people or of how diabetes develops. Therefore, methods for real-time pancreatic imaging are needed and could have significant implications for diabetes research, diagnosis, and treatment.

At the time of this workshop, several promising imaging agents were at various stages of development and validation. The workshop was designed to stimulate discussion about the current state of imaging of the pancreatic islet's  $\beta$  cells and their function in people. Attendees presented data on promising imaging agents and techniques, and discussed how such advances could be used to inform diabetes clinical care in the future. A roundtable at the end of the workshop focused on how to move the field forward, including identifying studies needed to promote development of experimental  $\beta$  cell imaging techniques into tools that could one day be used in the clinic.

# STORY OF DISCOVERY

## How Different Medications for Diabetes and Obesity Emerged from Basic Research on One Pancreatic Hormone

Basic research to understand and characterize the hormones controlling blood glucose (sugar) levels, including the discovery of the glucagon gene, ultimately led to two very important therapeutics with very different purposes. One of these therapies helps people with type 2 diabetes lower their blood glucose while reducing their risk of cardiovascular disease and also helps people with obesity lose weight; the other helps raise blood glucose levels in people with type 1 or type 2 diabetes if they develop hypoglycemia. Remarkable advances along the way came from studies in a variety of model organisms including not only typical lab animals like mice and rats, but also organisms like the deep-sea anglerfish and the desert-living Gila lizard.

### **GLUCAGON: INSULIN'S HORMONAL OPPOSITE IS ALSO ITS ESSENTIAL PARTNER**

In healthy individuals, the pancreatic “islets”—small, densely packed groups of several different types of cells—have a central role in maintaining optimal glucose levels in the body. One islet cell type, designated  $\beta$  (beta), responds to elevated blood glucose levels by releasing insulin, the hormone that induces cells to absorb sugar. When blood glucose levels are too low, another type of islet cells— $\alpha$  (alpha) cells—release a hormone called glucagon, which signals the liver to release glucose into the blood. These two critical hormones also regulate one another—rising insulin levels help inactivate

lingering glucagon, and vice versa—to ensure agile transitions between periods of fasting and of caloric plenty. The net effect is to provide precise regulation of glucose levels within a narrow range that supports the optimal function and the long-term health of the body's cells and organs. In diabetes, this perfectly choreographed regulatory dance is disturbed either by loss of the insulin-producing  $\beta$  cells (type 1 diabetes) or by inadequate amounts of insulin to compensate for a weakened response to the hormone by other cell types (type 2 diabetes).

The 1921 discovery that purified insulin could be used to treat diabetes meant that for the first time in history, children diagnosed with what we now call type 1 diabetes could live to adulthood. However, the dangers of over-treating diabetes soon became clear: depending on severity, hypoglycemia—low blood glucose levels—can cause symptoms ranging from clumsiness, irritability, or confusion, to lost consciousness, seizures, and even death. In contrast, high glucose levels may not cause acute symptoms until they are well above normal. Over time, however, high blood glucose levels have been shown to lead to the chronic complications of diabetes. The landmark NIDDK-supported Diabetes Control and Complications Trial (DCCT) changed this by showing that keeping blood glucose control close to normal is vital to slowing development and progression of long-term diabetes complications that can lead to disability and death. Researchers have long been vigorously searching for better ways to control blood glucose levels both safely and effectively.

# STORY OF DISCOVERY

Treating mild cases of low blood glucose levels is sometimes as simple as consuming a source of glucose, so schools, as well as individuals with diabetes who take insulin or certain other drugs that can cause excessive release of the hormone, often keep glucose tablets on hand for use in such situations. But one of the greatest concerns for people with type 1 diabetes, and those who love and care for them, is a drop in blood glucose levels that goes unnoticed because it occurs during sleep, and therefore can become extremely dangerous. Glucose tablets are only helpful, of course, when hypoglycemia is recognized and when it occurs in someone who is conscious and able to eat or drink, so more severe episodes of hypoglycemia can be deadly. In a hospital setting, intravenous delivery of glucose can be a life saver if hypoglycemia is noted. Similar interventions can sometimes be necessary for children with diabetes if they refuse to eat, or if another disease like the flu prevents someone with diabetes from keeping food down. In schools and homes, however, there have been few practical options. Moreover, the danger of hypoglycemia is a major source of anxiety not only for people with diabetes but also for their caregivers and is a serious obstacle to achieving optimal glucose levels for long-term health. Furthermore, repeated episodes of hypoglycemia can lead to a weaker compensatory glucagon release from  $\alpha$  cells and also cause people to lose the ability to recognize hypoglycemic symptoms, increasing the risk for severe episodes. As a result, scientists have long recognized the potential of glucagon as an emergency medical treatment to combat dangerously low blood glucose levels.

Why did nearly 100 years pass after insulin came into widespread use to treat diabetes for its vital opposing partner in controlling glucose levels to start becoming more widely available and convenient to use? The factors that long frustrated therapeutic development of glucagon, and the innovations that are overcoming those problems, are part of a remarkable scientific story.

## FISHING FOR GLUCAGON

In fact, researchers developed a process for isolating glucagon from an animal pancreas in 1923, just 2 years after the landmark purification of insulin. Indeed, a preparation of glucagon was approved by the U.S. Food and Drug Administration (FDA) in 1960 for the emergency treatment of hypoglycemia, but two characteristics limited the product's therapeutic potential: the hormone rapidly forms insoluble, injection-clogging fibrils in water; and it quickly degrades if not kept frozen. Because it would be impractical to keep frozen, dissolved glucagon on hand at all times, the FDA approved the drug as a dried powder. Unfortunately, dissolving the hormone with sterile water and administering it in time and at the correct dose posed logistical challenges for non-medical professionals that limited its usefulness.

The first step to understanding and overcoming these problems was to find the glucagon-encoding gene; and the first glucagon gene to be identified came from what might seem a very unlikely source: the deep-sea-dwelling Atlantic anglerfish. These animals hide on the ocean floor, waiting for prey to come along, and glucagon is essential to maintain their glucose levels when that wait is a long one. But there was also a practical reason to study the hormone in anglerfish: their islets are encapsulated in easily identified and isolated structures, rather than hidden within the pancreas. Thus, anglerfish  $\alpha$  cells proved to be a convenient source for the NIDDK-supported scientists who first identified the glucagon gene in 1982. Having the anglerfish version in hand facilitated the search for corresponding mammalian glucagon genes, so researchers soon identified rodent and human versions as well.

These advances made it possible to put the gene into laboratory bacteria to produce significant quantities of the human glucagon protein—called “recombinant” glucagon—so that producing the hormone became more efficient, and the preparations more easily purified. However, it was

# STORY OF DISCOVERY

not until 1998, 5 years after publication of results from the DCCT establishing the importance of keeping blood glucose levels close to normal, that two different pharmaceutical companies developed recombinant glucagon as a commercial product and received approval from the FDA to make and market it for emergency treatment of severe hypoglycemia. Unfortunately, the recombinant hormone was just as likely as glucagon from other sources to form fibrils and degrade in water, so the barriers to its widespread use remained in place.

## NEW APPROACHES FOR GLUCAGON DELIVERY—AND NEW NEEDS

Two significant innovations facilitating use of glucagon were FDA approved for use in 2019. The first of these is a new method of delivering the hormone: by simply spraying the dried powder into the nose. This eliminates the need to dissolve it in water or inject it and therefore makes the prospect of giving the drug much less intimidating to untrained bystanders. The second, developed with NIDDK small-business grant support, takes the approach of dissolving the hormone in a non-toxic liquid called dimethylsulfoxide (DMSO), instead of water. Glucagon remains stable for months in room-temperature DMSO without forming fibrils. The DMSO-dissolved hormone is distributed in easy-to-use injector “pens” that automatically deliver an appropriate dose to raise glucose levels.

A need for smaller, non-emergency doses of glucagon is now arising as a result of another major advance in medical care for type 1 diabetes: development of “artificial pancreas” devices. In their simplest form, these devices continuously measure a person’s blood glucose levels and automatically administer an appropriate amount of insulin, if needed, to bring glucose levels down to healthful levels. This approach reduces the chances of developing hypoglycemia due to an accidental overdose of insulin. However, if glucose levels fall too low for any other reason—as a result of fasting, exercise, or illness, for example—the inability of such

an insulin-only device to react by providing glucagon is a major limitation compared to a healthy pancreas. A “bi-hormonal” artificial pancreas—one that can respond like a functioning biological pancreas by lowering glucose with insulin or supplying a low dose of glucagon to raise glucose levels, if necessary—might therefore be a great boon to patients, adjusting blood glucose to optimum levels before they get into a range that would cause the wearer to experience symptoms or suffer any negative long-term health consequences. Today, several companies, often with vital NIDDK academic and small-business grant support, are developing and testing methods for delivering low-dose glucagon, using some of the same methods that are either approved or in development for use with emergency glucagon pens. In the future, such formulations may improve on already beneficial artificial pancreas products, leading to better, simpler care with lower risk of hypoglycemia for people who require long-term treatment with insulin.

## AN UNEXPECTED BONUS HORMONE IDENTIFIED DURING THE HUNT FOR THE GLUCAGON GENE

The complementary effects of  $\alpha$  and  $\beta$  cells and their signature hormones would seem to offer a simple, tidy explanation of the way the body controls blood glucose levels; but that explanation turns out to be incomplete in fascinating ways. In the 1960s, researchers were surprised to discover that the pancreas releases more insulin when a given amount of glucose is absorbed through the digestive system than if it is injected directly into the blood. The underlying reasons were a mystery, but the scientists speculated that the presence of glucose or other food in the gut might prompt the release of some different, unknown hormone that signals the pancreas to prepare for an increase in glucose levels by readying its supply of insulin. The scientists referred to such hypothetical insulin production-promoting hormones as “incretins,” but decades passed before work in other laboratories proved that this idea was correct.

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In fact, the next clue to the incretin mystery was uncovered during the 1982 discovery of the anglerfish glucagon gene: an adjacent gene turned out to encode a protein that is notably similar to glucagon, yet clearly different from it. The researchers therefore called it a “glucagon-like peptide,” or GLP. Further work showed that, in contrast to fish, mammals do not have just two similar genes next to one another—they have three: the gene for glucagon, plus genes that came to be designated *GLP-1* and *GLP-2*. Additional NIDDK-supported research later demonstrated that a truncated form of the product of one of these genes may be able to act as an incretin: pancreatic  $\beta$  cells release more insulin in response to elevated glucose if they are first stimulated with part of the *GLP-1* protein. Thus, surprisingly, *GLP-1* turns out to work somewhat in opposition to the very similar glucagon, helping to lower glucose levels by boosting the release of insulin. In another contrast with glucagon, experiments demonstrated that *GLP-1* is produced not in the pancreas but by intestinal cells close to the stomach—and only when stimulated by the presence of food—helping establish that it is, in fact, an incretin. Experiments also demonstrated that *GLP-1* has at least one other important effect on the body: it briefly slows stomach emptying, delaying digestion for a few minutes so that insulin will be ready for release before glucose levels have risen significantly.

## DEVELOPMENT OF AN ENTIRELY NEW CLASS OF DIABETES MEDICATION

The effects of *GLP-1* sound very much like properties one might like to have in a treatment for type 2 diabetes: by boosting insulin secretion in response to food, *GLP-1* might bolster the natural insulin response of a person with the disease and thereby help keep glucose at healthier levels, while slowing digestion to allow this to happen. Unfortunately, scientists soon discovered a problem with the idea: *GLP-1* only lasts a few minutes in the blood stream before it is degraded by other proteins. A therapeutically useful form of the hormone would

therefore need to be much more stable in order to be a practical treatment for type 2 diabetes.

As it happens, scientists discovered a solution to this problem in what may seem like the unlikeliest of animals—a venomous lizard that lives in a habitat that could hardly be more different from that of the anglerfish, the U.S. Desert Southwest and Northwest Mexico. At about the same time that the glucagon-like peptides were being discovered by NIDDK grantees, NIDDK intramural scientists working with the lizard, called a “Gila monster,” discovered that mingling with the venom in the lizard’s saliva were proteins that appeared to “jump-start” its digestive system after the months of fasting that normally occur between its meals. Isolated from this protein mixture was a hormone they designated *exendin-4* that was notably similar to glucagon, and even more akin to *GLP-1*. Scientists showed that *exendin-4* and *GLP-1* are both capable of stimulating gastric secretions in guinea pigs, though *exendin-4* is the more potent of the two. They went on to show that both proteins work by stimulating the same cellular receptor, and that *exendin-4* is a potent incretin. Importantly, a small but significant difference between the *GLP-1* and *exendin-4* structures protects the latter from digestion in the blood, where *GLP-1* disappears within a few minutes, yet *exendin-4* persists for about 12 hours.

Based upon these critical, NIDDK-supported basic science discoveries, pharmaceutical companies developed “*exenatide*,” a synthetically produced but chemically identical form of *exendin-4*, as a medication for people with type 2 diabetes. Because “*exenatide*” cannot be absorbed in pill form, a pharmaceutical company developed an easy-to-use injection “pen” (not unlike the one later approved for administering emergency glucagon) that patients could use to give themselves the correct dose of the drug. In industry-supported randomized controlled clinical trials, this approach proved highly beneficial in participants with type 2 diabetes whose blood glucose was inadequately controlled. At the conclusion of the studies, participants who had received *exenatide* were found to have maintained

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significantly healthier blood glucose levels than those who had received a placebo; and those receiving a higher dose of exenatide had achieved better blood glucose control than those who received a lower dose. Because it does not directly increase insulin levels, but rather signals  $\beta$  cells to be ready to produce a robust insulin response if it is needed, those taking it did not tend to experience hypoglycemia. The drug therefore also proved to be a relatively safe method for improving blood glucose control. As a result, the FDA approved exenatide in 2005 as a supplementary treatment for type 2 diabetes in patients whose blood glucose is not otherwise well controlled.

## **NEW BENEFITS AND A NEW INDICATION FOR THE NEW CLASS OF MEDICINES**

Subsequent FDA approvals went to even longer-lived forms of GLP-1, like liraglutide, which lasts 24 hours, and semaglutide, which lasts an entire week. Together, these medications constitute a distinct and entirely new class of medications for type 2 diabetes called “GLP-1 receptor agonists.” Because the FDA wanted to be sure that these drugs help people to control their blood glucose levels without incurring risks that might worsen cardiovascular disease, the diabetes complication most likely to result in death, the agency ordered post-approval research of long-term outcomes in people taking them. As a result, we now know that the medicines in this class significantly reduce

the risk for heart attacks and other cardiovascular complications that are the leading killers of people with diabetes.

Another exciting finding from randomized clinical trials of these therapeutics is that people taking these medications typically lose a significant amount of weight. This “side effect,” of course, is quite valuable, because type 2 diabetes is associated with overweight and obesity. These findings spurred interest in testing GLP-1 receptor agonists for another purpose: treating obesity. Indeed, clinical trials have indicated that they are remarkably effective as weight-loss medications. Depending on the dose, for example, weekly semaglutide treatment led to an average weight loss of about 16 percent within 1 year in people with obesity who did not have diabetes, while being relatively safe for many people and fairly well tolerated.

Thus, basic research on the hormonal control of blood glucose levels, studies in animals as different as deep-sea fish and desert-dwelling lizards, and creative innovations in drug stabilization and delivery have helped lead to the development and FDA approval of two new classes of medication—glucagon and GLP-1 receptor agonists. These medications have very different effects, but together they are improving care and health for millions of people: reducing the risk of hypoglycemia in people with type 1 diabetes, improving blood glucose control in people with type 2 diabetes, and yielding weight loss for people with obesity.

## Testing a New Artificial Pancreas System for Managing Type 1 Diabetes

Type 1 diabetes is a condition in which there is an absolute deficiency of insulin that is required to maintain normal blood sugar (glucose) levels. As such, it is a very burdensome disease to manage. Every day, people with the disease must use insulin to mimic the job that the pancreas should be doing: specifically, deliver the hormone insulin in response to blood sugar levels. NIDDK-supported research has focused on developing technologies that make it easier for people to manage their type 1 diabetes, such as artificial pancreas devices. Recent exciting progress includes findings from a clinical trial that has led to a U.S. Food and Drug Administration (FDA)-approved artificial pancreas device, the Control-IQ™ system. Research advances such as these have relied on the contributions of countless volunteers with type 1 diabetes participating in artificial pancreas trials. (See inset for the story of a participant in the recent Control-IQ clinical trial.)

### ABOUT TYPE 1 DIABETES

In type 1 diabetes, the insulin-producing beta cells of the pancreas are destroyed by the immune system. Therefore, people with the disease must measure blood sugar levels throughout the day and night and administer insulin when needed via injections or an insulin pump. While insulin therapy helps keep blood sugar from climbing too high, it brings with it the risk of potentially life-threatening episodes of hypoglycemia (dangerously low blood sugar). The risk of hypoglycemia greatly limits people's ability to achieve the recommended level of blood sugar control that reduces the risk of long-term complications such as blindness and heart, kidney, and nerve disease.

Thus, a major goal of NIDDK-supported research has been to improve devices to help people keep their blood sugar levels in a healthy range.

### DEVELOPING ARTIFICIAL PANCREAS TECHNOLOGIES

An artificial pancreas, or closed-loop system, consists of a continuous glucose monitor (CGM) that measures blood sugar levels, an insulin pump, and a computer that calculates the amount of insulin needed based on the CGM's data. Artificial pancreas technology could help people with type 1 diabetes achieve recommended blood sugar levels while preventing hypoglycemia, which could alleviate the enormous burden associated with managing the disease and improve people's health and quality of life.

A first-generation closed-loop system was approved by the FDA in 2016, and many other systems are under development. The Control-IQ system was first developed at the University of Virginia with support from the NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program), which the NIDDK administers. In the Control-IQ system, the insulin pump is programmed with advanced control algorithms based on a mathematical model that uses glucose monitoring information to automatically adjust and administer the needed insulin dose. It also has a dedicated safety module to prevent hypoglycemia and gradually intensifies blood sugar control overnight to target near-normal blood sugar levels every morning.

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## TESTING CONTROL-IQ IN A MULTI-CENTER CLINICAL TRIAL

After developing, refining, and testing the Control-IQ technology over many years, scientists were ready to test it in a larger and longer trial. That trial was the multi-center International Diabetes Closed-Loop (iDCL) Study, which was funded by the NIDDK through the Special Diabetes Program. The iDCL Study enrolled 168 women and men ages 14 to 71 years with type 1 diabetes at 7 sites throughout the country. Participants were randomly assigned to use either the Control-IQ artificial pancreas system or a comparator treatment called sensor-augmented pump (SAP) therapy, which couples a CGM and insulin pump but does not automatically calculate and administer insulin doses. During the 6-month trial, participants lived their normal day-to-day lives and only had contact with study staff every 2 to 4 weeks to download and review device data. The participants were not monitored remotely so that the study would reflect real-world use.

Trial results showed that Control-IQ users significantly increased the amount of time with their blood sugar levels in the recommended target range (percent increase in time in range) by an average of 2.6 hours per day, while the time in range in the SAP group remained unchanged. Control-IQ users also showed improvements in their average blood sugar control (HbA1c levels) and had less high and low blood sugar levels. An improved HbA1c level over time has been shown to correspond with fewer diabetes complications. No severe hypoglycemia events occurred in either group.

Overall, the trial demonstrated that Control-IQ outperformed SAP therapy. Trial data were used by the FDA to authorize marketing of the Control-IQ technology, making it commercially available for type 1 diabetes management. This success story demonstrates the fruits of the sustained and long-term support of NIDDK artificial pancreas research from technology development to testing to commercial product.

## HOPE THROUGH RESEARCH

The NIDDK continues to support research to improve and test artificial pancreas technologies to develop next-generation devices, with a focus on testing artificial pancreas use in groups for which blood sugar control is particularly challenging, such as children, adolescents, older adults, pregnant women, and people who have frequent, severe episodes of hypoglycemia. Continued research could give people with type 1 diabetes a range of available devices so they can choose one that best fits their needs.

### ELENA'S STORY



*Elena, pictured, participated in an NIDDK-supported clinical trial testing a new artificial pancreas device*

Elena was diagnosed with type 1 diabetes 6 years ago at the age of 40. "It was a total shock," she recalls, not only for her, but also for her husband, Justin, and daughters Adeline and Laurel, who were teenagers at the time. However, little did Elena know that she would personally have a profound impact on advancing treatment approaches for herself and other people with type 1 diabetes. That impact



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comes from her dedication to participating in clinical trials testing new technologies for type 1 diabetes management, including the NIDDK's International Diabetes Closed-Loop (iDCL) Study. "I honestly have lost count," she says, but "I have been in the neighborhood of 10 to 12 trials."

***Says Elena of clinical study participation: "I would absolutely recommend anyone who is interested in a trial to take a look at what's available in your area."***

Elena's journey to participating in clinical trials began soon after her diagnosis when she did research on the Internet to figure out what diabetes management devices might work best for her. She decided to start using a continuous glucose monitor (CGM), which she liked because it let her see changes in her blood sugar levels in real time so that she knew when she needed to administer insulin. Even with the CGM, managing her type 1 diabetes was a lot of work. "It required constant attention," she says, "I really had to stay on top of it all the time." Through the Internet, Elena also heard about a peer support conference where people with diabetes got together to share experiences. That conference gave her needed perspective that she was not alone in trying to figure out how to manage her disease, and it was "where I first heard of the idea of getting involved in a clinical trial," she recalls.

Elena discovered that Sansum Diabetes Research Institute (SDRI) in Santa Barbara, California, was not too far from her home, and they were conducting trials testing new artificial pancreas technologies. Such trials were particularly appealing to Elena because she would be testing devices that could potentially manage her diabetes better than she could with less burden, so it did not take long for her to sign up for her first trial. Since then, Elena has personally witnessed the evolution of artificial pancreas clinical trials—from early trials when she stayed overnight at SDRI and study staff monitored her constantly to ensure that early prototype

systems did not cause a medical emergency, to the iDCL trial when device safety had advanced so far that she could do the trial at home without any remote monitoring.

When she first heard about it in August 2018, Elena was very excited about the iDCL trial and about possibly using the Control-IQ artificial pancreas system, so she signed up through SDRI—one of seven participating sites. Participants were randomly assigned to either the Control-IQ group or to the trial's control (or comparison) group—that is, the group who did not use the advanced system. This group used sensor-augmented pump (SAP) therapy, which includes a CGM and an insulin pump, but not the technology that automatically calculates and administers insulin doses. When Elena heard that she was assigned to the SAP group, "I felt really disappointed," she admits. However, she quickly realized, "Somebody has to be in the control group because ... there has to be some kind of comparison to show that the [artificial pancreas device] works and is effective."

After 6 months, participants in the SAP group, including Elena, were switched to the Control-IQ system as part of a trial extension phase. The timing for switching to the Control-IQ system could not have been better for Elena—it helped ease her diabetes management burden during some challenging personal times. When she received the Control-IQ system, her younger daughter had recently gotten engaged, so Elena was very busy helping with wedding planning. Even though she was extremely happy for her daughter, she was also soon facing an empty nest, as her older daughter was already married and out of the house. That would be a difficult transition for Elena, particularly because her daughters had been homeschooled and she was used to having them home all the time. After the wedding, she and her husband drove to the Midwest to help the recently married couple move. Between the wedding and the move, it was a chaotic time. "I felt like I had so many things to think about.... I just didn't have as much

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mental energy to spare on diabetes,” she remembers. She was happy that she did not have to put nearly as much work into managing her type 1 diabetes as usual—she relied on the Control-IQ system to do it for her. “I really felt like that [Control-IQ] study pump was fantastic,” she states.

Elena and her husband returned home to California from the Midwest, thinking that things would finally calm down. However, just a few days later, the morning of Independence Day 2019 brought more upheaval: a major earthquake. “Everything in my house sounded like it was going to fall down on the ground,” Elena describes. She and her husband spent their holiday cleaning up and feeling fortunate that they were not injured. Then on July 5: another earthquake. “It hit hard,” Elena states, “I could tell this was worse than the one we just had.” All Elena and her husband could do was try to survive while watching their belongings crash to the ground and parts of their house fall apart. Thankfully, they were not hurt, and again she felt grateful to have the Control-IQ system. As she explains, “I didn’t have a single spare second to think about diabetes.”

***While using an artificial pancreas system in a clinical trial, Elena says, “I definitely feel like my mental health improved.... I’m not having to babysit my blood sugar 24/7.”***

From these experiences, Elena realizes that the benefits of the artificial pancreas system for her were not measured by her traditional diabetes health numbers, such as HbA1c levels, which were already in the recommended range and improved modestly while on the system. Rather, “I definitely feel like my mental health improved.... I’m not having to babysit my blood sugar 24/7, and yet I’m getting as good or slightly better results [managing

blood sugar levels] as I was doing on my own.” She also says that the device was a huge help at night. “Prior to using the closed-loop system, I was waking up every night because of diabetes,” she recalls. With the closed-loop system, “I didn’t wake up anymore for high or low blood sugars. I could just sleep as much as I could sleep because the pump was able to handle it.... I woke up every morning with a clean slate.”

Elena also says that a big benefit to using an artificial pancreas system is that a computer, unlike a person, “is unemotional.... It can take care of your blood sugar better than you can because it doesn’t get tired or frustrated or annoyed.” During the trial, the computer was unfazed by serious personal stress—whether it be the happy stress of a wedding or the life-threatening stress of earthquakes. The system managed her diabetes through challenging times when Elena would have had difficulty doing so herself.

As for her clinical trial experiences, “I cannot say enough good things about the study team at SDRI,” Elena says. “I have always felt that they have been encouraging, helpful, and respectful.” She quickly adds: “I would absolutely recommend anyone who is interested in a trial to take a look at what’s available in your area.”

Elena is also happy that her steadfast participation in clinical trials has contributed to the availability of new type 1 diabetes management devices. When she sees people get excited about a new device that she helped test and talk about how it works great for them or their children, she thinks to herself: “That’s really neat. I had something to do with that.” It is only through the generous contributions of Elena and other clinical trial participants that new artificial pancreas devices and other type 1 diabetes management technologies have come to fruition.

## Contributing to Type 2 Diabetes Prevention Research

Type 2 diabetes is the most common type of diabetes and develops when the body can no longer overcome “insulin resistance” to keep blood sugar (glucose) levels from getting too high. Our bodies extract energy from the foods we eat, converting it into the form of blood sugar that is the main fuel used by our body’s cells. The hormone insulin is made by the pancreas and acts in the tissues of the body (e.g., muscle) to promote absorption of sugar from the blood. In some people, their bodies can become resistant to insulin, requiring the pancreas to produce more of the hormone to keep blood sugar at a healthy level. Type 2 diabetes develops when the pancreas loses its capacity to produce enough insulin to compensate for the body’s insulin resistance. More than 100 million Americans have type 2 diabetes or are at risk of developing the disease, which increases risk of cardiovascular disease, kidney disease, blindness, and numerous other serious complications. The good news is that thanks to years of research, we now know steps we can take to prevent or delay its development. With the help of thousands of research participants from around the country, NIDDK-supported scientists embarked upon a decades-long journey to demonstrate that type 2 diabetes is preventable as demonstrated in the highly successful, landmark Diabetes Prevention Program (DPP) clinical trial. (See inset for the story of a DPP participant.)

### A LANDMARK STUDY IS LAUNCHED

In the early 1990s, the prevalence of type 2 diabetes was increasing at an alarming rate, and evidence from observational and interventional studies suggested that lifestyle factors might be the cause. In 1996, the NIDDK launched the DPP—a randomized, controlled clinical trial conducted at 27 clinical centers—to assess whether a lifestyle

intervention or the drug metformin (a safe, generic medicine used to treat type 2 diabetes) could prevent or delay the disease. The DPP was also co-sponsored by others. The trial enrolled 3,234 participants who were at high risk of developing type 2 diabetes. Among the participants, 55 percent were Caucasian, and 45 percent were from racial/ethnic minority groups at disproportionately high risk for the disease. Many of the participants were over 60 years old, were women who had developed gestational diabetes during pregnancy, or had a family history of type 2 diabetes—all factors associated with higher risk for the disease. Participants were then randomly assigned to 1 of 3 groups: (1) a lifestyle intervention group that received intensive training and coaching to help participants lose a minimum of 7 percent of their body weight and maintain that weight loss through diet and enhanced physical activity (defined as moderate exercising at least 150 minutes per week); (2) a metformin group in which participants took metformin twice a day and received standard advice about diet and physical activity; and (3) a placebo group that received pills with no therapeutic effect, rather than metformin, along with the same standard advice about diet and physical activity. The metformin and placebo study components were “blinded,” meaning that neither the participants nor the study scientists who worked with them knew which people were in group 2 or group 3.

### SUCCESS IS ACHIEVED

After 3 years, the DPP showed that participants assigned to the lifestyle intervention lowered their chances of developing type 2 diabetes by 58 percent compared with participants who took a placebo. The intervention was effective for all participating racial

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and ethnic groups and in both men and women. It worked particularly well for participants ages 60 and older, lowering their chances of developing the disease by 71 percent.

Taking metformin was also found to prevent the disease, though to a lesser degree overall. Participants who took metformin lowered their chances of developing type 2 diabetes by 31 percent, compared with those who took a placebo pill. Metformin was effective for all participating racial and ethnic groups and both men and women. It was most effective in women with a history of gestational diabetes, in people who were between the ages of 25 and 44 when they began taking the medication, and in people with obesity who had a body mass index of 35 or higher.

Because the results were so compelling, the trial ended early in 2001. Soon thereafter, all participants were provided a modified, group-based version of the DPP's lifestyle intervention.

## BUILDING UPON THE SUCCESS

Beginning in 2002, the DPP Outcomes Study (DPPOS) began monitoring most of the participants initially enrolled in the DPP to determine if the lifestyle intervention or metformin continued to delay the development of type 2 diabetes over time, whether they affected other measures of health and well-being, and whether they were cost-effective. There were some changes made to the groups: while each group was offered lifestyle-change classes, the original lifestyle intervention group received more intensive coaching to reinforce self-management behaviors for weight loss; and the metformin group continued to take metformin, but not in a blinded fashion. (The original placebo group no longer took a placebo pill.)

After 10 years, the DPPOS found that participants enrolled in the intensive lifestyle intervention continued to have a lower rate of disease development by 34 percent compared to the original placebo group, and those who were 60 years or older when first enrolled in the DPP continued to have an even

lower rate of disease by 49 percent with the intensive lifestyle intervention compared to placebo. Those who were in the metformin group had a lower rate of disease by 18 percent compared to placebo. Participants from all three groups improved their risk factors for cardiovascular disease, but those in the lifestyle intervention group required fewer medications to do so than those in the other groups. In addition, the lifestyle intervention was shown to be cost-effective, and metformin was shown to be cost-saving. At the 15-year follow-up, participants enrolled in the lifestyle intervention continued to experience a 27 percent lower rate of disease onset, while participants taking metformin had an 18 percent lower rate of disease development.

The NIDDK continued to build upon the success of the DPP/DPPOS findings by funding research to develop cost-effective adaptations of the lifestyle intervention that could be delivered efficiently to millions of Americans who would stand to benefit. The Centers for Disease Control and Prevention also scaled up related, national efforts, calling it the National Diabetes Prevention Program. And in 2018, the Centers for Medicare & Medicaid Services began coverage of certain lifestyle change program providers for Medicare beneficiaries with prediabetes.

The current phase of the DPPOS aims to determine the effects of metformin on the prevention of cancer, cardiovascular disease, and other age-related health issues and continues to assess diabetes prevention.

The NIDDK-supported DPP/DPPOS is one of the largest and longest ongoing prevention studies of its kind. Its results demonstrate that prevention or delay of type 2 diabetes is possible and can yield other important health benefits. The long-term durability of the response to lifestyle intervention and metformin in preventing or delaying development of diabetes, still persisting many years after participants entered the program, is a testament to the power of the interventions and their value in reducing disease. The success of this program will continue to depend upon the thousands of participants that contribute their time and efforts to advancing this important research effort.

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## PAMELA'S STORY



*Pamela, pictured, participated in an NIDDK-supported clinical trial to prevent or delay type 2 diabetes*

Pamela, a 72-year-old communications specialist who lives in the Washington, D.C., area and has written for both *Reader's Digest* and *McCall's Magazine*, had always lived an active lifestyle, having been an avid runner and even a member of a ski team. It's not surprising she takes her health seriously since her mother, who had type 1 diabetes, always taught Pamela and her five siblings from a young age to value their health and made sure they recognized the importance of maintaining a healthy lifestyle. So, in the summer of 1997 when Pamela received a postcard in the mail that invited her to be tested to see if she qualified for participation in a new research study on possible ways to delay or prevent the development of type 2 diabetes, she jumped at the chance. "I went in, got tested, and found out I had prediabetes, which qualified me for the study ... so I signed up right away." She was randomized to the Diabetes Prevention Program (DPP) lifestyle intervention group on October 1, 1997, and so her journey of participating in a clinical trial began.

After several months of diet and exercise with support from DPP clinicians, Pamela achieved

her initial goals and even surpassed her 7 percent weight-loss target. She does admit, though, that it was not always easy. In the beginning, she did not quite care for documenting everything she ate, though she appreciated the study coordinators. As she puts it, "I was judging myself ... but the study coordinators had no judgment. They were data-driven and incredibly supportive and encouraging to all of the participants." She says the intervention changed the way she approached her daily activities—it forced her to pay close attention to exercise consistency, portion sizes, and reading nutrition labels.

After those initial months of the lifestyle intervention, the good results for Pamela just kept coming. She put in the effort and learned that, with the support of her DPP doctor and study coordinators, she had the power to change the course of disease. Part of that support included the fact that the DPP team organized group events, such as holiday dinners and baseball games, so that participants could meet and inspire each other. The study team even encouraged them to bring along friends, which turned out to be helpful to Pamela. "If I bring a friend to an outing, maybe the next day I recruit them for a run. It's easier to exercise with a friend."

***"Historically," Pamela says, "it has been difficult to get African Americans to participate in any research study. I realized if I don't participate [in the Diabetes Prevention Program/ Outcomes Study], scientists won't have the critical data they need.... Diseases manifest differently in different races and sexes ... it's so important."***

Soon after the DPP came to an end, and the DPPOS was beginning, Pamela knew she would remain a participant. She had worked hard and had seen the fruits of her labor—losing weight and preventing her prediabetes from progressing to

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type 2 diabetes—but that wasn't the only reason. She was also motivated by her mother's fight with her illness, and she realized the significance of her participation in clinical research. "Historically," she says, "it has been difficult to get African Americans to participate in any research study. I realized if I don't participate, scientists won't have the critical data they need.... Diseases manifest differently in different races and sexes ... it's so important."

Beyond the recommended goals of weight loss and exercise, Pamela also noticed the DPP lifestyle program provided her with other health benefits like better stress management. Life has a way of handing you challenges, and it certainly did for Pamela. Throughout her years in DPP, she drove her mother to medical appointments because her job afforded her more flexibility than her siblings, and she helped her mother deal with many of the complications common to both major forms of diabetes. In 2002, Pamela's region was rocked by a frightening development—a sniper began terrorizing the area at random. This effectively halted her outdoor runs. And, in 2008 the economic recession hit, which negatively impacted Pamela's consulting job as a writer. But she looked to the knowledge she had gained about lifestyle change from being a DPP participant and was able to minimize her stress through breathing techniques, in addition to keeping her diet and exercise routine as healthy as possible when each change in circumstances arose.

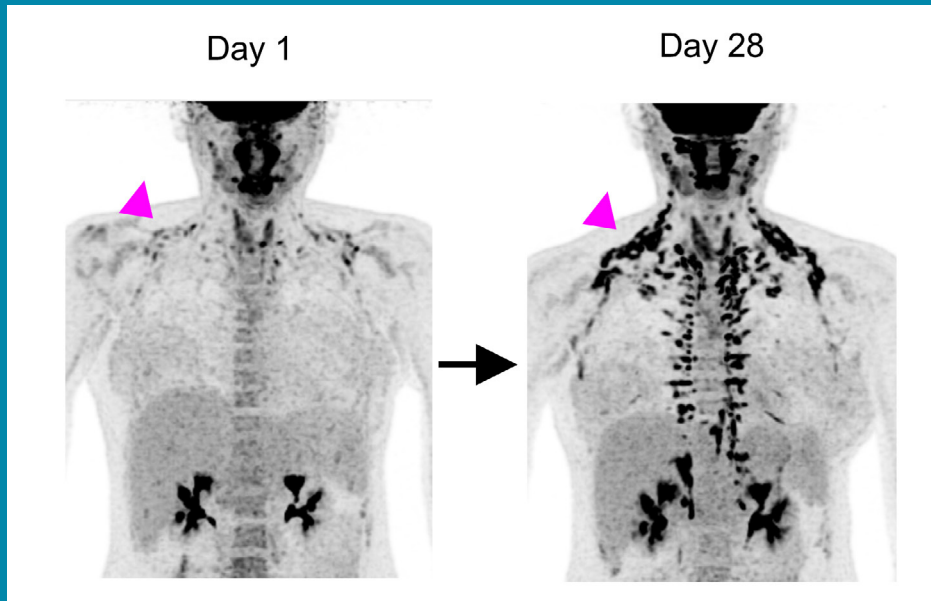
Pamela has now been a participant in DPP/DPPOS for more than 23 years, a remarkable contribution to scientific research—and also to her own

health. Today, not only has she prevented the development of type 2 diabetes, but she no longer has prediabetes and has achieved and maintained an impressive 12 percent weight loss—a testament to her incredible dedication to maintaining a healthy lifestyle as a DPP/DPPOS participant. When discussing her appreciation and respect for the DPP doctors and nurses, she goes so far as to say if she had to do it all over again, she would choose a career in science or medicine. "This is one of the best things to ever happen to me, to have had this opportunity to be part of this program.... Self-management is a discipline. It's not always easy, but it's something we need to strive for. It's a journey, and DPP was the catalyst for me."

***Talking about her experiences in the Diabetes Prevention Program clinical trial, Pamela says: "This is one of the best things to ever happen to me, to have had this opportunity to be part of this program."***

Pamela is proud to have contributed to the DPP's success, and when asked what she would tell someone considering participating in a similar clinical trial she doesn't hesitate: "I'd tell them to do it! And, I'd even go with them!" Without Pamela and her fellow DPP/DPPOS participants, there might still be no proven way to prevent type 2 diabetes. Thanks to their efforts, a healthier world has become possible.





As described in this chapter, researchers are studying new approaches to increase brown fat levels in people as a strategy to combat metabolic disorders. The human body contains multiple types of fat. White fat stores calories, and too much white fat increases the risk for the myriad co-morbidities associated with obesity, such as type 2 diabetes. A less abundant type of fat called brown fat burns calories and may help regulate blood glucose (sugar) and cholesterol. In a recent study, NIDDK intramural researchers examined whether the drug mirabegron can increase the levels of brown fat in healthy women to potentially fight the negative effects of weight gain. (This drug is currently approved for treating a different condition, overactive bladder.) As measured by body scans known as PET/CT, shown here, they found that brown fat activity increased after 28 days of mirabegron treatment (magenta arrow, right panel) compared to day 1 of the study (magenta arrow, left panel). The women also had increased insulin sensitivity, a marker of reduced diabetes risk. Examining other health outcomes, the researchers found improvements in some heart disease risk markers, although at the amount of drug used in the study, higher than the currently approved dosage, the participants also had increased heart rate and blood pressure. In future research, scientists could examine the effects of this drug in people with insulin resistance, a risk factor for developing type 2 diabetes, and test other potential medications that work similarly, to see if they have reduced cardiovascular risks. This chapter also includes a summary of a research advance by another team of scientists, who studied the effects of mirabegron on beige fat in a different group of people. The results from these studies could thus lead to a safer, effective way to activate brown/beige fat and potentially treat metabolic disease.

*Images courtesy of Dr. Aaron M. Cypess, NIDDK. Republished with permission of the American Society for Clinical Investigation, from Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity, O'Mara AE, Johnson JW, Linderman JD,...Cypess AM, J Clin Invest, Volume 130 (5), Copyright 2020; permission conveyed through Copyright Clearance Center, Inc.*



# Obesity

*Obesity has risen to epidemic levels in the United States. Individuals who have obesity may suffer 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 the NIDDK's mission. More than 40 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</sup> More than 19 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>2,3</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 that promote increased caloric intake and sedentary lifestyles. Diet, activity, and aspects of our environment may also modify biologic 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.

The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental interventions in families and in health care 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.

The 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.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter.

## **BARIATRIC SURGERY: NEW INSIGHTS INTO EFFECTS ON WEIGHT LOSS AND METABOLISM**

### **Comparing Surgical Treatment and Non-surgical Care for Long-term Weight Loss:**

Researchers have found that people with severe obesity who underwent bariatric surgery had significantly more short- and long-term weight loss compared to those who did not have surgery. Bariatric surgery can be an effective tool for treating severe obesity, leading to significant weight loss and improved health outcomes. However, few people with severe obesity opt to undergo bariatric surgery. This suggests that more data are needed about the long-term outcomes in people who have undergone bariatric surgery compared to those who have not had surgery, to help inform clinical decision making.

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<sup>1</sup> Hales CM, et al. 2020. CDC. National Center for Health Statistics Data Brief No. 360.

<sup>2</sup> Fryar CD, et al. 2020. CDC. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats.

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

To help fill this knowledge gap, scientists analyzed data from the health records of women and men with severe obesity enrolled in a managed health care system. The study sample included over 31,000 people who had undergone a bariatric surgery procedure—either Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG)—as well as nearly 88,000 people who did not have bariatric surgery. Those who did not have surgery received usual medical care, which typically did not include treatment specifically for obesity. The scientists examined the level of total weight loss at 1, 5, and 10 years post-surgery, and at similar timepoints for those in the non-surgical group. After 1 year, people who had RYGB or SG lost about 28 and 23 percent of their body weight, respectively, which was much higher than the 0.2 percent weight loss observed in the non-surgical group. After 5 years, there was some weight regain in the people who had bariatric surgery, so the total weight loss decreased to about 22 percent in the RYGB group and 16 percent in the SG group. However, those levels still exceeded the 2.2 percent weight loss seen in the non-surgical group after 5 years. After 10 years, significant differences persisted: 20 percent weight loss in the RYGB group and 4.8 percent in the non-surgical group. The 10-year data could not be assessed for the SG group because it is a more recent procedure, though it is now the most common form of bariatric surgery. Although the data showed that people who underwent bariatric surgery regained weight over time, regain to within 5 percent of their pre-surgical weight was rare.

Overall, the researchers found that, for people with severe obesity, both RYGB and SG resulted in much more short- and long-term weight loss compared to non-surgical care. Bariatric surgery has serious surgical risks, and lifetime risk remains unknown; however, severe obesity also increases risks for serious diseases. Thus, this study contributes important new information for people with severe obesity and their health care providers as they consider both the risks and benefits of different treatment approaches.

Arterburn DE, Johnson E, Coleman KJ,...Haneuse S. *Weight outcomes of sleeve gastrectomy and gastric bypass compared to nonsurgical treatment.* *Ann Surg* PMID: 32187033, 2020.

**Diet Versus Surgery for Metabolic Health: Weighing the Benefits for People with Obesity and Type 2 Diabetes:** New research shows that the metabolic benefits of gastric bypass surgery and diet in people with obesity and type 2 diabetes are similar and related to weight loss itself with no evidence of clinically significant effects independent of weight loss.

Studies have suggested that surgical procedures to treat obesity that involve bypass of part of the gastrointestinal tract, such as Roux-en-Y gastric bypass, have unique therapeutic effects on blood glucose (sugar) control that are independent of weight loss. However, results of such studies are complicated by the differences in weight loss among people who undergo procedures. To investigate these effects further, researchers in this study evaluated markers of glucose control before and after matched amounts of weight loss induced either by gastric bypass surgery or diet alone in 22 women and men with obesity and type 2 diabetes. The scientists used techniques to measure how well an individual metabolizes glucose and how sensitive an individual is to insulin. Following weight loss of about 18 percent of their initial weight, participants had their blood glucose tested after a meal. Levels of blood glucose were lower in both the surgery and diet groups than before weight loss, indicating metabolic improvements. There was a higher initial peak, followed by a decrease, in blood glucose in the surgery group after food consumption, likely due to the marked increase in rate of delivery of nutrients into circulation due to a restructured gastrointestinal tract. The researchers also found that insulin sensitivity (a measure of how well the body responds to insulin) in the liver, skeletal muscle, and adipose (fat) tissue increased similarly in both groups after weight loss. In addition, beta cell function (a measure of insulin secretion relative to insulin sensitivity) increased similarly in both groups.

The nearly identical benefits of matched weight loss in the surgery and diet groups underscore the profound effects of substantial weight loss on metabolic function in people with type 2 diabetes, and these results challenge the notion that gastric bypass surgery has clinically meaningful effects on metabolic health that are independent of weight loss. However, there remains difficulty in achieving

and maintaining substantial weight loss with diet and other lifestyle changes alone. Therefore, further research is needed to attain the same long-term metabolic outcomes in people with obesity and type 2 diabetes without surgical intervention.

*Yoshino M, Kayser BD, Yoshino J,...Klein S. Effects of diet versus gastric bypass on metabolic function in diabetes. N Engl J Med 383: 721-732, 2020.*

## STIMULATING BEIGE FAT FORMATION

### **Beige Is All the Rage: Drug Treatment Stimulates Beige Fat Formation Resulting in Metabolic Health Benefits in People with Obesity:**

Researchers have shown that treatment with the drug mirabegron, which is approved to treat overactive bladder, stimulates the formation of beige fat tissue in people with insulin resistance and overweight/obesity resulting in several metabolic health benefits, including improved blood glucose (sugar) metabolism. Among different types of fat tissue, brown fat is a form of fat that burns calories (energy) to generate heat, unlike white fat, which is more abundant in the body and stores energy. Beige fat cells, which have similar energy-burning properties to brown fat, can be formed in white fat by cold exposure or through activation of the protein  $\beta$  (beta)3 adrenergic receptor ( $\beta$ 3AR), which is present in fat cells and some bladder cells and can be stimulated by mirabegron. Recent studies in mice have demonstrated that beige fat cells can improve glucose metabolism. However, no study had demonstrated a link between beige fat and glucose metabolism in humans.

Investigators recruited 13 women and men, who had overweight/obesity along with either prediabetes or metabolic syndrome, and treated them with mirabegron at the maximal dose approved (50 mg/day) for 12 weeks. Following mirabegron treatment, more than half of the participants who had prediabetes prior to treatment no longer met criteria for that condition. This finding was consistent with overall improvement of glucose tolerance, a marker of how well the body handles blood glucose. Researchers then further examined the participants to measure the function of  $\beta$  cells, which produce the insulin

necessary for processing glucose, and how well other tissues respond to insulin (insulin sensitivity). The results indicated that an improvement in both measures led to the improved glucose tolerance. Typically, improved glucose tolerance in people with prediabetes or type 2 diabetes is associated with weight loss. However, interestingly, the participants in this study did not experience weight loss. When the researchers examined how mirabegron treatment affected certain molecular markers known to be present in beige fat, they saw an increase in several of these markers in white adipose tissue, indicating the formation of beige fat cells in response to the drug. These changes correlated with the improved glucose metabolism. The scientists then examined effects on skeletal muscle, and they found that mirabegron treatment induced a beneficial switch in the type of muscle fibers in this tissue, which could account for improvements in insulin sensitivity in muscle. Remarkably, neither  $\beta$  cells nor skeletal muscle cells have the  $\beta$ 3AR protein—and thus the beneficial effects of the drug must have been indirect, likely via mirabegron-induced changes in fat tissue. In further experiments, using muscle cells in laboratory culture dishes, the researchers deduced that the effects on fiber type were a result of white adipose tissue “beiging” and sending out a signal to the skeletal muscle cells.

This study demonstrated for the first time in people with overweight/obesity and insulin resistance that mirabegron treatment improves multiple measures of glucose metabolism by inducing beige fat formation in white adipose tissue. In contrast to the increase in beige fat, an increase in brown fat was not observed in this study, but another recent study conducted by intramural NIDDK researchers demonstrated that brown fat is activated by mirabegron in a group of healthy women. While more research is needed to determine the long-term effects of mirabegron treatment on metabolism and if mirabegron can delay the onset of or even reverse type 2 diabetes, the present study brings scientists closer to identifying a safe, effective way to induce beige fat formation and potentially treat metabolic disease.

*Finlin BS, Memetimin H, Zhu B,...Kern PA. The  $\beta$ 3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. J Clin Invest 130: 2319-2331, 2020.*

## UNDERSTANDING HOW HIGH-FAT FOODS AFFECT CALORIE CONSUMPTION

### Your Brain on High-fat Food: Why Diets May Fail:

Researchers have discovered that consumption of a high-fat diet (HFD) suppresses the desire to eat healthier, more nutritional food, and that this devaluation of healthy food is rooted in the brain.

It is well known that humans prefer to consume energy-rich, high-fat foods and that exposure to such diets can lead to overconsumption of calories, weight gain, and the numerous health complications that can accompany overweight/obesity. The urge to consume high-fat foods is compounded by an accompanying lack of desire to eat nutritional food that may be perceived as less palatable. However, the reasons behind this remain poorly understood. To determine how high-fat food affects calorie consumption, researchers split adult male and female mice into two groups. Both groups began with unlimited access to a nutritionally balanced standard diet (SD). One group remained on the SD for the duration of the study, while the other group was given unlimited access to both the SD and 60 percent HFD for 8 weeks, followed by removal of the HFD for a 2-week withdrawal period. HFD-exposed mice exhibited an immediate preference for the high-fat food in lieu of the healthier SD, and only the HFD-exposed mice increased total daily calorie consumption and gained weight. Every HFD-exposed mouse displayed a marked reduction in SD consumption, and, remarkably, HFD removal resulted in rapid weight loss and a failure to consume daily required calories from the SD. This self-restricted caloric deprivation indicated that the mice no longer valued SD food. Moreover, after 2 weeks without access to a HFD, body weight and caloric consumption did not recover to baseline levels, indicating a prolonged physiological adaptation. Since several brain circuits, namely in a region of the brain called the hypothalamus, govern the drive to eat, the researchers next recorded activity of brain cells called AgRP neurons in mice transitioned to and from a HFD and compared those to recordings from mice on a SD. Hunger activates AgRP neurons and stimulates the drive to eat; food intake then suppresses AgRP activity. When the researchers presented the mice with a SD, they observed robust inhibition of AgRP activity, followed by similar food intake in each feeding session. However, when mice were provided with a HFD, they had significantly reduced AgRP responses

to a SD—indicating that they no longer perceived SD as something that could alleviate their hunger. Notably, SD still did not quiet the hunger signals from AgRP neurons even after a 2-week HFD withdrawal, analogous to a strict diet in humans, emphasizing a prolonged effect from a HFD on this neural signaling system. In addition, the researchers observed changes in the brain chemical dopamine, known to play a critical role in reward pathways. Dopamine release was enhanced in mice that were fed a SD. However, after 1 week of HFD access, the scientists observed reduced dopamine release in response to a SD, further enforcing the concept of devaluation of nutritional food after exposure to a HFD.

Though these findings will need to be confirmed in humans, taken together, they reveal a neural basis behind why we may be driven toward calorie dense, highly palatable, less nutritional food and help explain the challenges of dieting in an obesogenic environment—where such food is readily available. Further research will be critical to developing therapeutics that can potentially target specific brain signaling pathways in response to certain diets.

*Mazzone CM, Liang-Guallpa J, Li C,...Krashes MJ. High-fat food biases hypothalamic and mesolimbic expression of consummatory drives. Nat Neurosci 23: 1253-1266, 2020.*

## MOLECULAR UNDERPINNINGS OF EXERCISE

We know exercise is good for us. It helps build muscle, burn fat, and can even improve our moods. But long before we notice changes in our physique, there are hidden, more immediate, molecular and cellular changes taking place inside our bodies—changes that could improve blood glucose (sugar), metabolism, or even stave off disease. It has been posited for some time that communication between different types of cells is critical for regulating metabolism and organ function, but the exact players involved remained unknown. Moreover, previous studies have examined selected changes in metabolic, cardiovascular, and immune pathways, but a systemic molecular response to exercise has not been fully characterized. In the recent advances described below, researchers performed a system-wide, comprehensive, molecular profiling before and after a brief bout of intense physical activity and investigated adaptive immune changes in response to sustained exercise. Their

findings provide insight into why exercise is beneficial to our health, highlight precise molecular factors involved, and have potential implications for diagnostic tests in a health care setting.

### **A Physiological Dance: How a Brief Bout of Exercise Initiates a Molecular Choreography of Events:**

Through a highly comprehensive analysis, researchers have revealed molecular changes involved in a choreography of biological processes, including metabolism, inflammation, cardiovascular function, and tissue repair, that occur in humans in response to an acute bout of exercise. By analyzing blood components before and after a controlled session of physical activity, they provide a window into the dynamic nature of the impact of exercise on human molecular physiology.

To understand how exercise is beneficial to our health, a team of researchers set out to identify the precise molecular fluctuations that are triggered by physical activity and which lead to improved health and fitness. In this study, they took hundreds of thousands of measurements from 36 male and female participants, ages 40 to 75 years; many of the participants also had insulin resistance, a condition associated with obesity, diabetes, and prediabetes. Before a treadmill test, the researchers took a baseline blood sample. Participants then wore an oxygen-measuring mask and exercised for about 8 to 12 minutes, until they reached peak oxygen consumption—the gold standard for measuring aerobic fitness. The researchers took blood samples from participants 2 minutes, 15 minutes, 30 minutes and 60 minutes after they stopped exercising. It turns out that shortly after exercise, the body experiences a whirlwind of molecular activity. Molecular markers of an immune response, inflammation, and “oxidative stress” spiked sharply in most people directly following exercise, which is indicative of skeletal muscle strain and tissue healing as the body begins to recover. They also saw an increase in markers of lipid (fat) metabolism. Exercise also triggered the release of several hormones to restore metabolic balance, and the researchers observed a distinct positive correlation between glucose and insulin levels; insulin secretion enhances the body’s ability to absorb glucose to meet higher energy demands. The team also observed a decrease in the appetite-associated hormones leptin and ghrelin, similar to previous studies. This finding suggests a role of physical activity in appetite regulation. Moreover, as part of the study, they

compared the molecular response of individuals who had insulin resistance to those who could process glucose properly. Several biological pathways were altered in individuals with insulin resistance, including a dampened immune response post-exercise. Finally, the team noticed clear associations between sets of molecules and peak oxygen consumption. For example, higher levels of molecules known to reflect poor metabolic health were associated with lower peak oxygen while healthy molecular profiles were associated with higher peak oxygen, therefore indicating enhanced cardiopulmonary capacity. These associations allowed the team to develop prediction models of fitness revealing potential resting blood biomarkers of peak oxygen consumption.

Taken together, these findings provide a first-of-its-kind comprehensive profile of post-exercise molecular fluctuations and illustrate the complex interplay between multiple biological processes. The results provide a window into why exercise is good for us and offer the potential to someday be implemented into health care settings as a personalized blood test for fitness to determine an optimal fitness regimen.

*Contrepois K, Wu S, Moneghetti KJ, Snyder MP. Molecular choreography of acute exercise. Cell 181: 1112-1130.e16, 2020.*

### **The Role of an Immune Protein in Metabolic Conditioning of Muscle to Sustained Exercise:**

Researchers have discovered that the immune protein interleukin-13 (IL-13) is activated by exercise, sustained by endurance training, and leads to enhanced muscle efficiency and improved blood glucose (sugar) in a coordinated manner that improves metabolic fitness.

It is known that exercise reduces the risk of developing many conditions, including metabolic syndrome and obesity, and previous studies suggested that immune signals may mediate the metabolic effects of exercise. To identify circulating factors induced by exercise, scientists examined a panel of proteins from the blood plasma of normal-weight sedentary women, endurance-trained female athletes, and women with obesity. They found that endurance-trained women had substantially higher levels of circulating IL-13, which is made by immune cells embedded in skeletal muscle, compared with the other groups. They found similar results when they analyzed blood plasma of normal-weight sedentary and endurance-trained men: male athletes had significantly higher levels of

IL-13 than their non-athletic counterparts. To gain more insight into the effects of IL-13, the scientists examined mice with and without this immune protein. When they genetically deleted IL-13 in mice and performed treadmill-running tests, the mice lacking the protein displayed a substantial reduction in running time and distance. Next, the researchers examined the levels of activity of genes in muscle tissue samples from normal and IL-13-deficient mice, with and without exercise. The results were consistent with the notion that exercise promotes a metabolic switch in muscle tissue from burning glucose as fuel to burning fatty acids, or the building blocks of fat, which maximizes energy efficiency. This metabolic reprogramming was lost in IL-13-deficient mice. Furthermore, the researchers found that endurance training, through IL-13 signaling, improved the running capacity and blood glucose levels of both male and female mice compared to untrained animals.

These results demonstrate that endurance exercise activates an adaptive response, which is an interaction between immune cells and muscle cells, that leads to a metabolic conditioning of muscle as a strategy for sustained physical activity while improving glucose tolerance. This research highlights the importance of immune signaling in metabolic fitness.

*Knudsen NH, Stanya KJ, Hyde AL,...Lee C-H. Interleukin-13 drives metabolic conditioning of muscle to endurance exercise. Science 368: eaat3987, 2020.*

## GUT MICROBIOME AND BODY WEIGHT

### How the Gut Microbiome Controls Daily

**Metabolic Rhythms:** New research has clarified how the microbes in the gut (*i.e.*, the gut microbiome) regulate mice's daily metabolic rhythms, affecting weight gain and metabolic health. An organism's metabolism changes in response to the cycle of day and night, and this "circadian rhythm" is associated with sleeping and feeding cycles. Some of these metabolic changes are regulated via modification to a cell's histones, the protein "spools" around which DNA is wound. Depending on histones' chemical modifications, they may allow or block access to genes, effectively turning specific genes on or off. Since the gut microbiome has also been linked to daily metabolic cycles, researchers asked if the microbiome uses host histone modification to control cyclic gene activity in the gut. To answer this question, the

scientists studied histone modifications in the small intestines of either normal or "germ-free" mice that lack all microorganisms. They found that histone modifications in germ-free mice's intestinal cells did not cycle daily as they did in normal mice. To study how the microbiome was causing this difference in histone modification, researchers surveyed the proteins, called histone deacetylases, which cause many of these modifications. The scientists identified one histone deacetylase in mice, HDAC3, that was not as abundant in germ-free mice as in normal mice and that, like the histone modifications, cycled differently in the presence or absence of a microbiome. Upon further study, researchers confirmed that the microbiome was required for HDAC3's recruitment to histones at target genes, suggesting that the microbiome was affecting HDAC3 activity. Studying a mouse model with an intact microbiome but without HDAC3 in its intestinal cells gave further clues to HDAC3's importance: a lack of HDAC3 resulted in disruptions in the daily activity cycles of over 2,700 genes in the intestinal lining. Taken together, these findings demonstrated that the microbiome controls HDAC3 activity to produce wide-reaching effects on the body. For example, many of HDAC3's target genes in the intestinal lining are involved in nutrient transport and metabolism. Furthermore, researchers discovered that HDAC3 controlled how intestinal cells took up nutrients during digestion, ultimately affecting the concentrations of metabolic products and lipids in the mice's blood. Because of these effects on nutrient uptake, the researchers also investigated HDAC3's role in diet-related obesity. They found that HDAC3 in the intestinal lining was required for the microbiome to promote obesity and other negative metabolic effects when mice were put on a high-fat diet. They even found that HDAC3 was important in weight gain induced by experimental jet lag, demonstrating another link between circadian rhythm, the microbiome, and obesity. Overall, these findings highlight a possible way in which the gut microbiome's regulation of its host's metabolism has significant impacts on metabolic health. Although future research is needed to determine if the microbiome and HDAC3 play similar roles in people, these experiments have identified possible new targets for the treatment of metabolic disease.

*Kuang Z, Wang Y, Li Y,...Hooper LV. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. Science 365: 1428-1434, 2019.*

# NIH Seminar Series: Obesity and Women's Health

## Obesity and Women's Health Virtual Symposium

September 10, 2020

NIH Obesity Research Task Force Seminar Series



Obesity prevalence continues to rise in the United States despite recognition of its many adverse health effects. More than two in three U.S. adults are considered to have overweight or obesity. Among women, although obesity and severe obesity have increased in all racial/ethnic groups over the past several years, the prevalence of both are greater in non-Hispanic Black women and Mexican American women compared to non-Hispanic White women. These disparities are particularly concerning given that obesity is a risk factor for adverse outcomes from the novel coronavirus, which has disparate outcomes in communities of color. In addition to its contribution to cardiovascular disease, breast cancer, and worse outcomes from COVID-19, obesity in women increases the risk for adverse conditions affecting almost every organ system including the reproductive system and lower urinary tract. To accelerate the development of new and innovative treatments for obesity in women and to close knowledge gaps, four leading scientists highlighted their research at a September 2020 virtual symposium. The research presented was supported by the NIDDK among other Institutes. The seminar was organized as part of the NIH Obesity Research Task Force Seminar Series.

Dr. Mercedes Carnethon from Northwestern University presented her research on the cardiovascular consequences of obesity in women. Her work focuses on multi-level risk factors including biological influences, individual health behaviors,

interpersonal and cultural aspects, and environmental factors. Vulnerable periods in a woman's life, such as the reproductive years and menopause, can trigger weight gain, which can in turn affect cardiovascular health. Individual behaviors including poor dietary intake and sleep disturbances (insomnia is more common in women than men) can all lead to metabolic disruptions like weight gain, altered glucose (sugar) metabolism, and hypertension. Moreover, social and environmental determinants such as income, education, socioeconomic status, and neighborhood safety disproportionately affect female-headed households and may increase risk for obesity in women in underserved minority communities. Finally, analyses have shown that weight loss interventions during critical periods of life when cardiovascular health declines are less effective in women than men. Further research is needed to tailor interventions to the cultural and interpersonal factors faced by women.

Dr. Richard Legro from Pennsylvania State University gave a thought-provoking presentation on obesity and female reproduction. Ample amounts of observational data suggest that obesity in women is associated with infertility and adverse pregnancy outcomes. However, Dr. Legro challenged this notion and questioned if the impact of obesity on fertility might be overestimated. He discussed results from several studies that assessed the impact of weight loss on pregnancy outcomes in women with obesity. One such study evaluated the effects of Roux-en-Y gastric bypass surgery on

female reproductive function and found that weight loss had no effect on the quality of ovulation. In another study that evaluated pregnancy outcomes after bariatric surgery, the investigators found that while weight loss was associated with reduced risk of gestational diabetes, the women who lost the most weight were at greater risk for preterm birth and for having infants that were smaller than average, compared to women with obesity who did not have surgical treatment. Finally, in the NIH-funded FIT-PLESE trial, researchers compared an intensive lifestyle intervention to a standard lifestyle intervention in women with obesity and unexplained infertility before the women had fertility treatment. While women in the intensive intervention group experienced greater improvements in metabolic syndrome, there were no differences between the two groups in healthy live births. Therefore, improvements in metabolic health did not equate to improvements in reproductive fitness. Dr. Legro concluded that while obesity is certainly a risk factor for many harmful conditions, obesity alone is not a major contributor to infertility and pregnancy complications.

Dr. Jennifer Ligibel from the Dana-Farber Cancer Institute at Harvard Medical School presented research linking obesity to breast cancer risk and outcomes. Observational evidence shows a strong link between obesity and breast cancer risk. In addition, obesity is linked to recurrence in breast cancer survivors and mortality rate. The strongest evidence that weight loss could reduce cancer risk comes from bariatric surgery studies—bariatric surgery was associated with a lower risk of cancer, including postmenopausal breast cancer, in women with severe obesity. The National Cancer Institute-supported **Breast Cancer WEight Loss (BWEL)**

clinical trial enrolled participants with stage II-III breast cancer who also had overweight/obesity, and randomly assigned them to either a health education and weight loss intervention group or a health education alone group to assess the impact of a weight loss intervention on survival. This large-scale study is ongoing. BWEL and other ongoing trials have the potential to provide more definitive evidence regarding whether weight loss and other lifestyle changes after cancer diagnosis could reduce the chance of recurrence and improve survival.

Dr. Leslee Subak from Stanford University presented research on lower urinary tract symptoms (LUTS) and obesity in women. LUTS include issues such as urinary incontinence (UI) or loss of bladder control, frequency of urination, and urgency of urination, among others. Urinary incontinence is highly prevalent among women and has a negative impact on quality of life. The biggest risk factor for developing UI is body weight, and the majority of women with UI have overweight or obesity. As part of the Program to Reduce Incontinence by Diet and Exercise (PRIDE), Dr. Subak described studies that assessed the effect of weight loss on UI. The studies found that a reduction in weight was associated with substantial improvements in UI and other urinary tract symptoms such as urgency. Similarly, the Longitudinal Assessment of Bariatric Surgery (LABS) observational study found that a substantial reduction in weight could lead to UI remission.

The seminar also included a lively discussion among speakers and participants on current challenges and opportunities. Continued research in this important area can potentially reveal better ways to prevent and treat obesity in women, thereby preventing many adverse health outcomes.







As described in this chapter, researchers have developed a groundbreaking new mouse model of celiac disease that, in the presence of dietary gluten, mimics the immune system features and gluten-dependent intestinal damage seen in people with this disease. Celiac disease is an autoimmune reaction in the small intestine that is triggered by consuming gluten, a protein found mainly in foods containing wheat, barley, and rye. Shown here are cross-sectional images of the small intestine in the new mouse model, which is the most accurate animal model for celiac disease to date. These mice have a healthy small intestine when fed a gluten-free diet (far left image), with the wall of the small intestine lined with fingerlike structures, called villi, that project into the intestinal space and help the gut absorb materials by increasing its internal surface area. However, the villi become damaged (middle image) when mice eat gluten for 30 days. This damage is reversed (far right image) when mice that were given gluten are put back on a gluten-free diet. This mouse model could be a useful research resource for gaining new insights into the underlying causes of celiac disease and for discovering and testing new therapies.

*Images provided by Drs. Valérie Abadie and Bana Jabri, University of Chicago. Reprinted by permission from Springer Nature: [Nature](#); 11-15, gluten and HLA-DQ8 drive tissue destruction in coeliac disease; Abadie V, Kim SM, Lejeune T,...Jabri B; 578: 600-604. Copyright 2020.*

# 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. The latest concerted effort to address the burden of all digestive diseases combining multiple 2016 national data sources 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 2016 national inpatient samples identified 4.1 million hospitalizations with a primary diagnosis of digestive diseases and 15.9 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 19.2 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling \$94.9 billion in 2016.<sup>3</sup>*

Some digestive diseases are common and others quite rare. Yet collectively, they strike individuals across the lifespan, exacting a significant toll on public health in terms of their effects on quality of life, years lost due to premature death, and costs associated with hospitalization and pharmaceutical and surgical interventions. NIDDK-supported scientists are vigorously pursuing research with the ultimate goal of reducing the public health burden associated with digestive diseases. Such efforts aim to better understand how widespread these diseases are across the United States and in specific population groups, to identify their causes and how they progress, and to test new interventions for prevention and treatment, including drugs, surgery, and behavior modification.

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, are marked by damaging inflammation in the intestinal tract leading to rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. These diseases often strike early in life, with a peak age of onset in adolescence or young adulthood. Treatment frequently requires prolonged use of multiple drugs and may require surgery, including removal of the affected region of the intestine. Scientists are investigating the complex interactions among the genetic, environmental, immune, microbial, and

other factors that contribute to, or protect against, the development of IBD. The continued discovery of predisposing genetic variations, potential autoimmune and microbial influences, and new methods to repair damaged intestinal tissue will help catalyze the design of novel therapeutic strategies. Research on controlling intestinal inflammation has potential benefits not only for patients with IBD, but also for those at risk of developing colorectal cancer.

Diseases of the stomach and intestines include some of the most common digestive diseases, such as peptic ulcer disease, which is typically caused by an infection with the bacterium *Helicobacter pylori* or use of non-steroidal anti-inflammatory

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<sup>1</sup> National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), U.S. Centers for Disease Control and Prevention; available at: [www.cdc.gov/nchs/ahcd/index.htm](http://www.cdc.gov/nchs/ahcd/index.htm).

<sup>2</sup> Healthcare Cost and Utilization Project (H-CUP) National Inpatient Sample (NIS), Agency for Healthcare Research and Quality; available at: [www.hcup-us.ahrq.gov/nisoverview.jsp](http://www.hcup-us.ahrq.gov/nisoverview.jsp).

<sup>3</sup> Healthcare Cost and Utilization Project (H-CUP) Nationwide Emergency Department Sample (NEDS), Agency for Healthcare Research and Quality; available at: [www.hcup-us.ahrq.gov/nedsoverview.jsp](http://www.hcup-us.ahrq.gov/nedsoverview.jsp).

drugs. Stomach and intestinal disorders also include functional gastrointestinal disorders, which can cause symptoms of abdominal pain and altered bowel habits. For example, irritable bowel syndrome (IBS) causes pain and constipation or diarrhea. IBS more frequently affects women, who may display a different range of symptoms and respond differently from men to pharmacologic treatments for the disease. While diet and stress contribute to this disorder, its underlying causes are unknown. Gastroesophageal reflux disease, in which stomach acids rise up into the esophagus, is a common functional gastrointestinal disorder that can lead to a condition known as Barrett's esophagus. This condition, in which cells lining the esophagus turn into an intestinal type of cell, is associated with a heightened risk of esophageal cancer—one of the cancer types still on the rise in the United States. Gastroparesis, another type of functional gastrointestinal disorder, is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. Most cases of gastroparesis are of unknown origin, which makes it difficult to treat. Most current therapies are directed toward helping people manage this chronic condition so they can be as comfortable and active as possible. Fecal incontinence, or impaired bowel control, is a disorder that poses a major public health burden. Although fecal incontinence is more common in older adults, it can affect people of any age. Because it is difficult to talk about, many people suffer without seeking professional treatment for this surprisingly prevalent condition. Researchers thus aim both to examine barriers in addressing fecal incontinence and to develop improved treatment strategies. Scientists continue to strive for a deeper understanding of the causes of gastrointestinal disorders, which will lead to improvements in diagnosis and management for patients with these conditions.

Some digestive diseases can be triggered by the body's reaction to certain foods. For example, in individuals with celiac disease, the immune system reacts to ingestion of gluten—a protein component of wheat, barley, and rye—and damages the small intestine. This damage interferes with the ability of the intestine to absorb nutrients from foods and can result 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. Recent and continued 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 new ways to treat this condition in the future.

The microbes that inhabit the GI tract are important factors in maintaining or tipping the balance between digestive health and disease. These bacteria, viruses, and other microorganisms can affect long-term health and nutritional status in some surprising ways, 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.

The exocrine pancreas, which secretes enzymes required for digestion, is vulnerable to disorders such as acute and chronic pancreatitis and their complications. Common causes of pancreatitis include gallstones, heavy alcohol use, inherited genetic factors, and some medicines. In all forms of 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, but 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 disorder.

The liver is an organ within the digestive system that performs many critical metabolic functions, including processing and distribution of nutrients such as fats. When the liver is functionally compromised by disease, serious adverse effects on health can occur, which sometimes leads to complete liver failure. Some liver diseases primarily affect children, such as biliary atresia (a progressive inflammatory liver disease), while others generally affect adults, such as a form of nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). In recent years,

however, NAFLD has been increasingly diagnosed in children in the United States as well, concurrent with rising overweight and obesity. 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 diverse 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. A healthy liver is necessary for life, and the only treatment for end-stage liver disease is a liver transplant. Because the number of livers available from deceased donors is limited, sometimes a healthy living person will donate part of his or her liver, most often to a family member who is recommended for a liver transplant. The living donor's liver eventually regenerates and grows back to normal size, as does the part of the liver that is donated. 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. Additionally, a unique web-based health information program on drug-induced liver disease called LiverTox, jointly sponsored by the NIDDK and the National Library of Medicine, provides concise, up-to-date information on more than a thousand medications and supplements and their potential to harm the liver (available at: [www.ncbi.nlm.nih.gov/books/NBK547852](http://www.ncbi.nlm.nih.gov/books/NBK547852)).

The number of Americans who are overweight or obese has risen dramatically in recent decades and is now at epidemic levels. Obesity is associated with numerous diseases, including type 2 diabetes, heart disease, and cancer. Multiple factors contribute to obesity. As scientists elucidate the molecular, genetic, microbial, behavioral, and environmental factors that influence appetite, metabolism, and energy storage, they are identifying potential avenues for the development of new intervention strategies to promote safe, long-term weight loss. In addition to new pharmacologic interventions for obesity that may arise from research, existing bariatric surgical techniques are being evaluated for their long-term impacts on weight loss, obesity-associated disease, and well-being. Investigators are also continuing research to help people achieve healthy lifestyles that include physical activity and improved diet. (Additional information on NIDDK-supported

research endeavors focusing on obesity is provided in the "Obesity" chapter.)

Other nutrition-related disorders under investigation 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 in order to understand dietary needs in health and disease. The NIDDK and its Office of Nutrition Research have played a leading role in the NIH Nutrition Research Task Force, chaired by the NIDDK Director and co-chaired by Directors of the National Heart, Lung, and Blood Institute, the National Cancer Institute, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The Task Force was established to coordinate and accelerate progress in nutrition research across the NIH, including the development of the first NIH-wide strategic plan for nutrition research (see feature later in this chapter).

## GUT MICROBIOME AND NUTRITION

**Studies Show Role of Human Gut Microbiome in Nutrient Absorption:** Researchers in the NIDDK's intramural research program, partnering with scientists at academic institutions in the United States and Germany, found that changes in people's gut microbiomes, due to diet or antibiotic use, directly altered nutrient absorption, backing up results from animal models and indirect associations in prior human studies. Decades of research, mainly in animal models, have illustrated how influential gut microbes can be in supplementing individuals' metabolic machinery and determining how much nutrition is extracted from the diet. Human studies in this area have produced similar but indirect associations. For example, one study showed that underfeeding (ingesting less calories than required to maintain current weight) remodeled the microbiome and reduced nutrient absorption, but it was unclear if the effects on nutrient absorption were directly caused by changes in the microbiome.

Scientists wished to test whether there was a causal relationship between human gut microbes and nutrient absorption in a controlled feeding

study in which the participants' microbiomes were altered by diet or antibiotics. This study design provided accurate assessment of dietary intake, with adult men and women, some of whom had obesity or impaired glucose tolerance, staying at the NIH Clinical Research Unit at the Phoenix Indian Medical Center in Arizona throughout the study period of 31 days. During this time, they were given prepared meals, which were closely monitored to ensure 95 percent of foods were consumed, and had samples taken. For the first phase of the study, all participants were overfed and underfed the same foods for 3 days each, in random order, with a weight-maintaining diet provided in between. In the second phase, they were fed a weight-maintaining diet and given either the oral antibiotic vancomycin or a placebo pill. The scientists measured nutrient absorption by monitoring the calories passed in stool and urine samples. They also tracked the activity and composition of the gut microbiome by measuring plasma biomarkers of host and microbial metabolism and the number and types of gut bacteria present in the stool. Both underfeeding and antibiotics reduced nutrient absorption (*i.e.*, more nutrients were lost in the stool). In the case of underfeeding, the scientists attributed this to lower nutrient availability for gut microbial metabolism. These short-term dietary changes altered the composition of gut microbes slightly, and antibiotic treatment changed it more dramatically, with a loss of diversity in gut microbial species, which may have hampered the metabolic capacity of the remaining gut microbes. In fact, a marker for microbial metabolism was lower in the people who were underfed or treated with the antibiotic, pointing to reduced nutrient metabolism by the microbiome under these conditions.

This study offers high-quality evidence for a direct role of gut microbes in the amount of nutrients a given person can extract from their food, including the impact of environmental factors such as diet and antibiotic use. These findings also bolster the validity of animal models in which similar results were found. Additional, larger human studies are needed to determine the potential therapeutic implications of this research.

*Basolo A, Hohenadel M, Ang QY, ... Krakoff J. Effects of underfeeding and oral vancomycin on gut microbiome and nutrient absorption in humans. Nat Med 26: 589-598, 2020.*

## TOWARD PREDICTING EFFECTIVE TREATMENTS FOR INFLAMMATORY BOWEL DISEASE

### A Cellular Signature Reveals Why Current Crohn's Disease Therapy Does Not Work for Some People:

Scientists have identified a tell-tale combination of cells in people with Crohn's disease who do not respond to one of its most effective treatments, shedding light on the nature of the disease and revealing potential new targets for therapy. Crohn's disease, a form of inflammatory bowel disease characterized by chronic inflammation in parts of the small intestine, can cause debilitating flares of diarrhea and abdominal pain, leading to malnutrition and weight loss. Treating Crohn's disease is challenging because the response to therapy varies greatly from person to person, and no single treatment works for everyone. Well-tolerated anti-inflammatory medications, for example, do not work in many people with Crohn's disease. Stronger medications that block a major component of the inflammatory response called tumor necrosis factor (TNF) have been approved to treat Crohn's disease and are effective for many whose health did not improve with the milder anti-inflammatory drugs. However, for unclear reasons, a substantial portion of people do not respond to TNF-blocking drugs and must eventually resort to more drastic approaches to control the inflammation, which usually means surgically removing the affected areas.

In a recent study, scientists applied state-of-the-art technology to determine why some people do not benefit from certain Crohn's disease treatments. They started by isolating and identifying single cells from intestinal lesions of 11 men and women with Crohn's disease. Comparing these cells with cells from healthy intestinal tissue from the same patients, the researchers found a specific combination of cells—including activated immune cells and cells that make up connective tissue—in the lesions from several of the study participants. When the researchers looked for this cellular "signature" in a larger, well-characterized group of male and female children with Crohn's disease, they found it was more likely present in those whose symptoms did not respond to anti-TNF therapy. Analysis of how the cells communicate with each other showed that this particular cellular combination does not rely solely upon TNF to maintain gut inflammation, which may explain why TNF-blocking drugs are ineffective.

Importantly, this analysis also identified several other molecular targets for other potential therapies that, if used in combination with TNF-blocking drugs, might be able to prevent inflammation in people with Crohn's disease who do not respond to anti-TNF medications alone.

This study builds upon recent findings showing that there are probably at least several distinct types of Crohn's disease, which could explain why treatment responses vary so widely from person to person. The results also show that the cellular makeup of the inflammatory lesions could affect how well different Crohn's disease medications will work. Biological signatures such as this could help health care providers predict which therapies would be most effective, and they could provide the basis for new treatments for people with this disease.

Martin JC, Chang C, Boschetti G,...Kenigsberg E. Single-cell analysis of Crohn's disease lesions identifies a pathogenic cellular module associated with resistance to anti-TNF therapy. *Cell* 178: 1493-1508.e20, 2019.

**A Common Fungus Sets the Stage for Successful Fecal Microbiota Transplantation in People with Ulcerative Colitis:** A recent study found that high levels of a common fungus in the gut could signal whether a microbe-based treatment would be successful for people with ulcerative colitis. Changes or disruptions in the gut's microbiome—the community of bacteria, viruses, and fungi that naturally inhabit the intestines—have been implicated in inflammatory bowel diseases like ulcerative colitis. One treatment that researchers are investigating is fecal microbiota transplantation (FMT), whereby a sample containing gut microbes from a healthy donor is introduced into a person with colitis to help reestablish a more functional gut microbiome. While FMT has proven to be a successful therapy for people with *Clostridioides difficile* (*C. diff*) bacterial infections, with over 90 percent of people cured after a single treatment, FMT is less successful for people with ulcerative colitis: in a recent clinical trial, less than half the participants with colitis experienced remission after FMT. Knowing why the treatment works only in some people is important, because it would allow health care providers to predict which individuals with ulcerative colitis would benefit from FMT as opposed to another treatment strategy. One possibility is that FMT's success may be dependent upon the makeup of the recipient's microbiome. For example,

FMT is less likely to succeed as a *C. diff* treatment for people who have high levels of *Candida*, a type of fungus found in the guts of nearly everyone. *Candida* is an opportunistic pathogen that can exacerbate inflammation when the immune system is weakened or the microbiome is disrupted. Moreover, high levels of *Candida* could determine FMT outcomes by affecting the levels of other microbial members of the gut. Thus, like in people with *C. diff*, high levels of *Candida* may also play an important role in determining the outcomes of FMT in people with ulcerative colitis.

To determine whether gut microbes such as *Candida* may be affecting FMT for people with ulcerative colitis, researchers studied the microbiomes of 24 men and women who had received FMT as a trial treatment for the disease. Unlike in people with *C. diff* infections, the study participants who had higher levels of *Candida* before FMT were more likely to have improved colitis symptoms and clinical features following treatment. After FMT, levels of *Candida*—and the immune response against *Candida*—were lower in these people compared to those who received a placebo. This raises the possibility that introducing gut microbes from healthy donors suppresses the overgrowth of *Candida*—and the inflammation caused by it—in people with ulcerative colitis. The researchers also found that study participants who had higher pre-FMT levels of *Candida* were more likely to have higher pre-FMT levels of certain gut bacteria that have been linked to successful FMT outcomes for ulcerative colitis. This suggests that a high level of *Candida* may create a permissive environment for FMT in people with ulcerative colitis by encouraging the growth of specific gut bacteria in the microbiome. Overall, the results of this study hint of an intricate relationship between *Candida* and other members of the microbiome, whereby high levels of *Candida* in people with ulcerative colitis make the microbiome more receptive to FMT. In turn, FMT results in reduced levels of *Candida* and the inflammation associated with it. In this manner, *Candida* levels could be a promising marker to predict whether FMT may be effective for people with ulcerative colitis.

Leonardi I, Paramsothy S, Doron I,...Iliev ID. Fungal trans-kingdom dynamics linked to responsiveness to fecal microbiota transplantation (FMT) therapy in ulcerative colitis. *Cell Host Microbe* 27: 823-829. e3, 2020.

## NEW MOUSE MODEL OF CELIAC DISEASE

### **New Mouse Model Mimics Celiac Disease in People:**

Researchers have developed a new mouse model that mimics the immune system features and gluten-dependent intestinal damage seen in people with celiac disease, providing a new research tool for discovering and testing therapies. Celiac disease is an autoimmune reaction in the gut that is triggered by consuming gluten, a protein found mainly in foods containing wheat, barley, and rye. This autoimmune reaction—where the body targets its own cells—damages the small intestine, interfering with the intestine's ability to absorb nutrients from foods. This can result in chronic diarrhea, bloating, anemia, and, in children, slower growth and short stature. The only treatment for celiac disease is a strict gluten-free diet, which is difficult for many people. Scientists are trying to identify non-dietary treatments for celiac disease, but research has been hampered by the lack of animal models that accurately mimic the human form of the disease.

In new research, scientists used their understanding of human celiac disease to genetically engineer a new model of the disease in female and male mice. In people, the presence of certain genetic variants in the human leukocyte antigen (HLA) region of the genome—which is responsible for regulating the immune system—increases the likelihood of developing celiac disease. Additionally, people with the disease have high levels of an immune system-produced protein called interleukin-15 (IL-15) in their small intestines. The researchers engineered a mouse model with similar characteristics. Just like in people, the mice developed damage to their small intestines after eating gluten for 30 days, and the damage was reversed when the animals were no longer fed gluten. The animals' immune systems also produced some of the same types of antibodies that are commonly used to diagnose celiac disease in people, and the mice had similar gene activity in the presence and absence of gluten as observed in people with the disease, suggesting that the mouse model could be useful for testing therapies before they are tried in humans. Further experiments suggested that the model could be useful for drug discovery. For example, the model gave insights into the critical role for IL-15 in the disease. The researchers also found that they could prevent small intestine damage by treating gluten-fed mice with a drug that inhibits a protein known to be involved in the underlying cause of celiac disease. Thus, this new

animal model that replicates features of human celiac disease upon introduction of gluten could be a useful research tool not only for increasing understanding of the underlying biology of celiac disease, but also for identifying new therapeutic targets and testing novel prevention and treatment strategies before they are tested in people.

*Abadie V, Kim SM, Lejeune T,...Jabri B. IL-15, gluten and HLA-DQ8 drive tissue destruction in coeliac disease. Nature 578: 600-604, 2020.*

## CLINICAL RESEARCH ON BILIARY ATRESIA

### **Testing a New Screening Approach for Early Diagnosis of Biliary Atresia:**

Researchers have found that a two-step newborn screening approach measuring bilirubin levels could identify those with biliary atresia—progress toward a goal of more successfully treating babies earlier in the course of disease. Biliary atresia is a rare and serious progressive liver disease diagnosed in infancy that leads to a back-up of bile into the liver. The disease must be treated with a surgery to restore bile drainage called hepatoportoenterostomy or HPE (also referred to as the Kasai procedure) or a liver transplant. Children who undergo HPE before 30 days of age have the best chance of delaying or preventing the need for a liver transplant, but HPE often occurs after that window because biliary atresia is difficult to detect in its early stages. Thus, an important research goal is to identify ways to diagnose biliary atresia soon after birth to facilitate early treatment and improve health outcomes.

In new research, scientists used knowledge that infants with biliary atresia have elevated levels of bilirubin (a major component of bile) at birth to design and test a 2-stage screening strategy in over 124,000 newborn girls and boys. In the first stage, they analyzed data on babies' bilirubin levels in blood measured shortly after birth, which was collected as part of routine newborn tests at the 14 south Texas hospitals where the research was conducted. If the newborns had high bilirubin levels in stage 1, they underwent repeat bilirubin testing at or before their routine 2-week well-child doctor's visit. Infants who tested positive in stage 2 were referred for additional tests to see if they had biliary atresia. The results showed that the screening approach successfully identified all seven children who were



subsequently diagnosed with biliary atresia in the study population. However, it also identified another 112 children who did not have the disease—so-called false positives. Tests on those children showed that a few of them had other conditions that benefitted from early detection and treatment, but about half were not diagnosed with any disease or condition. The researchers also conducted a second, smaller study of 43 infants with biliary atresia to compare clinical outcomes of babies who underwent HPE either before or after the screening strategy was implemented. They found that children in the screening group underwent HPE at a younger age, suggesting that the screening approach may facilitate earlier treatment.

This research demonstrates promising progress toward newborn screening for biliary atresia, but the scientists noted several limitations that would have to be overcome before such a screening approach could be recommended on a national scale. For example, screening only occurred at South Texas hospitals, potentially limiting the applicability of the study's results to other populations. Also, the outcomes study included a relatively small number of children, so it is unknown if similar results would be observed in a larger study. Additional research could help to address these limitations, as well as to study the cost-effectiveness of implementing a population-wide screening approach, as has been done in other countries, and identify ways to reduce the number of false positives. Such research could accelerate further progress toward longer-term goals of early diagnosis and treatment of biliary atresia to improve the health of children.

*Harpavat S, Garcia-Prats JA, Anaya C, ...Shneider BL. Diagnostic yield of newborn screening for biliary atresia using direct or conjugated bilirubin measurements. JAMA 323: 1141-1150, 2020.*

**Gene Activity Signature Predicts Survival in Young Children with Biliary Atresia:** Researchers identified a unique signature of gene activity levels at diagnosis that predicts survival in young children with biliary atresia—knowledge that could help determine disease progression and inform new treatment approaches. Biliary atresia is a rare and serious liver disease that occurs during the first few months of life in which bile ducts that drain from the liver to deliver bile acids to the intestine become inflamed and scarred, leading to a back-up of bile into the liver. To restore bile drainage, children with this

disease must be treated with a surgery called hepatoportoenterostomy or HPE (also referred to as the Kasai procedure), but even after this surgery, the liver can develop progressive damage requiring a liver transplant. Because the clinical course of biliary atresia is variable, it would be extremely valuable to have biological markers that predict disease progression, to inform the development of new and personalized treatment approaches.

Toward this goal, researchers studied liver biopsy tissue from girls and boys with biliary atresia, including those enrolled in the NIDDK's Childhood Liver Disease Research Network (ChiLDRen). By comparing the gene activity patterns of children who survived until age 2 after the HPE surgery without the need for a liver transplant to those who did not, they identified a set of 14 genes with activity levels at diagnosis that predicted transplant-free survival at 2 years of age. Further experiments suggested that the 14-gene activity pattern coupled with total bilirubin level (a major component of bile) measured 3 months after surgery was an even better predictor of 2-year survival without a liver transplant than the gene activity signature alone. Researchers next explored differences in overall gene activity in the children and how those differences may contribute to disease progression, finding increased activity of genes associated with liver injury and scarring in the children with lower transplant-free survival. They also found increased activity of genes involved in metabolism of glutathione (an antioxidant produced in the liver) in the children who survived without a transplant, suggesting that restoration of cellular glutathione may help protect against biliary atresia-associated liver damage. Investigating this concept further, studies of mouse models of biliary atresia showed reduced bile duct obstruction and improved survival when the animals were treated with N-acetylcysteine (NAC), a drug that restores cellular glutathione and was shown to treat acute liver failure in children and adults by other NIDDK-sponsored studies.

This study suggests that the newly identified 14-gene activity signature could be a useful biological marker to predict how biliary atresia will progress in young children after surgery. It also shows that restoring cellular glutathione may be a possible approach to decrease progressive liver damage caused by the disease. Further research could help determine if using NAC or another

approach to increase cellular glutathione in children with biliary atresia could halt liver damage and improve overall health.

Luo Z, Shivakumar P, Mourya R, Gutta S, and Bezerra JA. *Gene expression signatures associated with survival times of pediatric patients with biliary atresia identify potential therapeutic agents. Gastroenterology* 157: 1138-1152.e14, 2019.

## DIETARY CONTRIBUTORS TO NONALCOHOLIC FATTY LIVER DISEASE

### How High Fructose Intake May Trigger

**Fatty Liver Disease:** A team of researchers supported by the NIDDK, as well as other NIH Institutes, discovered that consuming high amounts of fructose may promote nonalcoholic fatty liver disease by damaging the intestinal barrier, which leads to inflammation and effects on the liver. Fructose is a common type of sugar in the American diet, including its processed form called high-fructose corn syrup that is used to sweeten a variety of foods. Studies have linked excessive consumption of high-fructose corn syrup and other added sugars to health problems like obesity, diabetes, heart disease, and nonalcoholic fatty liver disease (NAFLD), in which too much fat is stored in liver cells. Fatty liver disease can lead to liver inflammation and liver damage, resulting in a more aggressive disease called nonalcoholic steatohepatitis (NASH) that can progress to scarring of the liver (cirrhosis), liver cancer, and liver failure. Scientists have been unsure how high fructose consumption might contribute to NAFLD.

A research team set out to explore fructose's role in NAFLD. The researchers gave male mice either a high-fructose diet or a control diet with equivalent calories from corn starch, which breaks down into glucose, the sugar cells use for energy. Within a few months, mice on the high-fructose diet developed fatty livers and had greater rates of liver tumors than mice on the control diet. Mice bred to be prone to develop NASH showed clinical signs of the disease on the high-fructose diet. The team found that mice fed the high-fructose diet for long periods showed not only liver inflammation, but also deterioration of their intestinal barrier, which normally prevents bacteria and toxins in the gut from leaking into the bloodstream. Mice fed a high-fructose diet also had higher circulating levels of endotoxins—toxins

released from certain bacteria when they die. The team discovered that leaked endotoxins prompted immune cells in the liver called macrophages to react and increase the production of cell signaling proteins like tumor necrosis factor (TNF) that can cause inflammation. Further experiments showed that these signaling proteins boosted enzymes that convert fructose into fatty deposits in the liver. Restoring the mice's intestinal barrier prevented this fatty buildup in the liver. Using drugs and genetic manipulations, the team was able to stop the gut barrier deterioration from excessive fructose intake and prevent the onset of severe fatty liver disease and liver tumors. Experiments in human liver cells showed that a similar cellular process could take place in people: adding TNF to the human liver cells increased the conversion of fructose into fat.

Overall, this study points to a pathway in which high fructose levels could trigger a breakdown in the intestinal barrier and leakage of gut microbial products into the liver, thereby exacerbating inflammation and boosting the conversion of fructose into fatty deposits. The findings from this study could lead to new ways to treat and prevent NAFLD, which affects an increasingly large percentage of the U.S. population. For example, future studies could test agents that restore the integrity of the intestinal barrier in people at risk for NAFLD.

Todoric J, Di Caro G, Reibe S,...Karin M. *Fructose stimulated de novo lipogenesis is promoted by inflammation. Nat Metab* 2: 1034-1045, 2020.

(Information adapted from original article by Ms. Erin Bryant, published on September 15, 2020, in *NIH Research Matters*.)

## NEW INSIGHTS INTO BASIC LIVER CELL BIOLOGY

**Insights into How Immune Cell Recruits Are Programmed To Defend the Liver:** Researchers working with a mouse model have gained insights into the genetic and cellular factors that drive the transformation of circulating immune cells into Kupffer cells, part of the liver's "special forces" of immune cells. This research focuses on a type of immune cell called the macrophage—derived from the Latin for "large" and "thing that devours"—that protects the body by engulfing pathogens and

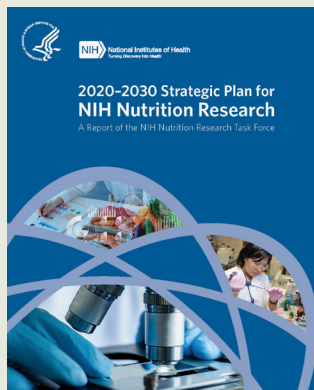
cellular debris. The Kupffer cell is a special type of macrophage residing in blood vessels within the liver. During early life, Kupffer cells develop in the liver, where they perform important functions lifelong, including clearing cell debris and toxins produced by gut bacteria, as well as playing a role in iron metabolism. Kupffer cells also play critical roles in some liver diseases and therefore could be targets for therapy, but little is known about the factors involved in the formation and maintenance of these unique liver defense cells.

Researchers aimed to address this knowledge gap by using a mouse model in which these cells can be experimentally depleted. They studied both female and male mice over a 2-week period, analyzing cells from blood and liver samples using techniques that show gene activation. In the first 12 hours after the mouse Kupffer cells were depleted, circulating monocytes (white blood cells in the immune system that can turn into more specialized immune cells as needed) had already started to colonize the liver. Within 24 hours of residing in the liver environment, the monocytes showed signs of a transformation, including activation of over half of the roughly 300 genes unique to Kupffer cells. A combination of

sequential signals emanating from surrounding liver cells, including those lining blood vessels (called liver sinusoidal endothelial cells) and underlying liver cells called hepatocytes, were important for transforming the monocytes and maintaining their new identities as Kupffer-like cells. In the first step of the process, monocytes migrating to the liver interacted with sinusoidal cells that produced a protein called DLL4, setting off a cascade of gene activation needed to transform the cells. The second step involved signals such as transforming growth factor-beta and desmosterol released by the surrounding liver cells that further fine-tuned the gene activation program to resemble a Kupffer-like cell. These findings offer insights into the developmental program triggered in circulating immune cells—and within cells in the local tissue environment that sense a need to replace lost defenses—to form the Kupffer cells that protect the liver. Future directions for this research include plans to explore how Kupffer cells function in a disease context, such as a form of severe fatty liver disease called nonalcoholic steatohepatitis.

*Sakai M, Troutman TD, Seidman JS,...Glass CK. Liver-derived signals sequentially reprogram myeloid enhancers to initiate and maintain Kupffer cell identity. Immunity 51: 655-670.e8, 2019.*

# Strategic Plan for NIH Nutrition Research



In May 2020, the NIH released its first agency-wide strategic plan for nutrition research. The *2020-2030 Strategic Plan for NIH Nutrition Research* presents a bold vision for advancing NIH-supported nutrition research over the next decade to

answer fundamental questions, such as “what should we eat to stay healthy?” The *Strategic Plan* provides a framework to answer this and other important questions in nutrition research, to advance the field of nutrition science as a whole, and ultimately to promote health and reduce the burden of diet-related disease.

The *Strategic Plan* is structured around a core vision of advancing “precision nutrition” research to address the impacts of diet and nutrition on individuals, with the goal of moving research closer to enabling personalized dietary recommendations for what, when, why, and how to eat. Through its strategic goals and associated objectives, the *Strategic Plan* identifies current research challenges and opportunities to advance nutrition science. The *Strategic Plan* also identifies cross-cutting research areas that underpin successful future activities across the field of nutrition research: addressing minority health and health disparities; the health of women; rigor and reproducibility; data science, systems science, and artificial intelligence; and training the scientific workforce.

The *Strategic Plan* was developed by the NIH Nutrition Research Task Force with broad stakeholder input, described below. The Task Force was established by the NIH Director, Dr. Francis Collins, and chaired by

Dr. Griffin Rodgers, NIDDK Director, with co-chairs Dr. Gary Gibbons, Director of the National Heart, Lung, and Blood Institute; Dr. Norman Sharpless, Director of the National Cancer Institute; and Dr. Diana Bianchi, Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The NIDDK Office of Nutrition Research provided support for the strategic planning process, with the Office’s Director, Dr. Christopher Lynch, serving as Executive Secretary of the Task Force. The Task Force was assisted in this effort by other NIH staff who represented the NIH’s many Institutes, Centers, and Offices that support nutrition research.

The Task Force sought extensive stakeholder input throughout the development of the *Strategic Plan*. Activities included a “crowdsourcing” website to solicit ideas from researchers and members of the public; a Thought Leaders Panel of federal and external nutrition experts who provided their input on research opportunities; and online posting of the draft research plan for public comment. Throughout the planning process, the Task Force convened regularly to discuss research priorities and progress.

Implementation of the *Strategic Plan* is already under way, being led by a number of Implementation Working Groups with NIDDK staff participation. For example, plans for a large study supported by the NIH Common Fund will answer key questions about precision nutrition by studying participants in the NIH *All of Us* cohort. The NIH invited public input on this study through a Request for Information notice in 2020 and a workshop on precision nutrition research in January 2021. In the years ahead, the NIH will implement the recommendations made in the *Strategic Plan* to advance nutrition research, while remaining responsive to emerging opportunities and the ever-changing scientific landscape.

For additional information on the *2020-2030 Strategic Plan for NIH Nutrition Research*, please visit: [www.niddk.nih.gov/about-niddk/strategic-plans-reports/strategic-plan-nih-nutrition-research](http://www.niddk.nih.gov/about-niddk/strategic-plans-reports/strategic-plan-nih-nutrition-research).

# Consortium Advancing Childhood Pancreatitis Research

A collection of recent advances enhances understanding of pancreatitis development and management in children—the latest in a long line of important contributions to the field over the past decade made by participants and investigators in the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) study.

Pancreatitis, an inflammation of the pancreas, has been more commonly diagnosed in children in recent years. Yet, pediatric pancreatitis is still frequently missed on initial evaluation, often delaying diagnosis. It can occur in acute (short-term), acute recurrent (two or more acute episodes), or chronic (long-lasting) forms. While all three forms could lead to complications, acute recurrent and chronic pancreatitis, in particular, can increase risk for diabetes and pancreatic cancer. Since 2010, the NIDDK has supported the INSPPIRE study—the first and largest multi-center group dedicated to studying acute recurrent and chronic forms of pancreatitis in children. This study grew out of a collective effort by an international group of investigators at sites throughout the United States, Canada, Israel, and Australia. This multi-center approach powers research by gathering a sufficient number of participants for studying the relatively rare disease of pediatric pancreatitis. Currently in its second iteration as INSPPIRE 2, it is now part of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer co-sponsored by the NIDDK and the National Cancer Institute, and features an even larger and more diverse study population of children and adolescents with pancreatitis.

In a recent report from the INSPPIRE study, researchers analyzed data from 479 children across INSPPIRE study sites and identified regional differences in the clinical presentation or management of pediatric pancreatitis that could affect disease outcomes. For example, participants at U.S. versus non-U.S. sites more frequently had the chronic form of pancreatitis, and therapies were more frequently utilized. Within the United States, the greatest disease

burden—based on measures of pain, emergency room (ER) visits/hospitalizations, and missed school days—was observed in western and midwestern study sites; also variants in the gene *PRSS1*, which are risk factors for pancreatitis, were more common at midwestern study sites, and gallstones were more frequently found at southern study sites. These regional differences may be due to the distribution of genetic risk factors and patterns created by different clinical practices and referrals. These study findings can inform a more streamlined and personalized approach to improve outcomes in children with pancreatitis.

Another study of INSPPIRE participants aimed to find out whether diabetes, a disease that commonly develops in adults with pancreatitis, similarly affects children with pancreatitis. Following 397 children with pancreatitis over 5 years, they found that 24 (or about 6 percent) were diagnosed with diabetes—a 30-fold higher rate than in the general population of children. The children diagnosed with diabetes tended to be older when they first developed pancreatitis and were more likely to have elevated blood lipids or autoimmune disease, which are known risk factors for diabetes. They also had signs of atrophy in the pancreas, indicating more advanced disease. These results may be helpful in the future for monitoring children with pancreatitis, in order to identify individuals at risk for developing diabetes.

In addition to their original research, investigators have conducted reviews of the medical literature on pediatric pancreatitis, much of it generated by the INSPPIRE study, to provide up-to-date information for physicians caring for these children. One analysis, conducted by INSPPIRE investigators and using diagnostic criteria developed in the INSPPIRE study, reviewed available medical literature to assess the extent to which a rare cause of pancreatitis in adults, called functional pancreatic sphincter dysfunction (FPSD), can contribute to pediatric pancreatitis. FPSD is one form of functional sphincter dysfunction, a condition of reduced flow of bile or pancreatic fluid from the liver and pancreas through a muscular valve

and into the small intestine, causing backup of these digestive fluids and associated abdominal pain and pancreatitis. Surveying the literature, including both adult and pediatric studies, the group developed a consensus on expert recommendations, based on available evidence, for approaches to diagnosis and treatment in cases in which FPSD is suspected as the cause of pediatric pancreatitis. For example, they generated recommendations for when to consider the use of invasive diagnostic and surgical treatments. These include endoscopic retrograde cholangiopancreatography—an invasive diagnostic procedure used to visualize the pancreatic and bile ducts with potential risks as well as benefits—and an associated surgical therapy called endoscopic sphincterotomy. While many gaps in knowledge remain and clinical care options are limited, these recommendations specific to children with these conditions give their health care providers more evidence-based tools to optimize care.

Turning to available treatments for pediatric pancreatitis, opioids are often used to control the severe abdominal pain often associated with the disease. But their use comes with concerns about addiction, particularly in light of the opioid overdose epidemic in the United States and elsewhere. INSPPIRE investigators surveyed 427 children/parent participants and their physicians about patient patterns of opioid use for pain management. Nearly one in five children with pancreatitis in the study reported daily or weekly opioid use, based on self-reports. Factors associated with more frequent opioid use included an older age at the time of diagnosis, *PRSS1* genetic risk factor, insufficient production of pancreatic enzymes that help digest food, antidepressant use, and constant pain that impaired daily functioning. Rates of frequent opioid use were also higher in participants living in the western and midwestern regions of the United States. These findings can help identify children with pancreatitis who may be at risk of frequent opioid use for pain management, so that other medical or psychological treatments can be considered early on.

One potential therapeutic alternative is the first psychological intervention to be tested for management of pancreatitis-related pain. In this pioneering clinical trial, researchers at INSPPIRE study sites will test an intervention based on cognitive behavioral therapy (CBT) to reduce pancreatitis-related pain. Investigators and staff

aim to enroll 260 young people ages 10 to 18 with pancreatitis in the trial of this web-based intervention, compared to a web-based educational program. The web-based CBT intervention includes relaxation and pain coping strategies for the youths, as well as behavioral and communication techniques for their parents, with weekly assignments for both to practice their new cognitive and behavioral skills. The researchers will test whether the intervention is effective over 2 to 3 months for reducing abdominal pain and improving health-related quality of life, as well as whether its effects are retained 6 months after the intervention. If this web-based psychological intervention is found to be effective, it would represent an economical, convenient, and potentially wide-reaching option for helping to manage pancreatitis-related pain.

The INSPPIRE study will continue to pursue these promising new directions toward better understanding, diagnosing, and optimally managing pancreatitis in children and adolescents. This study is leading the way in filling long-standing gaps in knowledge about how this disease manifests in children, and how best to diagnose and treat them for achieving the highest quality of life in the many years they have ahead.

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# Recent Advances from the Gastroparesis Clinical Research Consortium: Toward Better Understanding, Diagnosis, and Treatment

After food is swallowed, muscles in the stomach wall grind it into smaller pieces and push it into the small intestine to continue digestion. In people with gastroparesis, however, these muscles work poorly—or not at all—and the stomach takes too long to empty its contents. This slower movement is called “delayed gastric emptying,” and it can cause chronic nausea, vomiting, and abdominal pain, often leading to malnutrition, dehydration, and other serious complications. People with gastroparesis typically need to adhere to strict, low-portion diets that are low in fat and fiber, and at times they may need to avoid solid foods altogether.

Developing treatments for gastroparesis has been challenging, largely because the underlying causes are unclear. For unknown reasons, women are significantly more likely to develop the disorder than men. Diabetes, surgery, and other conditions are known to cause gastroparesis in some people, but idiopathic gastroparesis—in which the cause is not identified—is more common. In 2006, the NIDDK established the Gastroparesis Clinical Research Consortium to accelerate research on the causes and progression of this disorder and to explore new approaches for treatment. The Consortium is made up of several clinical research centers across the country, allowing researchers to share techniques and tools and, importantly, to assemble the Consortium’s most valuable resource: a broad spectrum of hundreds of people with gastroparesis who volunteered to be a part of the Gastroparesis Registry. The Registry is the largest clinical and physiologic data repository for gastroparesis in the world, containing a large body of information accessible to qualified researchers, such

as detailed test results, samples, and questionnaires. Women make up the majority of participants, reflecting the higher incidence of gastroparesis in this group. The information collected in the Registry is used by researchers to link symptoms, severity, and treatment responses to patient characteristics—a critical step toward understanding the causes, progression, and outcomes of the disorder. Consortium scientists can also access the Registry when recruiting people for clinical trials, which could benefit Registry participants who are eager to try new therapies. Over the years, the Consortium has undertaken several such trials to test treatments for gastroparesis. This Gastroparesis Registry includes only adult participants, but the Consortium recently built upon its success to establish the first national pediatric registry (the Pediatric Gastroparesis Registry, or PGpR) for children and adolescents with gastroparesis. Enrollments for both registries are ongoing.

Recent studies from the Consortium have leveraged information from the adult Registry to help improve diagnosis of gastroparesis, which can be challenging because many of its symptoms are not specific to the disorder and could be mistakenly attributed to something else, like indigestion. Consortium researchers are trying to help with diagnosis by identifying groups of people who are at higher risk. For example, the Consortium recently studied people in the Registry who have both diabetes and symptoms of gastroparesis, and they found that those with delayed gastric emptying had a higher number of diabetic complications than those who showed normal gastric emptying. Retinopathy

(damage to blood vessels in the eye) was particularly associated with delayed gastric emptying, which suggests that people with diabetic retinopathy are also more likely to have gastroparesis. However, gastroparesis can occur in people who do not have complications of diabetes.

Consortium researchers are also using information from the Registry to investigate the underlying causes of gastroparesis, including why the stomach is not working properly. One possibility is that there could be defects in the activity of the nerves that envelope the stomach and control its muscles. Specifically, the researchers wanted to know whether the sympathetic and parasympathetic parts of the nervous system, which both control involuntary actions such as heart rate and stomach muscle activity, could be important in gastroparesis. While both sympathetic and parasympathetic systems are always active at some level, they exist in balance: the sympathetic component is more active during periods of stress, slowing the stomach's activity, while the parasympathetic system counters the sympathetic system and is more active during rest. The researchers found that this delicate balance is disrupted in many people with gastroparesis, with the parasympathetic system less able to offset the effects of the sympathetic responses, even when the body is at rest. Studies such as this, which identify the key mechanisms underlying gastroparesis, could identify potential new avenues for treatment.

Other recent studies from the Consortium focused on symptom management. For example, one study found that approximately 12 percent of people with gastroparesis participating in the Registry acknowledged that they used cannabis for symptom relief. Registry participants who were experiencing severe nausea and abdominal pain were more likely to use cannabis and likely to report that it helps ease their symptoms. Research on cannabis for various health conditions is in its early stages, but these results should raise health care providers' awareness that people with gastroparesis may be using cannabis to manage their symptoms, and that U.S. Food and Drug Administration (FDA)-approved synthetic products related to cannabis might be effective therapeutic agents. In fact, a portion of Registry participants were using at least one of these approved products, and they too were likely to report that it helps them manage their symptoms.

The Consortium also sought to determine whether a procedure called gastric electrical stimulation (GES) is effective for treating symptoms of gastroparesis. GES involves implanting an electronic device in the abdomen to deliver mild electrical impulses to the stomach's nerves and muscles. The device has been controversial because evidence on its effectiveness has been slow to accumulate, primarily because the procedure is expensive and requires additional visits and maintenance, making clinical trials difficult. Again using information from the Registry, researchers gathered information on people who underwent GES and determined that the procedure was effective for treating nausea in the participants with more severe gastroparesis. However, larger clinical trials would be necessary to test its efficacy more fully and to identify which people with gastroparesis would most likely benefit from this procedure.

These studies are only a recent sampling of research endeavors from the Consortium. Future years will see the Consortium continuing to undertake clinical studies to further understand, diagnose, and treat gastroparesis. The disorder can be devastating, but this research gives strong hope that the lives of people coping with gastroparesis will continue to improve.

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# STORY OF DISCOVERY

## Porphyrias Research

Decades of scientific research discoveries have advanced understanding of and care for a group of potentially severe and debilitating disorders called porphyrias. These advances include the identification of genetic factors underlying many of its forms, development of animal models for exploring these genetic factors and other contributors, and continuing findings from collaborative, large-scale clinical research on these rare disorders. In recent years, this research progress has led to new treatments, meaning that some forms of these disorders—recognized since ancient times—are now treatable. One major driver of this progress has been the NIDDK and its support of research on liver and hematologic (blood) diseases, particularly the Porphyrias Consortium, as well as many additional research studies conducted by investigators across the United States.

### A RARE AND VARIED SET OF DISORDERS

Derived from the Greek word for purple, porphyrias were so named for the unusual reddish-purple color of urine when exposed to sunlight in samples from people with this condition. Some have speculated that major historical figures such as King George III may have had a form of this disorder. Porphyrias result from an overabundance of heme precursors originating in the liver or bone marrow, where red blood cells are produced. Heme is the red, iron-rich component of the hemoglobin proteins used by red blood cells to deliver oxygen to cells throughout the body, and heme is also found in liver proteins called cytochromes that break down hormones, medications, and other chemicals. The heme precursors, called porphyrins, are essential for heme production, but they can also be toxic to tissue in high concentrations.

Porphyrias are typically inherited, due to a genetic variant in any one of several enzymes within the

multi-step pathway that transforms biochemicals into heme. The altered enzymatic function causes buildup of porphyrins in the liver or bone marrow. This results in the various forms of porphyria, which can be divided into two broad categories: “acute” and “cutaneous.” The acute forms include acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and aminolevulinic acid dehydratase deficiency porphyria (ADP). These are marked mainly by sudden attacks of stomach pain that can be severe and persist for many days, as well as pain in the chest, limbs, or back; nausea, vomiting, or constipation; urinary retention; confusion, hallucinations, or seizures; and muscle weakness. Some acute forms disproportionately affect certain groups of people; for example, AIP is more common in women of reproductive age, with severe abdominal pain attacks related to hormonal changes during the menstrual cycle. The cutaneous forms of porphyria, which include hepatoerythropoietic porphyria (HEP), congenital erythropoietic porphyria (CEP), erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP), and porphyria cutanea tarda (PCT), are associated with skin issues, such as blistering, itching, swelling, scarring, pain, or redness upon exposure to sunlight. Each of these disorders can profoundly compromise quality of life, often beginning in early childhood, due to pain or the need to avoid the sun or wear sun-protective clothing over the entire body and face, to avoid potentially disfiguring tissue damage. PCT is the most common form of the disorder found in the United States, and can be triggered by factors such as excessive iron accumulation from the diet, heavy alcohol use, taking certain drugs containing estrogen, smoking, and as a complication of infection with the hepatitis C or HIV viruses.

Diagnosing porphyrias is based on clinical symptoms and high levels of porphyrins in the blood, stool, or urine, but can be challenging because these disorders are rare and the symptoms overlap with

# STORY OF DISCOVERY

other conditions, which often results in missed or incorrect diagnoses. Treatment depends on the specific form of porphyria, but may involve use of heme-based or glucose treatments that reduce porphyrin production in the liver; liver transplantation; avoiding sunlight as much as possible; removal of some blood (therapeutic phlebotomy); and medications, including pain relievers. Genetic testing may also be used to confirm a particular inherited form of porphyria and determine appropriate care, for individuals and their potentially affected family members.

## RESEARCH ADVANCES IN UNDERSTANDING AND MANAGING PORPHYRIAS

NIDDK-sponsored efforts helped lay the groundwork for understanding the underlying mechanisms and clinical symptoms of porphyrias and developing diagnostic tests and treatments. In the 1980s, researchers capitalized on the unique fluorescent properties of porphyrins to identify diagnostic plasma markers for forms of porphyria such as VP. Also during this time, researchers documented responses in individual patients to treatments for CEP, such as oral activated charcoal to lower porphyrin levels or continuous blood transfusions to suppress red cell production. Building on findings supported by others to develop a form of heme called hematin as a therapy for acute porphyrias, and its U.S. Food and Drug Administration (FDA) approval in 1983, the NIDDK sponsored continuing research in the 1990s to further develop this treatment.

NIDDK research in the 1980s to 1990s helped to test the use of liver transplantation to treat people with some forms of porphyria, sometimes in combination with a pre-treatment to lower blood porphyrin levels, such as hematin or plasmapheresis (a procedure involving removal, treatment, and reinfusion of blood plasma). Research at this time also aimed to understand the burden of porphyrias in the population, such as studies in the 1990s

documenting mortality in people with AIP and characterizing PCT and its risk factors, including hereditary hemochromatosis gene mutations and hepatitis C infection. Advances in recent decades demonstrated the influence of factors, such as nutrition, alcohol use, and smoking, on heme biosynthesis and their impacts on different forms of porphyria.

In parallel with, and supportive of, these advancing clinical efforts, NIDDK-supported researchers helped map out the intricate pathway of heme biosynthesis, identifying the key enzymes that catalyze reactions at multiple steps to convert porphyrins into heme. Scientists supported by the Institute also identified and sequenced some of the genes that encode enzymes of the heme synthetic pathway, and helped to define numerous genetic mutations associated with different forms of porphyria. For example, in the 1980s, scientists purified the enzyme that is impaired in CEP and isolated the gene encoding it. A study in 1990 identified the gene coding for the enzyme at the first step in the heme biosynthetic pathway, delta-aminolevulinic acid synthase 1 (ALAS1)—mutations in which are responsible for some of the acute hepatic porphyrias—from human liver samples. Studies in the 1980s and 1990s also characterized and purified the enzyme underlying PCT and HEP, including multi-generational family genetic studies that shed light on relationships between genetic traits, enzyme activity, and clinical symptoms. In the 1990s to 2000s, through several studies in animal models and people, researchers identified the genetic mutations responsible for the symptoms of EPP in the final enzyme within the heme biosynthetic pathway that result in reduced enzymatic activity. Throughout the 1990s, researchers continued to identify mutated forms of genes coding for enzymes responsible for other forms of porphyria, such as ADP and HCP. Later studies provided additional insights into these enzymes, including their structures—key information for understanding their functioning and role in disease processes. In 2005, the NIDDK initiated support for a Center for Excellence in Molecular Hematology that enabled additional discoveries

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about the molecular mechanisms in the porphyrias, including clues to the underlying pathways involved in PCT. Further genetic discoveries, related to EPP and XLP, were made by the Porphyrias Consortium, described below.

Scientists have utilized this explosion of new knowledge about the genetic factors underlying each of the porphyrias to develop unique animal models in which to study disease pathways and processes, as well as to test new treatments. For example, in 1998, researchers developed a zebrafish model with a mutated form of the gene associated with HEP in humans, followed soon after by mouse models with the genetic mutations and symptoms present in PCT, VP, and CEP. In 2010, a research group used a mouse model with a genetic mutation causing AIP to successfully test a corrective gene therapy approach using a viral vector to target cells in the liver. A more recent mouse model of an AIP subtype that causes early-onset neurological impairment revealed mechanisms behind this severe form of the disorder. Researchers developed mouse models with distinct genetic mutations associated with different severities of human CEP to further understanding of these disorder subtypes.

## THE PORPHYRIAS CONSORTIUM

In 2009, building upon these decades of basic and clinical research, the NIH's Rare Diseases Clinical Research Network announced the establishment of the Porphyrias Consortium. The Consortium is supported by the NIDDK and the NIH's National Center for Advancing Translational Sciences, in collaboration with the American Porphyria Foundation. The present-day Consortium includes six centers in the United States and other satellite sites, which bring together scientists, patient advocates, and industry to address the current challenges in porphyria research by conducting collaborative, large-scale clinical studies on these rare disorders. The Consortium's multiple centers, covering several geographical areas, help researchers recruit enough

participants with these rare disorders for robust studies. The Consortium also focuses on training the next generation of clinicians and investigators in porphyria care and research, and provides information on porphyrias for patients and their families, health care professionals, and the public.

The Consortium has conducted several studies aimed at understanding the mechanisms and disease course of the multiple forms of porphyria and developing new approaches to their diagnosis, treatment, and prevention. In 2014, the Consortium reported on early observational findings in their U.S.-based study cohort, describing the key clinical and genetic features and current approaches to clinical care for acute porphyrias—including AIP, HCP, and VP—and documenting an average delayed diagnosis of more than a decade. In 2015, researchers reported variability in how different clinical laboratories were measuring red blood cell protoporphyrin, a molecule derived from porphyrin during heme production, that can lead to missed diagnoses, particularly for the EPP and XLP forms of porphyria. Results of a Consortium study in 2017 helped to identify the genetic mutations present in people with EPP and XLP and showed that higher levels of red blood cell protoporphyrin were associated with increased disease severity and risk of liver dysfunction. In addition to these original studies, the Consortium has also issued recommendations for the diagnosis, treatment, and counseling of patients with acute porphyrias that originate in the liver, to ensure optimal health outcomes.

## PROGRESS TOWARD NEW TREATMENTS

The decades of research advances on the porphyrias and the ongoing efforts of investigators involved in the Porphyrias Consortium have helped develop breakthrough treatments for two forms of porphyria—AIP and EPP. NIDDK-supported studies mapping out the biological pathways involved in these disorders provided the foundation for this work.

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In the case of AIP, a disease marked by severe abdominal pain attacks and fatigue, the main treatment since the 1970s has been intravenous infusions with hematin, containing heme extracted from red blood cells. However, this treatment proved relatively slow-acting and came with side effects such as inflammation in the veins and iron overload. In recent years, the NIDDK and other NIH Institutes supported research on a cutting-edge approach to therapeutics called RNA interference (RNAi) using small interfering RNAs (siRNAs)—short strings of genetic material that effectively turn off genes that produce disease-causing proteins. Research in a mouse model supported through the Porphyrias Consortium showed that this approach could be used to target ALAS1, an overactive enzyme in AIP: an infusion of the siRNA inhibiting this enzyme effectively prevented and treated the attacks associated with AIP. The NIDDK also supported early pre-clinical research to develop an injection-based form of the treatment and assays that monitored response. This important work paved the way for testing this therapeutic in humans as part of clinical trials sponsored by a pharmaceutical company, with the participation of many scientists and centers within the Porphyrias Consortium. In November 2019, the FDA approved this new therapeutic for AIP in the form of a drug called givosiran (Givlaari<sup>®</sup>), which is already improving quality of life for people with AIP.

The Porphyrias Consortium also worked closely with another pharmaceutical company on a clinical trial to evaluate a treatment for EPP, called afamelanotide (Scenesse<sup>®</sup>). Afamelanotide binds to a receptor in skin cells, stimulating them to produce a pigment that protects against sunlight. In clinical trials conducted by the pharmaceutical company in the United States and Europe, with additional support from the NIDDK and the NIH's National Heart, Lung, and Blood Institute, Consortium investigators worked closely with the company to evaluate the safety and efficacy of an implant under the skin containing afamelanotide for treating EPP. These trials found afamelanotide increased the amount of pain-free time people with EPP could

spend in sunlight, as well as their overall quality of life. The treatment was approved by the FDA in October 2019—the first agent available to help people with EPP experience pain-free sun exposure.

## FUTURE DIRECTIONS

Building on the past progress made possible by the Porphyrias Consortium and other NIDDK-supported investigators, the Institute is committed to continuing support for research to advance understanding of the porphyrias and discover better ways to manage these disorders. The Consortium is conducting ongoing clinical studies on natural history, diagnosis, and treatments for all forms of porphyria. The Consortium's active studies include a longitudinal study to characterize the long-term course and outcomes of several forms of porphyria. Ongoing clinical trials will determine the safety and efficacy of new therapies. Recent efforts by the Consortium include characterizing the natural history and clinical management of acute hepatic porphyrias in people with recurrent attacks, evaluating methods for measuring quality of life in people with AIP, and joining together with the European Porphyria Network to establish an international database with diagnostic information on genetic variants linked to all forms of porphyria. In addition to these Consortium-based activities, the NIDDK also continues to support investigator-initiated porphyria research, such as studies in cell and animal models to decipher specific mechanisms of cell injury caused by an overabundance of porphyrins. Together, these research efforts will continue to advance our understanding of porphyrias, and help lead the way to new treatments, with the overarching goal of improving the lives of people with these disorders.

For more information on the Porphyrias Consortium, please visit:  
[www.rarediseasesnetwork.org/cms/porphyrias](http://www.rarediseasesnetwork.org/cms/porphyrias).

## Developing New Diagnostic and Treatment Options for Children with Biliary Atresia

Biliary atresia is a rare but severe liver disease that begins in infancy. This disease is marked by inflammation and scarring of the bile ducts, the tubes that carry bile from the liver to the gallbladder and intestines to aid digestion. The resulting back-up of bile in the liver leads to jaundice, liver damage, and if untreated, liver failure and need for liver transplantation.

NIDDK-supported research has focused on efforts to improve the understanding of biliary atresia and other pediatric liver diseases and to advance care of children with these conditions. Toward this goal, the NIDDK established the Childhood Liver Disease Research Network (ChiLDRen) in 2009 by combining the NIDDK-supported Biliary Atresia Research Consortium (BARC) and the NIDDK-supported Cholestatic Liver Disease Consortium (CLiC). This Network is a collaborative team of doctors, scientists, research coordinators, medical facilities, patients and their families, and patient support organizations at sites in the United States and Canada focused on improving the lives of children and families dealing with rare liver diseases such as biliary atresia. The Network's research constitutes the largest study of biliary atresia in the world, with past results shedding light on contributors to disease development and testing new treatment approaches. However, research on new treatments has not yet yielded significant improvements in altering the course of this liver disease and its associated complications. As such, ChiLDRen continues to conduct clinical trials, facilitate the discovery of underlying causes of disease, and search for new diagnostic and treatment options for children with rare liver diseases.

### ABOUT BILIARY ATRESIA

Typically, the first sign of biliary atresia is yellowing of the skin and whites of the eyes, called jaundice, which results from the buildup of bile in the body. Bile contains a reddish-yellow substance called bilirubin. Infants often have jaundice from other causes in the first 2 weeks of life, so it is not easy to identify biliary atresia in newborn infants based on this symptom alone. Jaundice that lasts beyond 3 weeks of age may be the first sign of biliary atresia. Infants with biliary atresia may also have pale yellow, gray, or white stools if bilirubin is not reaching the intestines.

Diagnoses can be delayed because biliary atresia is just one of many possible causes of blocked bile flow in newborns. If not caught early and treated with a surgery called hepatportoenterostomy or HPE (also referred to as the Kasai procedure), the disease is potentially fatal and an early liver transplant may be required. During the HPE procedure, the damaged bile ducts outside the liver are removed and a loop of the infant's small intestine is used to connect the liver directly to the small intestine. This allows bile to flow directly from the liver to the small intestine. The procedure is not curative, but may slow or, in some cases, prevent the development of cirrhosis (liver damage and scarring) and liver failure. In children with biliary atresia, cirrhosis may cause complications such as portal hypertension, which is increased blood pressure in the portal vein, a blood vessel that carries blood from the intestines to the liver. As a consequence of portal hypertension, children with biliary atresia may have an enlarged spleen—setting up a condition in which platelets are sequestered in the spleen and

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are not readily available in circulating blood to stop bleeding. Even after surgery, many children with biliary atresia develop severe disease requiring liver transplantation by the time they reach adulthood.

While the causes of biliary atresia are not fully understood, studies indicate that genetic, environmental, and infectious factors may play a role. Researchers funded by the NIDDK through ChiLDReN and other grants have set about to uncover how biliary atresia develops and progresses, as well as how to improve management of this disease.

## ChiLDReN

To better understand the causes of biliary atresia and develop improved treatments, ChiLDReN has conducted research related to diagnosis and disease progression, and currently has several ongoing clinical studies.

For example, researchers recently reported that a protein called matrix metalloproteinase-7 (MMP-7) may be a potentially useful clinical biomarker for diagnosing biliary atresia. MMP-7 was found to be at high levels in blood from infants with biliary atresia compared with other liver diseases, especially when combined with another marker of impaired bile flow called  $\gamma$ -glutamyltranspeptidase. Scientists have also identified *PKD1L1* gene variants in some infants with biliary atresia with splenic malformation (BASM), a syndrome occurring in about 10 percent of patients with biliary atresia. The gene variants code for a protein called PKD1L1 found in bile ducts. PKD1L1 is important for key biological processes, including proper positioning of internal organs during embryonic development, underscoring its possible role in BASM syndrome. Furthermore, investigators have described a set of 14 genes with activity levels at diagnosis that predicted transplant-free survival at 2 years of age in contrast to those who require liver transplantation or succumb to the disease. This finding suggests that the newly identified 14-gene activity signature could be a useful biological marker

to predict how biliary atresia will progress in young children after the Kasai procedure (see research advance earlier in this chapter).

In two ongoing clinical research studies conducted by ChiLDReN—*A Prospective Database of Infants with Cholestasis* (PROBE) and *Biliary Atresia Study in Infants and Children* (BASIC)—clinicians are collecting clinical information and biological samples from infants, children, and young adults with biliary atresia. These types of prospective, observational studies will allow researchers to identify potential causative factors that lead to disease onset and follow the natural history of disease progression. In a third clinical research study called *FibroScan™ in Pediatric Cholestatic Liver Disease* (FORCE), researchers are evaluating the use of noninvasive monitoring of liver fibrosis (scar tissue formation in cirrhosis) as part of the clinical management of children with liver disease marked by bile duct blockage. While liver biopsy is often used in the initial diagnostic evaluation of children with liver disease, subsequent surveillance by liver biopsy is rarely performed in children because of its inherent invasiveness and risks. A noninvasive means of assessing fibrosis throughout the liver would be highly desirable and clinically useful in children with biliary atresia.

## HOPE THROUGH RESEARCH

The NIDDK continues to support research into biliary atresia through ChiLDReN and several investigator-initiated research projects. For example, investigator-initiated studies include those that seek to identify the biological basis of clinical outcomes, map disease pathways, and identify new therapeutic agents for biliary atresia. Researchers are also trying to improve early diagnosis of the disease, such as recent research showing that a two-step screening approach measuring newborns' bilirubin levels could identify those with biliary atresia—progress toward a goal of more successfully treating babies earlier in the course of disease (see research advance earlier in this chapter).

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## EMILIA'S STORY



Left to right: Lucia (mother), Emilia, Mateo (brother), and Marco (father)

Nine-year-old Emilia is an extremely talented young girl living in Colorado. She has many interests but is especially passionate about theater. “I am a theater person!” she exclaims. Her specialty is singing and dancing in musical theater productions. “One of my favorite songs is Welcome to Wonderland,” she shares, which is from the musical Alice in Wonderland. Most recently, she was cast in a production of The Jungle Book as the narrator and a singer. Emilia’s other interests include art, volleyball, basketball, swimming, skiing, and hockey. Clearly, she has not let a diagnosis of a serious liver disease called biliary atresia keep her down.

In addition to being busy with theater and other activities, in 2019, when she was only 7 years old, Emilia was selected to represent Children’s Hospital Colorado as an Ambassador—a great honor. In this role, she shared her story as someone living with biliary atresia, and participated in community fundraising events. For example, Emilia participated in a fashion show preceding a Colorado Avalanche hockey game and served as a host at the 2019 Children’s Hospital Colorado Gala. She was also asked to participate in an in-person interview with a Denver Bronco football player, and now as a result, Emilia says, “I have my medal as a junior reporter.” In describing all of her outreach activities, Emilia’s bright personality shines through.

Emilia also enjoys doing outdoor activities with her mother Lucia, father Marco, and younger brother Mateo. The family takes part in bike rides, walks, hikes, and swimming, whenever possible. Although they strive to maintain an active lifestyle, Lucia and Marco are well aware that Emilia has a serious liver disease and have to carefully plan the family’s activities accordingly. “She’s been pretty healthy and it’s just [a job for] us as parents to be aware and more cautious in everything she does. It’s hard for us, [and hard] for her to understand,” says Lucia. “But still, she’s a very happy girl.”

*“She’s been pretty healthy and it’s just [a job for] us as parents to be aware and more cautious in everything she does,” says Emilia’s mother, Lucia, explaining how the family avoids activities that may increase her risk of an unwanted bleeding event due to her biliary atresia.*

## DIAGNOSIS AND EARLY TREATMENT

During her 6-week-old checkup, the pediatrician noted that Emilia looked jaundiced, and lab test results indicated that she had elevated levels of bilirubin. The pediatrician subsequently made an appointment for Marco and Lucia to bring their baby daughter to see Dr. Ronald Sokol, a pediatric gastroenterologist at Children’s Hospital Colorado. During this initial visit with Dr. Sokol, a liver biopsy was conducted that confirmed that Emilia had biliary atresia. Three days later at approximately 55 days of age, Emilia underwent the Kasai procedure. It was “a big surgery ... we were extremely nervous,” recalls Marco. Thankfully, “it went pretty smoothly,” says Lucia. After a week in the hospital, Emilia was discharged and sent home. Lucia remembers those early days after the surgery: “We took care of her at home and she was ... pretty

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happy.” The only complication of the surgery was the build-up of fluids in her abdomen, but after a few months, the excess fluids resolved.

*“One of the hopes that we have is that soon, hopefully, there is a medicine that can reverse or stop the cirrhosis of the liver,” says Marco, describing how studies such as those conducted by the Childhood Liver Disease Research Network (ChiLDReN) may be able to help his daughter Emilia.*

From the time she was discharged from the hospital following the surgery, Emilia has taken a broad-spectrum antibiotic every day to prevent an infection called cholangitis. Cholangitis arises when bacteria normally residing in the intestine enter the liver and cause infection. Despite the daily use of the antibiotic, she has had two episodes of cholangitis, which required high-dose antibiotic treatment in the hospital to combat the infections.

## MAINTAINING LIVER FUNCTION AND OVERALL HEALTH

To maintain her liver function and overall health, Emilia and her parents take several proactive measures. Her liver function is monitored twice a year during her visits with Dr. Sokol. Marco recalls, “We kept her in good hands, and we followed the instructions from Dr. Sokol—and she’s been thriving health-wise.” Lab results indicate that her liver function has been fairly stable over time. In addition to liver function tests, her platelet levels are also measured. Because of her portal hypertension, Emilia has an enlarged spleen that “soaks up” more platelets from the blood than normal, making those blood cells unavailable to help stop episodes of bleeding. As a result, Marco and Lucia also keep a close eye on their daughter for any wound that isn’t healing as it should. Emilia refrains from activities that would increase her

risk of an unwanted bleeding event. Additionally, because children with biliary atresia often have nutritional deficiencies, she takes vitamin supplements daily along with a compound called ursodiol that aids in fat absorption. She also takes probiotic supplements. And, looking to the future, Emilia and her family participate in research.

*When asked how likely he would be to recommend clinical research participation to others whose children have liver disease, Emilia’s father, Marco, says: “Yes, participate. It’s basically how improvement and progress in medical studies goes on.... It’s progress toward the future.”*

## PARTICIPATING IN CLINICAL RESEARCH STUDIES

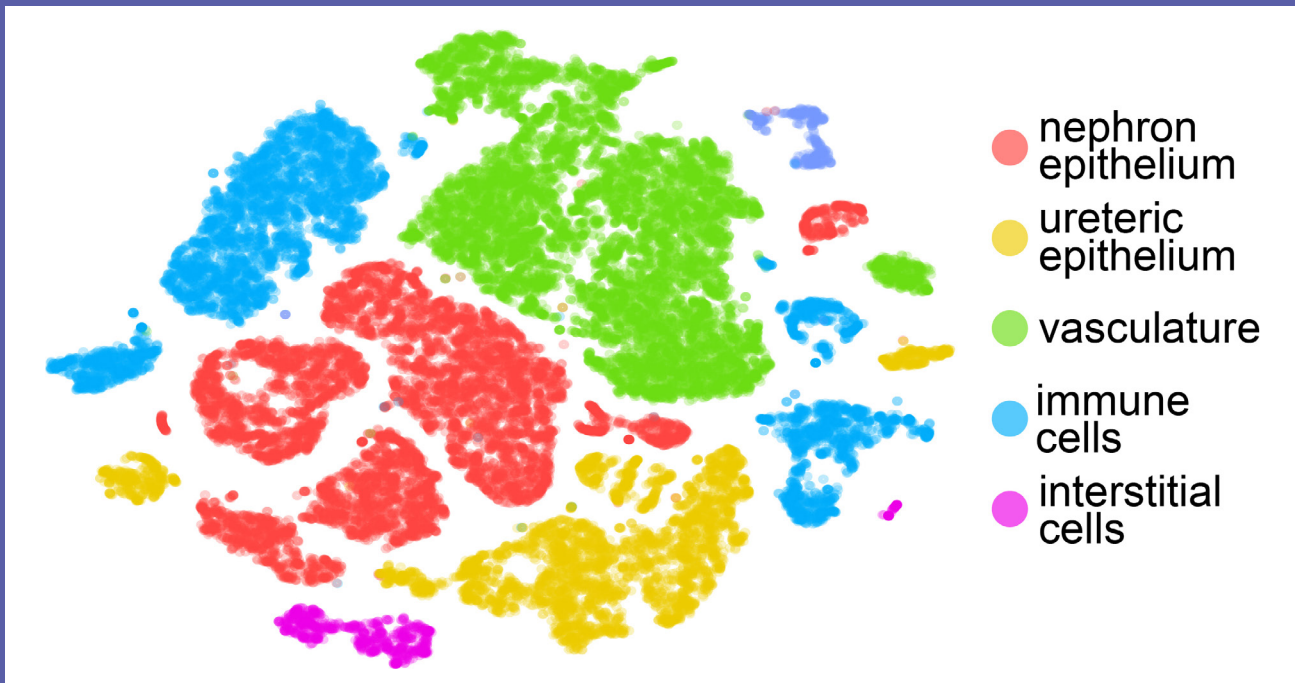
Given the diagnosis of a serious liver disease, it was an easy decision for Lucia and Marco to enroll Emilia as a baby in A *Prospective Database of Infants with Cholestasis* (PROBE) clinical research study conducted by the NIDDK-supported Childhood Liver Disease Research Network (ChiLDReN). Logistically, her participation in the clinical study is easy and convenient. Dr. Sokol serves as both Emilia’s liver specialist and as the principal investigator for the PROBE site at Children’s Hospital Colorado. Blood is drawn during her twice-a-year visits with Dr. Sokol, and a small portion is used by researchers in the PROBE clinical research study to understand how the disease progresses over time. Emilia has also been participating in ChiLDReN’s *FibroScan™ in Pediatric Cholestatic Liver Disease* (FORCE) clinical study for approximately 4 years, which seeks to determine whether noninvasive monitoring of liver fibrosis is as reliable and informative a tool in children as it is in adults. This portion of the visit is performed quickly and utilizes an ultrasound device to measure scarring in the liver.



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The family is happy to make these contributions to research that may not only one day improve Emilia's health, but also the health of other children living with biliary atresia or other serious liver diseases. "One of the hopes that we have is that soon, hopefully, there is a medicine that can reverse or stop the cirrhosis of the liver," says Marco. Additionally, Marco would encourage others to volunteer for research studies if the

opportunity arises. "Yes, participate," he says. "It's basically how improvement and progress in medical studies goes on.... It's progress toward the future." As for Emilia's future, she can't wait for the next opportunity to participate in a musical theater production where she will no doubt steal the show with her vibrant energy, passion, and talent.



As described in this chapter, researchers have reported significant new findings about kidney development and three-dimensional structure in mice. Normal, healthy kidneys filter waste products from blood. Millions of people have kidney disease and kidney failure, and a better understanding of the cellular functions and development of the kidneys is essential to developing approaches to prevent, reverse, or repair injured and diseased kidneys. The investigators used single-cell analysis combined with cell-fate mapping studies, in which early-stage cells are biologically labeled such that the specialized cells that derive from them also contain the label. These cutting-edge techniques enabled the investigators to gain new insights into how nephrons (filtering units of the kidney) differ in the outer versus middle parts of the kidney, the cellular origins of different structures and junction points of nephrons, and intriguing sex differences in nephron gene expression (*i.e.*, whether a gene is turned on or off). With this wealth of novel information, the researchers have constructed a Web-searchable, annotated anatomical database of the adult mouse kidney for use by the scientific community. An example of the kinds of data available in the database is shown and highlights the diversity of cells and organizational structures residing within the kidney. Furthermore, users can analyze the data set in various ways, for example, to learn about different genes, obtain a graphical representation of the anatomical location of a gene of interest within the kidney, and distinguish gene expression patterns by cell types in nephrons.

*Image provided by Dr. Andrew P. McMahon, Keck School of Medicine of the University of Southern California. Reprinted from Dev Cell; Vol 51; Ransick A, Lindström NO, Liu J,...McMahon AP; Single-cell profiling reveals sex, lineage, and regional diversity in the mouse kidney; Pages 399-413.e7; Copyright 2019, 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, the 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 the 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.

It has been estimated that 37 million American adults have impaired kidney function—also called chronic kidney disease (CKD).<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 likely to face serious health complications at an earlier age than people who historically have developed these conditions later in life.

One feature common to kidney diseases arising from varying causes is the deposition of fibrotic scar tissue in the kidney. Research supported by the 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. CKD, especially if undetected, can progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). People with ESRD require dialysis or a kidney transplant to live. In 2018, over 783,000 patients received treatment for ESRD: over 554,000 received either hemodialysis or peritoneal dialysis, and over 229,000

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 ESRD. Compared to Whites, ESRD prevalence in 2018 was about 3.4 times greater in African Americans, 1.9 times greater in American Indians or Alaska Natives, and 1.3 times greater in Asians.<sup>2</sup> Compared to all non-Hispanics, Hispanics had 1.5 times the risk for kidney failure.<sup>2</sup> In recent years, scientists supported by the NIDDK have uncovered important genetic clues that may play a role in some of the health disparities related to kidney disease susceptibility and progression in minority populations.

The Institute supports a significant body of research aimed at understanding the biology underlying CKD and developing treatment strategies. The NIDDK's chronic renal diseases program supports basic and clinical research on kidney development and disease, including the causes of kidney disease, the underlying mechanisms leading to progression of kidney disease to ESRD, and the identification

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<sup>1</sup> Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2019*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2019.

<sup>2</sup> United States Renal Data System. *2020 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, 2020.

and testing of possible strategies to prevent development or halt progression of kidney disease. In addition to research on kidney disease related to diabetes and high blood pressure, the 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. The CKD Biomarkers Consortium (CKD BioCon) promotes the discovery and validation of novel biomarkers for CKD initiation, progression, and development of complications. A more complete understanding of biomarkers could allow physicians to detect kidney disease earlier and perhaps identify people at greater risk of progression, allowing them to tailor treatments to a specific individual. The Kidney Precision Medicine Project is obtaining and evaluating human kidney biopsies from participants with acute kidney injury (AKI) or CKD for the purpose of creating a kidney tissue atlas, defining disease subgroups, and identifying critical cells, pathways, and targets for novel therapies.

Urologic diseases affect people of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life. The NIDDK's urology research program supports basic and clinical research on the normal and abnormal development, structure, function, and injury repair of the genitourinary tract. Areas of interest include the causes of and treatments for urologic diseases and disorders, such as benign prostatic hyperplasia, urinary incontinence, urinary tract infections, and urinary stone disease. To spur research in urinary stone disease, the Urinary Stone Disease Research Network (USDRN) is: (1) conducting a randomized clinical trial to investigate the impact of increased fluid intake and increased urine output on the rate of recurrence of urinary stones in adults and children; (2) conducting clinical research to understand and mitigate ureteral stent-related pain and symptoms; and (3) providing data and collecting biological samples from the studies to create a resource for future researchers.

Other disorders of the genitourinary tract, such as interstitial cystitis/bladder pain syndrome (IC/BPS)—also known as IC/painful bladder syndrome (PBS)—in women and men and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)

in men, are also important research topics of the NIDDK's urology program.

IC/BPS is a debilitating, chronic, and painful urologic disorder. Based on a recent large, national interview survey, it is estimated that among U.S. women 18 years or older, 3.3 million (2.7 percent) have pelvic pain and other symptoms, such as urinary urgency or frequency, that are associated with IC/BPS.<sup>3</sup> Using a community-based epidemiologic survey, researchers have estimated that among U.S. men ages 30 to 79 years old, 1.6 million (1.3 percent) have persistent urologic symptoms, such as pain with bladder filling and/or pain relieved by bladder emptying, that are associated with BPS.<sup>4</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. One example of an ongoing study is the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, which supports research designed to uncover the underlying causes of IC/BPS and CP/CPPS and to characterize the disease profiles in affected persons.

Based upon national public health surveys conducted over several years, it is estimated that about 54 percent of women (20 years and older) report urinary incontinence in the past 12 months. Urinary incontinence was self-reported by approximately 15 percent of men surveyed.<sup>5</sup> Many suffer in silence due to embarrassment and lack of knowledge about treatment options available. NIDDK-supported studies over the past several years have helped to advance knowledge about the efficacy of surgical treatment of urinary incontinence, as well as to provide new insights into non-surgical alternatives. As researchers continue to investigate treatment options, an equally important challenge is to identify and understand the important subgroups of people with lower urinary tract symptoms (LUTS) through improved measurement of patient experiences of LUTS in men and women. To address

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<sup>3</sup> Berry SH, et al. *J Urol* 186: 540-544, 2011.

<sup>4</sup> Link CL, et al. *J Urol* 180: 599-606, 2008.

<sup>5</sup> *Urological Diseases in America, 2018 Addendum*. NIDDK, NIH Publication Number 12-7865, 2018.

this challenge, the NIDDK supports the multi-site Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN). The NIDDK is also leading new efforts to explore whether it may be possible to prevent symptom onset and/or progression, thereby improving health. The NIDDK, in conjunction with the National Institute on Aging, the NIH Office of Research on Women's Health, and the NIH Office of Behavioral and Social Sciences Research, established the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium to develop the evidence base for normal or healthy bladder function and to identify behavioral and other risk factors for conditions associated with lower urinary tract symptoms in women.

The 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 system. Research efforts include studies of a number of blood diseases, including sickle cell disease, the thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, thrombocytopenia, and the anemia of inflammation and of chronic diseases. To promote high-impact basic or pre-clinical research, the Institute supports the Stimulating Hematology Investigation: New Endeavors (SHINE) program and includes the following current research topic areas: regulation of blood (hematopoietic) stem cells, factors that play a role in the development of different types of blood cells, and red blood cell maturation. The Institute's SHINE II program seeks to further catalyze research in basic or pre-clinical, proof of principle research projects that are tightly focused and directed at validating novel concepts and approaches that promise to open up new pathways for discovery in benign hematology research. The NIDDK is also keenly interested in the basic biology of adult hematopoietic stem cells, which are used clinically in bone marrow transplants and may have broader application in gene therapy research.

## CHRONIC KIDNEY DISEASE PROGRESSION IN CHILDREN

**Identifying Children at Increased Risk of Chronic Kidney Disease Progression:** A new study has described different trajectories of chronic kidney disease (CKD) progression in children that will aid in identifying those at high risk for progressive disease. The basic functional unit of the kidney

is the nephron, which consists of various cells and structures that work together to filter waste products, remove excess fluid from the blood, and balance various body chemicals. Of these structures, the glomerulus is the fundamental filtering apparatus. A common kidney function measurement called the glomerular filtration rate (GFR) is an estimate of blood filtered per minute by all the nephrons within the kidneys. The ability to predict CKD progression, as measured by declining GFR, is a major challenge for nephrology (the medical specialty focused on the kidneys).

Using publicly available Chronic Kidney Disease in Children (CKiD) study data through the NIDDK Central Repository, researchers employed a statistical modeling approach to establish GFR trajectories (i.e., changes in kidney function over time) in female and male participants with glomerular and non-glomerular diseases. CKiD is a multi-center study of children ages 1 to 16 years with mildly to moderately impaired kidney function. The CKiD researchers are monitoring the health of these children over time in several areas, including determining the risk factors for decline in kidney function, and defining how progressive decline in kidney function affects biomarkers of risk factors for cardiovascular disease, evaluating several brain functions (e.g., attention, perception, memory, language, and behavior), and assessing growth failure and its associated morbidity. Using data from CKiD, this study found two distinct GFR trajectories for glomerular disease while four distinct GFR trajectories were reported for non-glomerular disease. Glomerular and non-glomerular diseases displayed very different GFR trajectories—among those with glomerular disease, a subset of female participants had a rapid GFR trajectory decline indicating rapid loss of kidney function, whereas no difference was observed between sexes in those with non-glomerular diseases.

This valuable new information from a subset of girls with rapidly progressing glomerular disease will enable clinicians to better prepare their patients and their families for kidney transplantation or dialysis. Furthermore, girls have lower access to kidney transplantation in the United States than boys, and this study could help address this disparity.

*Bonnéric S, Karadkhele G, Couchoud C, Patzer RE, Greenbaum LA, and Hogan J. Sex and glomerular filtration rate trajectories in children. Clin J Am Soc Nephrol 15: 320-329, 2020.*

## NEW INSIGHTS INTO KIDNEY DEVELOPMENT

### **New Kidney Mapping Could Lead to Health Gold:**

Through studies in mice, researchers have gained fundamental new insights into kidney development and organization and how they differ between males and females—all of which could aid research efforts to battle human kidney diseases. Human and animal kidneys are highly complex. Within each kidney, myriad essential structural and functional units, called nephrons, are arranged radially in an interconnected pattern resembling a dense tree crown. Together, nephrons carry out the kidneys' primary function of filtering the blood to remove wastes, as well as other important activities. A better understanding of the cellular functions and development of nephrons—including sex differences that might underlie observed differences between women and men in protection from kidney injury—is key to finding ways to reverse, avoid, or repair kidney injuries and diseases.

In a major advance, researchers used a painstaking method called single-cell RNA sequencing to identify genes that are expressed (turned on or off) in adult male and female mouse kidney cells. To organize the results, they divided each kidney into three zones corresponding to its outer, middle, and innermost anatomical regions prior to extracting cells, and assigned representative cells from each zone into “clusters” based upon gene expression patterns. They then combined those results with the results of imaging studies that allowed them to visualize, trace, and compare the development and localization of different mouse kidney tissues and structures over time from the embryonic stage to maturity. Together, these experiments yielded a wealth of information, such as details on how nephrons differ in the outer versus middle parts of the kidney, the cellular origins of different structures and junction points of nephrons, and intriguing sex differences in nephron gene expression that provide new targets for study. For example, evidence suggests that female mice and humans are resistant to a type of kidney injury that primarily affects a section of the nephron called the proximal tubule. The researchers found that the expression of genes involved in transport of small molecules and metabolism of drugs, cholesterol, and hormones—all functions of the proximal tubule—differed between female and male mice. Interestingly, in a second recent

study, another team of researchers also found differences in gene expression between female and male mice when they examined the same section of the nephron post-injury, further bolstering the importance of this region—and these genes—as study targets in understanding kidney disease and kidney protection.

Researchers from the first study have used their results to generate a Web-searchable, annotated anatomical database for use by the scientific community. Although there are limitations on some of the data—for example, some kidney cell types were underrepresented in the study because they did not survive the experimental procedures—these results from mice can serve as a guidepost in similar mapping of human kidney. This research also points to potential explanations for both general vulnerabilities and sex-specific protective factors in kidney injury and ultimately a better understanding of kidney diseases and kidney failure—and thus new ideas for therapies.

*Ransick A, Lindström NO, Liu J,...McMahon AP. Single-cell profiling reveals sex, lineage, and regional diversity in the mouse kidney. Dev Cell 51: 399-413.e7, 2019.*

*Wu H, Lai C-F, Chang-Panesso M, and Humphreys BD. Proximal tubule translational profiling during kidney fibrosis reveals proinflammatory and long noncoding RNA expression patterns with sexual dimorphism. J Am Soc Nephrol 31: 23-38, 2020.*

**Unraveling the Molecular Nature of Blood Vessel Specialization in the Kidney:** Scientists have identified critical sets of genes turned on in individual cells within discrete, specialized zones of blood vessels in the mouse kidney during development and adulthood—findings that could have important implications for developing artificial kidney technologies. The activities of nephrons—the essential structural and functional units of the kidney—would be impossible without the blood vessels that intertwine with them. These blood vessels, or vasculature, are not uniform, but instead become specialized according to their position within a nephron to help carry out the precise function of each nephron segment or substructure (e.g., retention of sugars, reabsorption of water to help maintain fluid balance in the body). This vascular specialization by zone is essential for proper kidney formation and function, but the molecular pathways driving this specialization

have been unknown, hindering the development of promising technologies such as artificial kidneys. A research team recently identified critical molecules regulating this process in mice.

Using sophisticated cell-sorting techniques, the scientists isolated individual blood vessel cells, called endothelial cells (ECs), from the kidneys of developing mouse embryos, as well as from postnatal and adult male mice, and identified all the genes that were turned on in those individual cells. They also compared the genes turned on in ECs in bulk from kidneys to those of the lung, liver, and heart, to identify those with activity specific to kidneys. Comparisons of the kidney-specific EC gene “molecular profiles” revealed several distinct clusters of genes that correspond to the different structures and functional regions within the nephron; there were also significant differences between mouse embryonic and adult kidneys. Further examining ECs, the scientists found that different genes were active in different vascular zones, such as genes involved in regulating the absorption of specific molecules, providing developmental instructions to neighboring cells, or turning other critical genes on or off. The researchers then tested the importance of the gene *Tbx3*, which they had found to be particularly active in a critical segment of the nephron called the glomerulus. They genetically deleted *Tbx3* specifically in glomerulus ECs in male mice and found defects in the structure of the glomerulus that affected blood pressure and led to aberrant filtration of molecules from the blood. With other experiments, these results indicate that *Tbx3* governs genes important to glomerular blood vessel development and function. Importantly, the scientists also tested the gene in cultured human endothelial cells and found that human *TBX3* likely has a similar function as the mouse gene.

The distinct kidney EC molecular profiles identified in this study shed critical light on the processes that create and maintain discrete vascular zones in the nephron. These findings could provide a foundation to help accelerate the engineering of functional artificial kidneys.

Barry DM, McMillan EA, Kunar B,...Rafii S. *Molecular determinants of nephron vascular specialization in the kidney. Nat Commun* 10: 5705, 2019.

## RESEARCH ON LOWER URINARY TRACT SYMPTOMS

### Symptom-based Clustering in Men

**with Lower Urinary Tract Symptoms:** New research has employed an algorithm to identify novel subgroups of men with different lower urinary tract symptoms (LUTS) based on detailed symptom information—results that could help in understanding and treating LUTS in the future. LUTS are highly prevalent in both males and females, but many people who seek help from health care providers for LUTS experience neither total nor permanent resolution of their symptoms with current management approaches. One of the barriers to improving diagnosis and management of LUTS is incomplete knowledge and imprecise classification of subtypes of LUTS and their associated causes. There are a wide variety of LUTS that people can experience, such as problems with emptying (voiding) urine from the bladder, which may be caused by problems in the urinary tract or may originate elsewhere in the body. Even people with similar symptoms may have different underlying urinary tract conditions.

A study conducted through the NIDDK-supported Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) sought to overcome some of the barriers to diagnosis and management. Using a consensus clustering algorithm—a novel approach that did not rely on conventional clinical definitions to group patients—they analyzed responses to self-administered questionnaires to identify distinct symptom signatures in 503 care-seeking men with LUTS, the majority of whom were Caucasian with an approximate average age of 61. Four separate symptom clusters (CL1-4) were identified among participants, with the following characteristics. The 166 participants in CL-1 had predominant urinary symptoms of hesitancy (difficulty starting or maintaining urine stream), straining, weak stream, incomplete bladder emptying, frequency, and nocturia (waking from sleep to urinate)—a pattern suggestive of bladder outlet obstruction. The 93 participants in CL-2 mainly had symptoms of post-void dribbling and post-void urinary incontinence. The 114 participants in CL-3 had predominant symptoms of urinary frequency and nocturia without incontinence. The 130 participants in CL-4 had symptoms of severe urinary frequency, urgency, and urgency incontinence.

Future research may examine these four symptom clusters in the context of biomarkers, and how the brain and/or nervous system may be influencing bladder function. For example, neuroimaging may identify differences in brain structure and function as it relates to bladder control, and sensory testing could explore whether differences exist in nervous system responses to auditory (hearing) and pain stimuli. Findings from such studies could provide insight into the complexities of male LUTS, while validation studies can help to determine if the groupings are helpful to clinical diagnosis and management of LUTS across men in the U.S. population. Furthermore, the phenotypic clusters identified by the LURN consortium provide a foundation in which to test the effectiveness of treatments.

Liu G, Andreev VP, Helmuth ME,...Kirkali Z; LURN Study Group. Symptom based clustering of men in the LURN Observational Cohort Study. *J Urol* 202; 1230-1239, 2019.

## IMMUNE SYSTEM RESPONSES TO URINARY TRACT INFECTIONS

**Immune System Response Could be Undermining Ability To Fight Urinary Tract Infections:** New findings in mice about immune system responses to urinary tract infections (UTIs) could help explain the high rates of UTI recurrence in humans and suggest novel ways to treat them. UTIs are very common, especially in women, many of whom suffer repeated infections with symptoms such as painful urination and a frequent or intense urge to urinate. The most common cause of UTIs is a bacterium normally found in the human intestines, called *Escherichia coli* (*E. coli*); uropathogenic *E. coli*, or UPEC, are those able to infect the urinary tract and sometimes the kidneys. While UTIs can be treated with antibiotics, the threat of increasing bacterial antibiotic resistance is driving research to identify new therapeutic approaches.

To gain insights that could lead to potential therapeutic targets, researchers are examining not only bacterial factors that enhance UPEC infectivity, but also factors and responses in human and animal model hosts that can either help or hamstring the ability to ward off UTI-causing microbes. For example, one way both humans and

mice respond to UTIs is to shed infected cells lining the inside of the bladder—an early, innate response to UTIs that is mediated by certain immune system cells residing in the bladder. Though drastic, as it damages the bladder lining, cell shedding reduces infection in the bladder wall. Simultaneously, other cells of the immune system begin to organize so-called adaptive responses to the invading microbes that are supposed to help fight the bladder infection in a more targeted fashion, such as through developing antibodies. However, humans and mice appear not to develop a robust antibody response against UPEC that would help kill residual bacteria and protect against subsequent infections. Instead, researchers have now uncovered evidence in mice strongly suggesting that, rather than being balanced, the adaptive immune response to bladder infection by UPEC is highly biased toward aiding repair of the bladder lining and inhibits responses that would clear UPEC. The researchers used mouse models deficient in different adaptive immune responses and/or genetically engineered to enable detection of cells involved in these responses. Studying these mice, the scientists were able to identify distinct subsets of immune system cells responsible for initiating and executing this biased response and the steps involved in establishing it in the bladder. Moreover, when the scientists exposed mice to multiple rounds of UPEC infection, they observed that the bias toward tissue repair was reinforced over time and, in fact, led to a thickening of the bladder lining that ultimately reduced mouse bladder capacity.

Repair of the bladder lining is critical for protecting underlying cells from noxious waste molecules present in urine—a unique challenge posed by the innate response to UTIs. However, the high bias toward repair and consequent inhibition of a robust companion antibody response could be contributing not only to recurrent infection but also to development of bladder dysfunction, such as urinary urgency or incontinence. This possible connection can now be explored, along with methods to reestablish balance in the host response to UTIs that could improve outcomes and prevent recurrence.

Wu J, Hayes BW, Phoenix C,...Abraham SN. A highly polarized  $T_H2$  bladder response to infection promotes epithelial repair at the expense of preventing new infections. *Nat Immunol* 21: 671-683, 2020.



## PROGRESS TOWARD TREATING URINARY STONES

### Moving Objects with Ultrasound Beams—Potential Application to Urinary Stone Disease:

Researchers have developed a noninvasive technology using ultrasound beams to lift and reposition an object in a living animal—an advance that could potentially be used to treat people with urinary stone disease. Urinary stones (also referred to as kidney stones) are one of the most common disorders of the urinary tract. Smaller stones may pass with little or no pain, while larger stones may get stuck along the lower urinary tract and block the flow of urine, causing severe pain and/or bleeding. Current treatments for urinary stones, such as lithotripsy that breaks stones into smaller pieces, may leave behind residual stone fragments. Most fragments will pass on their own, but others may grow larger, cause pain, and may require the need for additional treatment.

Working to advance safe, effective, and more efficient ways to reposition and encourage the passage of urinary stones, researchers have developed a noninvasive strategy to essentially trap a stone in an ultrasound beam (*i.e.*, acoustic trapping). Trapped within this beam, the stone can be moved or repositioned by either moving the device that generates the ultrasound waves (*e.g.*, transducer) or electronically steering the ultrasound beam by altering the phase of the wave. The scientists first demonstrated that the ultrasound beam could trap, lift, and steer a 3-millimeter glass sphere under ideal conditions—in a water tank. They moved the sphere a total distance of 6 millimeters vertically and 6 millimeters horizontally. The researchers further reported that this noninvasive acoustic trapping approach successfully moved glass spheres in the urinary bladders of three female pigs. To accomplish this, a single 3-millimeter glass sphere was placed in the bladder of each anesthetized animal using a tube with a camera-equipped scope and a device carrying the glass sphere. The camera monitored the sphere movement and was used to evaluate changes to the bladder wall after each acoustic trapping manipulation. Importantly, the technology did not cause detectable injury to the animals' bladder wall.

This study demonstrates the ability to manipulate objects in the pig bladder using acoustic trapping,

with potential application to treating urinary stones as well as other medical uses. Future research will be needed to evaluate the safety and effectiveness of this approach with respect to variations in shape, structure, and composition of urinary stones along the entirety of the urinary system, as well as to determine if it could be used in people. The technology associated with this translational work has been licensed to a small business.

Ghanem MA, Maxwell AD, Wang Y-N,...Bailey MR.

*Noninvasive acoustic manipulation of objects in a living body.*

*Proc Natl Acad Sci USA* 117: 16848-16855, 2020.

## NEW INSIGHTS INTO BLOOD DISORDERS

### Putting the “Brakes” on Adult Blood Stem Cell

**Proliferation:** A recent study revealed a natural process that limits the ability of adult blood stem cells to proliferate (*i.e.*, divide to increase their numbers). The body's adult blood stem cells are able to replace blood cells damaged by disease, injury, or age. These cells can be found in either a state of quiescence or of proliferation. Previous research has shown that the transition from quiescence to the proliferative state requires the action of cellular structures called mitochondria, which take chemical energy from sugars and fats and convert it into fuel that is usable throughout the cell.

Recently, researchers reported that during proliferative growth the mitochondria of adult blood stem cells from both female and male mice accumulate defects that limit their ability to convert food energy into cellular fuel. When the cells return to their quiescent state, the resulting dysfunctional mitochondria are not repaired. Rather, their accumulation serves as a sort of record of each cell's replicative history. The researchers found that the mitochondrial defects result from loss of a protein called Drp1 that functions as part of the proliferative machinery. With each round of proliferative growth, Drp1 loss reduces the capacity of the blood stem cells to undergo future rounds of cell division. This phenomenon may effectively be an intrinsic “safety feature,” limiting the cells' ability to proliferate excessively. Because such unchecked cell division can lead to cancer, understanding this process could one day lead to improved methods for prevention or treatment of cancers. In addition, this research may

help in the development of therapies that overcome the limits on adult blood stem cell proliferation in a selective fashion, allowing regeneration of critical blood cells that might otherwise be irrevocably lost through disease or injury.

Hinge A, He J, Bartram J,...Filippi M-D. *Asymmetrically segregated mitochondria provide cellular memory of hematopoietic stem cell replicative history and drive HSC attrition.* *Cell Stem Cell* 26: 420-430.e6, 2020.

### **Identification of Small Molecule Compound that Reverses Experimental Telomere-related Diseases:**

New research has shown that it may one day be possible to treat people with telomere-related diseases using small molecule compounds that restore telomerase levels to normal levels. Telomeres are protective segments of DNA at the ends of chromosomes, and telomerase is the protein responsible for maintaining the telomere-forming DNA sequences. Each time a cell divides, the telomeres become shorter because the telomerase is not very efficient at reading the DNA sequence all the way to the end. Eventually, the telomeres become so short that the cell can no longer divide—leading to telomere-related diseases (e.g., blood diseases such as dyskeratosis congenita). Continued research over the past 30 years has illuminated many important molecules that regulate telomerase activity. Among them, the protein PARN (poly(A)-specific ribonuclease) has been shown to stabilize a component of telomerase, and thus the overall ability of telomerase to do its work. Notably, people with dyskeratosis congenita

have been shown to have mutations in the *PARN* gene. Opposing the action of PARN is the protein PAPD5 (poly(A) polymerase associated domain-containing protein 5), which destabilizes telomerase activity. Strategies that target PAPD5 could potentially maintain the optimal function of telomerase by balancing PARN and PAPD5 activities.

In this study, researchers employed a high-throughput screening approach to test over 100,000 small molecules (chemical compounds), and they identified the small molecule BCH001 as capable of inhibiting PAPD5 at very low concentrations. Using cells from people with dyskeratosis congenita, BCH001 improved telomerase activity and elongated telomeres in cells with PARN mutations. To underscore the strategy of targeting PAPD5 to improve telomerase activity, the scientists tested another PAPD5 inhibitor, called RG7834, for its ability to restore telomerase activity. In this set of experiments, mice were transplanted with human blood stem cells that contained an experimentally mutated *PARN* gene. The researchers then gave the mice RG7834. Remarkably, oral administration of RG7834 reversed telomere shortening in *PARN*-deficient human blood cells compared to a control. This first-in-class therapeutic lead is an exciting new direction for potential treatment of telomere-related diseases.

Nagpal N, Wang J, Zeng J,...Agarwal S. *Small-molecule PAPD5 inhibitors restore telomerase activity in patient stem cells.* *Cell Stem Cell* 26: 896-909.e8, 2020.

# Training Reimagined: Cultivating the Next Generation of Innovative and Collaborative KUH Researchers

The NIDDK's Division of Kidney, Urologic, and Hematologic Diseases (KUH) is reshaping and restructuring its Institutional Training Award program to cultivate a highly integrated cohort of trainees and early career investigators and to develop career development resources to accelerate research within KUH disease areas. This new "U2C/TL1" program, which replaces the NIDDK's previous "T32" grant mechanism, seeks to promote a true trainee community, with the overall goal of engaging, recruiting, preparing, and sustaining the next generation of kidney, urology, and hematology researchers. The first applications were submitted in the fall of 2020, and will be reviewed in 2021.

For decades, individual T32 training programs were typically small and focused on individual departments, at times resulting in multiple T32 programs at one institution with little research collaboration and no peer-to-peer networking among trainees across programs. However, despite large investments in KUH T32 programs, their trainees had a lower average rate of retention in research (as measured by the acquisition of subsequent research support) than trainees of the KUH "F"-series and "K"-series training programs. Some of the institutional T32 programs supported by KUH had markedly better outcomes than others, suggesting that there may be better practices and strategies that could be shared. To address these issues, the NIDDK convened the "KUH T32 Best Practices" meeting in May 2019, which provided a forum for sharing best practices and considering new approaches. Meeting attendees included T32 program directors, staff from the NIDDK and other NIH Institutes, and importantly past and present trainees. The group determined that in order to produce a diverse, modern workforce of researchers in fields relevant to KUH disease areas, a revitalized training program must:

- recruit talented individuals from diverse backgrounds;
- provide an environment to optimize trainees' ability to generate new knowledge;
- develop tailored and structured educational experiences;
- promote team and interdisciplinary science; and
- provide structured training in professional development, leadership, and mentorship.

Based on discussions, two clear themes emerged: (1) to support interdisciplinary collaborations, institutions need to create training programs that span multiple medical and graduate school departments; and (2) training experiences must be better structured to emphasize needed professional development in areas such as grant writing, presentation skills, and entrepreneurship. The new U2C/TL1 Institutional Network Award program was developed with these requirements and central themes in mind. Compared to traditional T32 programs, this new program will have fewer but larger Institutional Network Awards designed to cultivate the people and resources needed to propel KUH training and research.

The new U2C/TL1 programs will provide an environment designed to optimize the ability of trainees to conduct rigorous, ethical research to generate new knowledge, apply interdisciplinary approaches to research questions, and utilize principles of team science to further their leadership and problem-solving skills. Programs will also support the development of a peer-to-peer network and provide ample career development resources for the community of

kidney, urologic, and hematologic research trainees within the institution. To foster a true community, organizations will have only one U2C/TL1 program for all trainees across the entire research mission of KUH (i.e., trainees may be engaged in benign kidney, urologic, or hematologic research within a single program). Furthermore, a single, consolidated application from several institutions within the same metropolitan area, which include multiple departments with a different research focus, is strongly encouraged and preferred.

Trainees under this new and revitalized program should be able to use their skills to publish in the scientific literature, compete for additional research support, and be prepared to successfully navigate the next steps toward a scientific research career. Over time, it is expected that each Institutional Network Award will actively participate in a nationwide program—formed by the collection of individual KUH U2C/TL1 awards—to train a cohort of researchers capable of achieving the scientific breakthroughs necessary to improve the care of people with kidney, urologic, and hematologic diseases.



A robust research training program incorporates research activities, professional development activities, and outreach in an interdisciplinary and collaborative environment. The new KUH “U2C/TL1” program aims to address many of these components.

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# STORY OF DISCOVERY

## Advancing Understanding of Lower Urinary Tract Symptoms and Associated Conditions

Millions of women, men, and children in the United States currently experience symptoms affecting the lower urinary tract, including pain, bladder leakage, and problems urinating. For many years, research on treating these health problems focused predominantly on organs and structures of the lower urinary tract, such as the bladder, prostate, and urethra. A not unreasonable belief was that most symptoms attributed to the lower urinary tract would eventually correlate with a particular dysfunction rooted in those tissues. Evolutions in thought over the past two decades led researchers to appreciate that not only can similar lower urinary tract symptoms result from different problems within its organs and structures, but that not all symptoms may have their origin in the urinary tract itself.

One way that lower urinary tract symptoms, or LUTS, have traditionally been captured and their severity assessed has been through the use of questionnaires—also sometimes referred to as “tools” or “instruments,” depending upon the context—that allow individuals to self-report their symptoms and related issues, such as how much they are bothered by their symptoms. A question may require a person to report frequency of a symptom over a certain period of time or rate its impact on life activities. When administered in a clinical setting, questionnaires can complement physical exams to help arrive at a diagnosis and treatment plan. For example, the American Urological Association’s Symptoms Score Questionnaire is used by clinicians when evaluating benign prostatic hyperplasia in men. Some questionnaires, such as the Genitourinary Pain Index, were developed and/or are used at this time

mostly in clinical research settings. What many of these questionnaires have in common, however, is that when deployed in isolation, the result can be like the story of the five blind men and the elephant: each one may yield a partial description of a person’s symptoms, but may not provide the complete picture needed to identify and/or better understand and manage the underlying cause(s). New research approaches incorporating multiple questionnaires to study people with LUTS, evaluation of “standard” uses of questionnaires, and the careful development of comprehensive tools for assessing LUTS have now yielded information critical both for identifying subtypes of LUTS and/or LUTS-predominant conditions, and for conducting research and clinical assessments going forward.

### NEW UNDERSTANDING OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME

Chronic, often debilitating pain in the pelvic or genital areas with or without a frequent or urgent need to urinate are hallmark LUTS for a cluster of disorders referred to as urologic chronic pelvic pain syndrome (UCPPS). UCPPS serves as an umbrella term for the two most common forms of chronic pelvic pain, interstitial cystitis/bladder pain syndrome (IC/BPS, also called IC/painful bladder syndrome [PBS]), which predominantly affects women, and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which affects men. These conditions reduce quality of life and productivity and incur significant health care costs for millions of Americans.

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Despite many years of committed basic and clinical research efforts supported by the NIDDK and other research-funding agencies, the cause(s) of UCPPS has long remained elusive, as have widely or fully effective treatments. Moreover, diagnostic tests specific for UCPPS are not currently available, and many UCPPS symptoms are similar to symptoms of other conditions, such as invasive bladder cancer or endometriosis. Thus, those diseases need to be ruled out first—making IC/BPS or CP/CPPS a “diagnosis of exclusion.” Historically, attempts at clinical diagnosis have included questionnaires focused on bladder and prostate symptoms and pelvic pain, along with exclusionary medical tests.

## **Embracing Novel Approaches: MAPP Research Network**

By the mid-2000s, new perspectives from a diversity of research and clinical expertise and insights from other fields led to changes in the research approach for UCPPS. A comprehensive strategy was developed to take into account not only urologic contributors but also the influence of comorbid conditions and non-urologic factors on the onset or development of UCPPS and its symptoms—and how differences in LUTS and other symptoms among individuals diagnosed with UCPPS might be important to identifying clinically significant subgroups of patients. In 2008, the NIDDK established the multi-center Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network to conduct innovative, collaborative studies of UCPPS. Since its inception, the Network’s unique approach to IC/BPS and CP/CPPS has entailed approaches that “look beyond” the bladder and prostate—the traditional focal points for study of these syndromes—to uncover meaningful new insights into the clinical and biological features of UCPPS and its relationships with other chronic pain conditions, all to set the stage for future interventions and improved clinical management.

In its first phase, the MAPP Research Network recruited 424 individuals with UCPPS—233 women with IC/BPS and 191 men with either IC/BPS or CP/CPPS—in a central, Trans-MAPP Epidemiology

and Phenotyping study to better understand how these conditions progress over time and to learn if patients might fall into different, distinguishable subgroups based on differing symptoms that may arise from different causes—and, thus, may require different treatments. To achieve its many goals, the Network also recruited large numbers of “control” participants—both healthy persons without any pain syndromes, and those without UCPPS but with one or more chronic pain conditions often found in people with UCPPS, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome.

## **Distinguishing Characteristics: LUTS and Non-LUTS in People with UCPPS**

A large part of the Trans-MAPP study consisted of participants completing a variety of questionnaires to describe not only the key symptoms of pain and bladder dysfunction, but also commonly co-occurring chronic pain conditions such as irritable bowel syndrome; stress; and issues such as depression, sleep quality, and general quality of life. While the majority have already been employed in health care settings and in clinical research to assess the impact of UCPPS on individuals and the outcomes of clinical trials, respectively, a few of these questionnaires were developed or modified specifically for use in the MAPP Research Network.

By combining outcomes of the questionnaires assessing urologic, non-urologic, and psychosocial symptoms and quality of life with “body pain mapping,” MAPP researchers uncovered important new information about pain patterns and other symptoms in people with IC/BPS and CP/CPPS. Along with completing the questionnaires, the women and men participants with UCPPS were also asked to look at a “body map”—2 drawings representing the front and back of the body, partitioned into 45 numbered sites comprising 8 body regions—and to check off any site in which they had experienced pain in the past week. From the resulting data, MAPP investigators found that, whereas a quarter of participants reported pain only in the pelvic region, 75 percent reported pain in both pelvic and nonpelvic regions. Following

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this observation, the investigators created three subgroups for comparison: people with pelvic pain only; people who had pelvic pain along with pain in one to two nonpelvic regions, or “intermediate pain”; and people with pelvic pain and pain in three to seven nonpelvic regions, or “widespread pain.”

Intriguingly, there were no differences in pelvic pain severity or urinary symptoms across these three groups. In contrast, nonpelvic pain severity, prevalence of chronic overlapping pain conditions, worsening psychosocial health, and poor quality of life increased as the number of pain regions a person had increased. Notably, more women than men experienced widespread pain, and women were more likely to report a greater burden of nonpelvic and nonurinary symptoms and conditions as their pain locations increased. MAPP investigators also compared just the intermediate and widespread pain groups to see if there were any significant differences among study participants with UCPPS who reported nonpelvic pain. This comparison yielded similar results to those for the three-group comparison regarding pelvic pain and urinary symptoms, nonpelvic pain, and several other health measures, but also revealed more gender-specific differences. For example, compared to individuals whose pain was categorized as intermediate, men with widespread pain were more likely to have migraines and anxiety, while women were more likely to have irritable bowel syndrome and sleep disturbance.

## **Changing Approaches to Symptom Evaluation in People with UCPPS**

The differences—and similarities—found in the Trans-MAPP body mapping study among people diagnosed with UCPPS have significant implications for better understanding the cause(s) and/or development of these syndromes and associated LUTS, for research studies on potential treatment approaches, and for clinical diagnosis and personalized care. At the same time, the Network uncovered potentially “game-changing” information about how standard questionnaire data are collected and used for people with UCPPS. In the past, many questionnaires were used to generate a composite

“score” for UCPPS that combined pain (pelvic and/or genitourinary) and bladder symptoms. However, an analysis of data from a subset of questionnaires administered in the trans-MAPP study allowed Network scientists to determine that such a composite score can actually mask independent changes in each symptom area. Their analysis suggests that improvement or worsening can occur in pain independently of bladder symptoms such as urgency and frequency, and *vice versa*, and that a composite score limits the ability of researchers and clinicians to detect such changes. In addition, they found a differential impact of these key symptoms on an important comorbidity, depression: only pain symptoms were associated with depression. These MAPP Research Network findings indicate that, going forward, pain and urinary symptoms should be scored independently in UCPPS to enable more accurate research analyses and improved patient care.

## **TOOL DEVELOPMENT FOR UNDERSTANDING LUTS**

As the MAPP Research Network was developed and conducted its studies focused on syndromes associated with a subset of LUTS, a broader challenge remained: for the wide range of LUTS, we still need to learn more about differing etiologies and potential patient subgroups to improve management and treatment of symptoms. This is true even when a person’s LUTS have been linked to a problem in a structure or function in the lower urinary tract, as there still may be other factors influencing the symptoms he or she is experiencing.

## **Symptoms of Lower Urinary Tract Dysfunction Research Network**

To address the gaps in understanding and treating LUTS, the NIDDK established the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) in 2012. LURN is an interdisciplinary, cooperative research network with several long-term goals: to identify and explain the important subtypes of LUTS in women and men; to improve the measurement of patient experiences of

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LUTS; to disseminate novel findings to researchers, clinicians, and patients; and to generate data, research tools and biological samples for future studies.

To help attain these intertwined goals, LURN enrolled nearly 2,000 women and men from among individuals presenting with LUTS to a health care provider at a LURN research site. To limit duplication with the work of the MAPP Research Network, persons with pain as a dominant LUTS were not included. Working with these participants, LURN collected clinical data, health-related quality of life assessments, and self-reported symptom measurements at “baseline,” and characterized these and changes in LUTS over a 12-month period, yielding a wealth of data and enabling numerous informative studies.

## Measuring Patient Experiences of LUTS

A critical goal for LURN has been to develop improved means for finding clinically important subgroups, or subtypes, among people with LUTS. Their approach was to pursue an intensive questionnaire development process, casting a wide net over LUTS in both women and men to develop the most comprehensive and nuanced instrument they could that would: (1) be able to elicit granular and precise information about symptom experience from individuals; and (2) serve as a “pool” of questions from which more targeted questionnaires could be developed and validated for clinical and research purposes. Through the development process, they also wished to explore the boundaries of what was “measurable” for LUTS—*i.e.*, to what degree unique or abnormal experiences with LUTS could be captured through a person’s self-reported responses on a questionnaire.

The resulting questionnaire, called the Comprehensive Assessment of Self-reported Urinary Symptoms, or CASUS, was developed through an iterative process involving health care providers and women and men with LUTS who were not part of the LURN cohort. Vigorous steps were undertaken to ensure that the CASUS would be widely understandable, potentially translatable,

and acceptable to women and men from different educational and racial/ethnic backgrounds. Emphasis was placed on including new types of questions that could get at data gaps such as specific physical sensations accompanying LUTS, particularly sensations accompanying bladder leakage (incontinence). Over 90 LUTS-related items are included in the CASUS, covering multiple symptom categories, such as frequency (day and night), sensations (including pain), urgency, urine flow, incontinence, and incomplete emptying—as well as a person’s recall of any lifetime experience suggestive of LUTS. The CASUS was then put through its paces with over 1,000 participants from the LURN Observational Cohort Study. Their responses not only demonstrated that CASUS could be used in symptomatic persons to obtain a wide range of information about LUTS, but also revealed intriguing sex/gender differences in sensations associated with urinary incontinence that can be explored to look for potential causes.

## Adapting CASUS for Practical Application

The CASUS is an extensive menu of items that can be used in concert with other data from the LURN Observational Cohort Study to delve deeply and pursue extensive subgrouping of LUTS. However, it might not be easily administered in all situations, either research or clinical. At the same time, LURN investigators wanted to ensure that the aspects of CASUS that were missing from other assessment tools for LUTS were still retained as much as possible.

Starting from the CASUS, LURN investigators proceeded to develop, through a multi-step process, two scaled-down questionnaires—one for research use, and one for clinical use. These became the LURN Symptom Index-29 (LURN SI-29) and the LURN SI-10. The LURN SI-29 is intended to be a representative outcome assessment for use in research; it includes 29 items covering urgency, incontinence, voiding difficulty, nighttime voiding (nocturia), and pain. The briefer LURN SI-10 for clinical use is intended to elicit responses that would indicate whether there is a need for further clinical investigation and/or intervention; it includes 10 items assessing frequency, nocturia,



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urgency, incontinence, bladder pain, and post-voiding symptoms, and an additional item on symptom bother. Both have been validated against other questionnaires representing different aspects of LUTS. Both are also meant to be used with either women or men, rather than needing separate instruments.

Another aspect important to the application of CASUS, its derivatives, and other LUTS questionnaires is the accuracy of recall in self-report—*i.e.*, most questionnaires ask individuals to provide assessments of their symptoms within a specified time, such as the past 7 days. Because this could affect the robustness of LUTS data obtained via CASUS, *etc.*, LURN investigators performed another study, in which they obtained daily responses to 18 CASUS items over 7- and 30-day periods, averaged them, and compared them to the corresponding 7- or 30-day recall versions of responses to the items. This study demonstrated good tracking of recall responses with

averaged daily responses, with minimal bias—*i.e.*, over- or underreporting of symptoms—supporting the continued use of both 7- and 30-day recall questionnaires in the assessment of LUTS.

## LOOKING TO THE FUTURE

Much remains to be learned about LUTS—their causes, development, and how best to manage and treat people experiencing these symptoms. Through multiple activities—including the use and development of improved questionnaires—in MAPP, LURN, and other investigations such as the NIDDK's Prevention of Lower Urinary Tract Research Consortium (PLUS), more comprehensive subgrouping of people with LUTS and LUTS-predominant conditions is now possible, with important implications for future trial design and clinical management.

## Paving a Path to Personalized Kidney Care Through Participation in Research

Acute kidney injury (AKI) and chronic kidney disease (CKD) impose a significant personal and global health burden; however, only a few therapies are available for CKD, and none currently exist for AKI. Development of drug therapies for AKI and CKD has been hampered by many practical research issues, such as imperfect animal models, the inability to identify and prioritize molecular therapeutic targets in human kidneys, and a poor understanding of the underlying biology of human AKI and CKD. A growing consensus based on research findings suggests that neither CKD nor AKI are singular diseases; rather, there are specific subgroups of these diseases that are driven by different biological pathways. Thus, a better understanding of the biological pathways that lead to the diversity of kidney diseases will likely inspire the development of more effective individualized treatment options, an approach referred to as “precision medicine.” In 2017, the NIDDK launched the Kidney Precision Medicine Project (KPMP)—a bold research program that is beginning to chart a course toward a more personalized approach to clinical care for people with kidney diseases.

### THE KIDNEY PRECISION MEDICINE PROJECT

Imagine a future where a person with kidney disease could work with clinicians to answer important, patient-centered questions, such as: “What type of kidney disease do I have?” “What will happen to me?” “What can I do about it?” In this vision, a nephrologist (kidney disease specialist) might: (1) evaluate the person’s disease profile using blood and urine tests, (2) visualize the kidney in real-time

using advanced imaging technologies, (3) identify and biopsy areas of kidney damage, (4) analyze the biopsy tissue using a kidney tissue atlas—a tool designed to classify the location and health of kidney tissue components, and thereby (5) select the appropriate therapy to start individualized treatment.

The KPMP strives to achieve this individualized approach to patient care by working toward several goals with the overall objective of bringing precision medicine to AKI and CKD: to ethically and safely obtain and evaluate human kidney biopsies from research participants with a wide range of AKI or CKD—a procedure not typically done in the United States; create a kidney tissue atlas; define disease subgroups; and identify critical cells, extracellular components, and pathways that can be targeted for developing novel therapies. Researchers are now poised to begin constructing a kidney atlas due to the maturation of sophisticated technologies over the past several years, but only with the invaluable contributions of study participants. (See inset for the story of a KPMP participant.)

### HUMAN KIDNEY BIOPSIES—THE KEY TO UNLOCKING THE FUTURE OF PERSONALIZED KIDNEY CARE

In order to catalyze research toward personalized kidney care, KPMP research requires an essential component—human kidney biopsies. For nephrologists to take tailored approaches to kidney care, specific subtypes of AKI or CKD will need to be identified. However, advancing science to a point where disease subtypes are well defined will

# PERSONAL PERSPECTIVE

require technological leaps that can only be made by analyzing biopsy tissue from many people with kidney disease—altruistic study participants who will undergo the biopsy procedure, which carries some personal risk, to support the goals of KPMP to help people with kidney diseases in the future.

Human kidney biopsies obtained through the KPMP are being analyzed to identify new molecular “markers” that will reveal differences among cells and tissues in exquisite detail to define specific kidney structures. Markers characterized by the KPMP will help establish a complex kidney atlas that can classify and locate different cell types, cell states (such as healthy, injured, dying, recovering, undergoing repair), and molecules involved in the progression of kidney disease. These new markers will then be linked to important clinical outcomes. The emerging kidney tissue atlas will be used as a foundation to better understand the cellular and molecular diversity of kidney diseases, and help define specific disease subgroups. This knowledge can inform decision making by pathologists, nephrologists, and people with AKI and CKD.

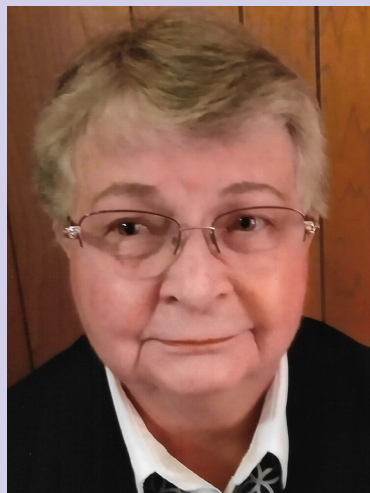
## STUDY PARTICIPANTS PAVE THE PATH FORWARD

KPMP’s bold, innovative approach hopes to build a foundation for new therapeutic development. However, this research would not be possible without the generosity and courage of study participants providing research kidney biopsies—contributions that are deeply appreciated by the research and clinical communities. For the patients KPMP aims to serve, currently kidney biopsies are of unknown individual benefit, and the biopsy procedure carries some risk for well-defined complications, such as bleeding, pain, and very rarely death. Thus, a central component of the KPMP has been to design the study with great care to build a strong case to explain to people with kidney diseases and their health care providers how biopsies could have long-term benefit because of their critical role in advancing research progress toward precision medicine. Toward this effort, patients have been an important part of the research design process, helping

to tackle issues such as community engagement, ethics, biopsy safety, and data-sharing strategies.

Over time, results and resources from the KPMP are expected to dramatically improve scientists’ understanding of human kidney diseases, which in turn is likely to catalyze the development of new therapies. Biopsy results will likely become more informative to clinical care as pathologists and nephrologists can better predict a drug’s effectiveness based on an individual’s specific kidney profile. Through their participation in KPMP, individuals with kidney diseases are helping to understand their own conditions, and paving a path toward a brighter future for people with kidney diseases.

## HARRIET'S STORY



*Harriet, pictured here, participated in an NIDDK-supported research study charting a course toward personalized treatments for kidney diseases*

For years, 77-year-old Harriet underwent regular medical tests to help understand an unusual pattern of test results that perplexed her physicians. “They were doing blood samples every 6 months ... that started about 10 years ago” she recalls. “I started to get

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strange numbers that were unexplained.... They tried various medications and nothing seemed to be explaining what was happening.” The doctors had found excess protein in the urine, a condition known as “proteinuria” that is an indicator of kidney dysfunction. Surprisingly, however, there were no other clinical markers of kidney disease, making it difficult to diagnose precisely her condition. Her physicians had also prescribed medications to control blood pressure and manage her prediabetes—factors that could affect kidney health.

About 2 years ago, one of her physicians referred her to a nephrologist for kidney-specific medical care at the Cleveland Clinic, which is not too far from her home. The nephrologist monitored her health for about a year, observing similar test patterns. The specialist then recommended that she consider participating in a new research study—the Kidney Precision Medicine Project (KPMP)—that was taking place at several sites across the United States, including the Cleveland Clinic, and enrolling participants to undergo kidney biopsies. Participation in KPMP could not only shed some light on her own condition, but also contribute to a potentially important research effort. Harriet, a former paint and coatings development researcher trained in chemistry, says that she, “having a research and development background, was kind of excited about it.”

Within weeks of enrolling in KPMP and meeting with the research team, Harriet underwent a biopsy procedure in January 2020 to collect samples from her left kidney. “The intention was to take between three and five samples, so that the samples could be sent to several different research centers, and one could be kept here at Cleveland Clinic,” she explains. The procedure started off well, “up until they attempted to take the third sample and had some trouble with that. So they went in and took the fourth sample, and then were very satisfied with the three good samples that they had.” With three

good samples in hand, the research team finished the procedure and Harriet headed home. The research team had explained to Harriet that there could be complications from the biopsy, but thankfully there were none. As she recalls, “they said I could expect ... some kind of bleeding. I didn’t have any kind of interior or exterior bleeding. It went very, very well.”

Shortly after the biopsy collection, one of the KPMP physician-scientists called Harriet not only to confirm that the quality of the samples was good, but also to share some interesting news: analysis of the biopsy revealed that she has a relatively rare kidney condition called fibrillary glomerulonephritis, in which the body produces unusual proteins that become trapped in and disrupt the filtration units of the kidney. This new diagnosis helped explain the unusual pattern of blood and urine tests, illustrating the utility of biopsy collection in classifying kidney diseases. As Harriet recounts, it was “an unusual thing that they weren’t expecting to find.” She added that the doctors were excited that they had finally found a diagnosis to explain the test results over the years. Now with this new information, she is better positioned to strategize future treatment plans with her medical providers.

***“They tried various medications and nothing seemed to be explaining what was happening,” says Harriet of her test results showing an unexplained excess of protein in her urine, prior to her diagnosis through participating in a clinical research study.***

Post-biopsy recommendations by the KPMP staff have been relatively straightforward. She has had one in-person visit with Cleveland Clinic staff and several conversations by phone. Research is ongoing to develop drugs for her particular kidney condition, but there are currently no effective therapies in common use. However, Harriet has

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been encouraged to continue with fairly standard practices, such as maintaining a healthy diet by limiting sodium and sugar intake. Harriet has been doing well in the months following the biopsy procedure. “I have no unusual side effects, nothing seems to be out of the ordinary,” she says. However, KPMP staff are closely monitoring her blood tests, and her kidney condition continues to be a problem. “They’re keeping a good eye on what’s going on, but the protein spillage [into the urine] has continued and increased.”

***“The exciting part was that the research is being done on the molecular level. So maybe they will be able to look into the mechanism that is behind what my problem is,” says Harriet of her participation in the NIDDK’s Kidney Precision Medicine Project, which facilitated her diagnosis of a rare kidney disease.***

The COVID-19 pandemic has affected Harriet’s daily life, as it has for everyone. She continues to be an avid reader, care for her husband, and walk her dog. But she misses being an usher with the Cleveland Orchestra—a role that she has

enjoyed for 11 years. Because of the pandemic, the orchestra cancelled their performances. “I knew nothing about classical music before I started ushering, and I have learned a tremendous amount and a great appreciation has grown for it,” she says.

Harriet’s career in research and development has shaped her perspective on the importance of KPMP in therapeutic development. “I understand the importance of having good samples to work with, and unusual samples to work with,” she explains. “The exciting part was that the research is being done on the molecular level. So maybe they will be able to look into the mechanism that is behind what my problem is.” She adds that “since they can look at an actual piece of tissue ... they can possibly determine what a better course of treatment would be.”

Harriet is hopeful that her participation will help others who have kidney disease. Of KPMP, she notes the “importance of having this kind of research program” because “more understanding of what maybe caused [her condition] or what they can do to control it, would be ... beneficial.” Indeed, thanks to the dedication of Harriet and other participants, KPMP research holds tremendous promise to improve the health and quality of life of people with kidney diseases.



# NIDDK Extramural Funding Trends and Support of Guiding Principles

*The NIDDK's guiding principles toward achieving its core mission include maintaining a vigorous investigator-initiated R01 research portfolio, supporting pivotal clinical studies and trials, promoting a steady and diverse pool of talented new investigators, and fostering exceptional research training and mentoring opportunities consistent with the vision of the NIDDK Director, Dr. Griffin P. Rodgers (see Message from the Director). To highlight its dedication to these principles, the NIDDK generates data and analyses of application and funding trends.*

## Maintaining Investigator-initiated Research

The NIDDK is committed to maintaining a strong investigator-initiated R01 research program, while also allowing appropriate flexibility for other priorities, such as training and career development of the next generation of scientists; infrastructure; key initiatives, including large clinical trials and consortia; and other efforts informed by input from various sources, including the scientific community. Historically, investigator-initiated research has been—and continues to be—the Institute's highest priority because it fosters ground-breaking and innovative research.

## Supporting Clinical Studies and Trials

The NIDDK supports a robust portfolio of clinical studies, from preliminary clinical feasibility studies to large multi-center studies. As part of this clinical research effort, the NIDDK seeks to ensure substantial representation and participation of women, minorities, and other historically underrepresented populations. The Institute also continues to expand investigator access to valuable research resources through ancillary studies and a central repository of data and samples.

## Promoting a Steady and Diverse Pool of New Investigators

The NIDDK creates opportunities to help new investigators advance scientific discovery in their own laboratories. Each year, the NIDDK sets a more generous payline for Early Stage Investigators (ESIs) with the aim of enhancing ESI representation among new grant awardees. (ESIs are new investigators who completed their terminal research degree or medical residency within the past 10 years, and who have not yet competed successfully for a substantial, competing NIH research grant.)

Data and analyses of application and funding trends are updated annually and available at: [www.niddk.nih.gov/research-funding/funded-grants-grant-history/funding-trends-support-core-values](http://www.niddk.nih.gov/research-funding/funded-grants-grant-history/funding-trends-support-core-values).

## Fostering Research Training and Mentoring

The NIDDK also continues to foster the growth of a diverse biomedical research workforce by providing training and mentoring opportunities for talented young investigators, including the NIDDK's fellowship (F), career development (K), and training (T) awards. These and other NIDDK-supported opportunities aim to promote a diverse research workforce pipeline.

In support of these guiding principles, the NIDDK funds a wide range of research awards across its extramural research portfolio, including investigator-initiated grants (R01s); other R grants (*e.g.*, SBIR/STTR and many other types of grants); awards made in response to initiatives such as Requests For Applications (RFAs), including most of the Institute's large clinical trials and consortia; collaborative grants (*e.g.*, P01s); centers; career development awards; training grants; contracts and interagency agreements (*e.g.*, some large clinical studies); and other research.

In these unprecedented times, the COVID-19 pandemic has created new challenges for the biomedical research enterprise. This past year, the NIDDK obtained input from its Advisory Council on the scope of COVID-19's impact on Institute-supported research. Both NIH-wide policy changes and NIDDK efforts have enabled the Institute to implement several of the

Council's recommendations, including strategies to reinvigorate research across the Institute's mission. The NIDDK continues to look for ways to alleviate the burden of COVID-19 on researchers, scientific progress, and ultimately public health. (For more information on NIDDK efforts to combat COVID-19, please see the "Cross-Cutting Science" chapter.)

The data that the NIDDK generates on application and funding trends help the research community understand application and funding dynamics over recent years and demonstrate the NIDDK's commitment to research and programs associated with the guiding principles. The Institute posts these data on its public website and updates them annually: [www.niddk.nih.gov/research-funding/funded-grants-grant-history/funding-trends-support-core-values](http://www.niddk.nih.gov/research-funding/funded-grants-grant-history/funding-trends-support-core-values).







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