

NIDDK

Recent Advances & Emerging Opportunities

January 2023



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



National Institute of
Diabetes and Digestive
and Kidney Diseases

NIH Publication Number: 23-DK-7962

Cover Legend: The NIDDK mission is to conduct and support biomedical research and research training and to disseminate science-based information on a broad array of diseases and conditions affecting people of all ages. This “word cloud,” built from terms representing this mission, highlights the varied research areas supported by NIDDK; the different communities that conduct, participate in, and contribute to this research; and the dissemination and implementation of discoveries to improve health for all. Highlights of these activities are presented in this annual publication.

Note: The word cloud design does not imply differences in Institute priorities and/or funding levels.

TABLE OF CONTENTS

MESSAGE FROM THE DIRECTOR

PATHWAYS TO HEALTH FOR ALL: NIDDK'S EFFORTS TO ADDRESS HEALTH DISPARITIES, ADVANCE HEALTH EQUITY, AND PROMOTE WORKFORCE DIVERSITY 1

DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES 6

Testing New Type 1 Diabetes Therapies 8

Research Toward Improving Treatment
of Type 2 Diabetes 9

Research on Diabetes Complications 10

Studying Links Between Structural Racism
and Diabetes Health Disparities 12

Understanding Cell Signaling
and Communication 13

Advancing Parathyroid Disease
Diagnosis and Treatment 15

Feature: Research on Type 2 Diabetes in Youth 17

Feature: Human Pancreas Analysis Program–
New Insights into Diabetes 18

Feature: Understanding the Pancreas,
Inside and Out: Efforts in Pancreatic Disease 20

Personal Perspective: Advancing Research on
Artificial Pancreas Devices for
Type 1 Diabetes Treatment 23

Personal Perspective: Contributing to
Research on Gestational Diabetes Mellitus 28

OBESITY 33

Pediatric Obesity Prevention Research 34

Studying Outcomes of Bariatric Surgery
for Obesity Treatment 34

Identifying a Link Between Exercise
and Food Consumption 35

Insights into Fat Tissue-Brain Communication 36

Feature: Symposium Held To Explore the
Global Impact of Obesity 37

Feature: Workshop Held To Explore
the Relationship Between Housing
Insecurity and Obesity 39

DIGESTIVE DISEASES AND NUTRITION 42

Important Roles of Bile Acids
in Health and Disease 44

Causes and Effects of Nonalcoholic
Fatty Liver Disease 45

Investigating How Gut Cells Sense
and Communicate with Their Environments 47

Factors Involved in Inflammatory Bowel Disease 49

Understanding and Treating Intestinal Infections ... 50

Feature: Liver Network Aims To
Transform Treatment 52

Feature: Inflammatory Bowel Disease Genetics
Consortium: Unearthing Genetic Factors
Underlying Chronic Gut Inflammation..... 53

Feature: Understanding the Pancreas,
Inside and Out: Efforts in Pancreatic Disease 55

Personal Perspective: Coordinating
Research on New Treatment for
Rare Childhood Liver Disorder 58

**KIDNEY, UROLOGIC, AND
HEMATOLOGIC DISEASES.....64**

Advancing Knowledge of Kidney Physiology 66

Research on Kidney Disease 66

Preventing Kidney Stone Recurrence 68

Identifying New Therapeutic Targets for
Benign Prostatic Hyperplasia 69

Research on Urinary Tract Disorders..... 70

Investigating Ways To Prevent Blood Disorders 70

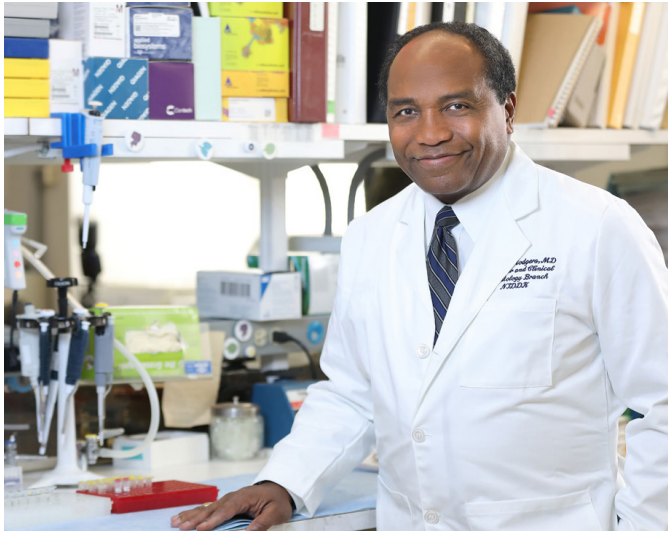
Feature: Workshop Held To Address
the Role of Structural Racism and
Importance of Achieving Health Equity
in People with Kidney Disease 72

Feature: Meeting Held To Discuss
Research on the Relationship
Between Enlarged Prostate and
Lower Urinary Tract Symptoms 74

Personal Perspective: Providing HOPE
for a Better Way To Manage Dialysis Pain..... 75

ACKNOWLEDGMENTS.....82

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. NIDDK has a broad research responsibility that includes some of the most common, debilitating, and costly conditions affecting Americans. These conditions include diabetes and other endocrine and metabolic diseases; liver disease and other digestive diseases and conditions, such as inflammatory bowel disease and irritable bowel syndrome; nutritional disorders; obesity; kidney diseases, such as polycystic kidney disease and glomerular disease; urologic diseases and conditions, such as interstitial cystitis/bladder pain syndrome, prostatitis, and urinary tract infection; and blood diseases.

The NIDDK Strategic Plan for Research continues to guide the Institute, presenting a broad vision for accelerating research to improve pathways to health for all. Many of the conditions within the NIDDK research mission disproportionately affect certain groups or communities, including those who have been historically marginalized by structural and systemic racism and other forms of discrimination, and those who experience injustice today. NIDDK recognizes that to improve the health of all we must accelerate efforts to eliminate disparities and promote health equity. This 23rd edition of NIDDK's annual report describes activities that highlight our commitment to these efforts and to cultivating a workforce of individuals with different backgrounds and experiences.

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

- New findings about diabetes treatment, including how a new oral therapy delayed type 1 diabetes progression and lowered insulin requirements for at least 2 years, and how two popular diabetes drugs, in combination with metformin, outperformed others when compared in a large clinical trial;
- Identification of factors critical for healing of diabetic foot ulcers, as well as confirmation that keeping blood glucose levels within a healthy range can reduce the risk of developing these ulcers;
- Development of a new experimental approach that identified possible new treatments for the endocrine disorder hyperparathyroidism;
- New information showing that bariatric surgery can lead to significantly more weight loss than nonsurgical care for people with severe obesity;
- Discovery of a molecule produced during exercise by various mammals, including people, that can reduce food consumption and obesity in mice;
- Experiments demonstrating that changes in a particular protein may impede healing in the guts of people with inflammatory bowel disease;
- Investigations studying the genetic factors underlying nonalcoholic fatty liver disease in children and tracking the outcomes of the disease in adults;
- How communication between cells in the esophagus may contribute to whether or not people with eosinophilic esophagitis go on to develop a more severe form of the disease;
- Development of an “atlas” that details the healthy adult kidney at a cellular level and dramatically deepens our understanding of human kidney physiology;
- Demonstration in mice of how in early stages of polycystic kidney disease, kidney damage can be reversed by reactivating an inactive gene; and
- Progress in developing new approaches for treating prostate enlargement.

This report also includes personal perspectives of those who have given time and effort to participate in or support NIDDK-sponsored clinical research. A young woman describes how volunteering to test a new bionic pancreas device introduced her to a less burdensome way of managing her type 1 diabetes. A mother tells her story of participating in a clinical study seeking to better understand how blood sugar levels change throughout pregnancy. Two men share their perspectives on living with kidney failure and their experiences with a study to improve pain treatment in people receiving dialysis. A professional with 20 years of experience in clinical research describes her work serving as the study coordinator for a trial testing a new treatment for severe itching in children with Alagille syndrome, a rare liver disorder.

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. Health information, news, and scientific advances related to NIDDK research are also available on our Twitter feed: @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 NIDDK, including the Director's guiding principles:

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

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

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

Director

National Institute of Diabetes and Digestive and Kidney Diseases

National Institutes of Health

U.S. Department of Health and Human Services



Pathways to Health for All

NIDDK's Efforts To Address Health Disparities, Advance Health Equity, and Promote Workforce Diversity

NIDDK's research mission includes some of the most common, chronic, and costly diseases and conditions affecting the health and quality of life of Americans. Many of these disproportionately affect certain groups or communities, including those who have been historically marginalized by structural and systemic racism and other forms of discrimination, and those who experience injustice today. Such injustices can be based, for example, on race, ethnicity, sexual orientation, gender identity, age, language, ability, socioeconomic status, and geographic region. Health disparity research seeks to understand the influences and causes of health differences that adversely affect disadvantaged populations and to translate that knowledge into interventions. This research, along with other efforts, aims to advance health equity—where everyone has a fair and just opportunity to be as healthy as possible regardless of their social position or other socially

NIDDK recognizes that to improve the health of all we must accelerate efforts to eliminate disparities and promote health equity.

determined circumstances. NIDDK recognizes that to improve the health of all we must accelerate efforts to eliminate disparities and promote health equity. In addition, NIDDK is committed to cultivating a workforce of diverse individuals within the Institute itself and in the broader extramural research community.

NIDDK'S STRATEGIC PLAN FOR RESEARCH

The overarching theme of the [NIDDK Strategic Plan for Research](#), published in December 2021, highlights NIDDK's commitment to pursuing "pathways to health for all." In keeping with the theme, research to reduce health disparities and achieve health equity is emphasized as crucial to the Institute's mission. Opportunities for pursuing health for all are presented throughout the Strategic Plan, in all areas of study—from research to advance understanding of biological and environmental contributors to health and disease, to clinical trials of prevention and treatment approaches, to dissemination and implementation research. Several cross-cutting topics are also highlighted, including the value of strengthening biomedical research workforce diversity and training.

The Strategic Plan also emphasizes the importance of stakeholder engagement—including patients and others as true partners in research. With input from people who have diseases in the Institute’s mission, family and other caregivers, community-based organizations, patient advocacy groups, and others, NIDDK-supported research can more effectively improve the lives of all people, including those experiencing health disparities. These community members were also key stakeholders in the strategic planning process: people with the lived experience of diseases in our mission were included on the Strategic Plan Working Group of Council along with researchers, and many individuals and organizations responded to NIDDK’s requests for broad public input.

The NIDDK Strategic Plan for Research highlights the Institute’s commitment to pursuing “pathways to health for all.”

DEVELOPING THE NIDDK HEALTH DISPARITIES AND HEALTH EQUITY RESEARCH IMPLEMENTATION PLAN

To strengthen and build upon NIDDK’s research toward reducing health disparities and achieving health equity, the Institute embarked on the development of the inaugural NIDDK Health Disparities and Health Equity Research Implementation Plan. The Implementation Plan will complement the Strategic Plan by elaborating on specific research needs and opportunities NIDDK could pursue to enhance the Institute’s health equity research portfolio. It is slated for publication in 2023.

For this effort, a Health Disparities and Health Equity Working Group of Council (WG) was established in January 2021 to identify a range of research opportunities and actionable recommendations. The WG comprises external researchers from across the country with expertise in interdisciplinary research fields related to health disparities and health equity; community members with diverse perspectives and valuable, lived experiences to inform our efforts; and NIDDK staff.

The NIDDK Health Disparities and Health Equity Research Implementation Plan will strengthen and build upon the Institute’s research toward reducing health disparities and achieving health equity.

Subgroups of the WG addressed a range of health disparities and health equity research topics, including engaging communities and building partnerships, community perspectives, and multiple aspects of social determinants of health (SDOH), which are the conditions in places where people live, learn, work, and play that influence health. SDOH include health care access and quality, education access and quality, economic stability, availability and access to healthy food and safe places to be physically active, and other conditions. Areas of focus on SDOH included the effects of SDOH on the biology of health and disease; interventions to address the effects of SDOH, eliminate disparities, and improve health; and upstream causes of SDOH and health disparities. Community engagement was central to all of the WG’s efforts. Most of the Subgroups included community members along with researchers, while the Subgroup focused on community perspectives was comprised entirely of community members—people living with or at risk for diseases within NIDDK’s mission who shared their perspectives, experiences, values, and priorities.

The planning process has also been informed by discussions with the Institute’s Advisory Council and other NIDDK and NIH-wide activities.

HIGHLIGHTS OF RECENT NIDDK HEALTH DISPARITIES AND HEALTH EQUITY RESEARCH INITIATIVES, WORKSHOPS, AND FINDINGS

In parallel with the development of the Implementation Plan, NIDDK has been enhancing its health disparities and health equity efforts through multiple recent and ongoing initiatives, workshops, and other research. For example, the Institute held a workshop in 2022 on designing interventions that address structural racism to reduce kidney health disparities, and the workshop informed the launch of a new NIDDK initiative on this critical topic (see Feature in “Kidney, Urologic, and Hematologic” chapter). NIDDK also convened a workshop in 2022 to explore the role of housing insecurity in obesity-related health disparities, the evidence base for housing-related interventions to address these disparities, and future directions to advance health equity for all (see Feature in “Obesity” chapter). Opportunities identified in an earlier NIDDK workshop, on addressing disparities in obesity and type 2 diabetes, are also informing existing efforts.

In recent research on diabetes disparities, an NIDDK-supported study showed associations between historic

practices of redlining (denying services to residents of specific neighborhoods or communities) and present-day diabetes mortality, a sobering finding that highlights the long-term impact of structural racism on health outcomes (see advance in “Diabetes, Endocrinology, and Metabolic Diseases” chapter). The Institute also spearheaded new diabetes initiatives to establish national Stakeholder Engagement Innovation Centers for advancing equity in type 1 and type 2 diabetes research. A primary goal of the Centers is to accelerate equitable engagement of diverse individuals and communities, particularly those who are underserved and experience diabetes-related health disparities. In ongoing NIDDK-supported clinical studies of kidney disease, people with lived experience of the disease serve in important roles on the research teams—as Patient Advisors, for example—to help ensure that the studies meet the needs of the participants (see Personal Perspective in the “Kidney, Urologic, and Hematologic” chapter). In digestive diseases research, NIDDK recently renewed the Inflammatory Bowel Disease (IBD) Genetics Consortium. In its current phase, the Consortium is focusing on higher recruitment of study participants from diverse ancestries currently underrepresented in IBD genomic studies, to provide a clearer picture of how genetic factors influence risk for the disease across all populations (see Feature in “Digestive Diseases and Nutrition” chapter).

These and other research activities reflect NIDDK’s multifaceted efforts toward “pathways to health for all.”

NIDDK EFFORTS TO DIVERSIFY THE BIOMEDICAL WORKFORCE

The scientific challenges and opportunities within NIDDK’s mission require that the broader extramural research community include individuals with different backgrounds and experiences and a range of skills, perspectives, and creative approaches. Yet, the Institute has long recognized that while scientific talent is well represented across all populations, opportunity is not. For these reasons, NIDDK has a long history of investing in programs that nurture talent from communities underrepresented in biomedical research.

For example, NIDDK’s Short-Term Research Experience Program to Unlock Potential (STEP-UP) provides summer research experiences in extramural laboratories for high school and undergraduate students from underrepresented racial or ethnic groups, disadvantaged circumstances, or who have a disability. NIDDK’s Diversity Summer Research Training

Program complements the STEP-UP program by offering undergraduates from diverse backgrounds the opportunity to work in NIDDK intramural laboratories. Other NIDDK support for a diverse research workforce includes partnering with the National Medical Association (NMA), which represents African American physicians and the patients they serve. NIDDK cosponsors the NIDDK/NMA Travel Awards Program for African American residents and fellows to encourage research in disease areas that disproportionately impact the health of underserved and minority communities. NIDDK supports a similar program with the National Hispanic Medical Association, which represents Hispanic physicians and other health care professionals and students.

NIDDK also supports efforts to increase diversity in the scientific workforce through programs in specific research areas. For example, NIDDK’s National NIH Physician Scientist DiabDocs-K12 Program prioritizes the career development of physician scientists underrepresented in type 1 diabetes research. The Institute’s Program to Advance the Career Development of Scientists from Diverse Backgrounds Conducting Nutrition, Obesity, Diabetes, and Related Research led to the establishment of a consortium to support postdoctoral and early faculty talent from underrepresented scientists in these research areas. NIDDK also supports the Aspironaut™ Summer Research Internships in STEM, which are laboratory experiences in kidney biology and disease research for high school and undergraduate students from rural and disadvantaged backgrounds. These are just a few examples of NIDDK’s commitment to supporting talented researchers from all backgrounds.

PROVIDING NIDDK STAFF WITH TOOLS TO ADVANCE HEALTH EQUITY

NIDDK recognizes that its efforts to bolster research on health disparities and health equity are dependent upon an internal workforce that has the necessary expertise and tools and reflects the diversity of the American public. NIDDK is dedicated to fostering respect, inclusivity, and equity in its workforce.

NIDDK’s Inclusion, Diversity, Equity, Accessibility, and Civility (IDEA-C) Program was created to promote meaningful and systemic change at NIDDK in these areas. Led by the NIDDK Deputy Director, Executive Officer, and Senior Advisor for Workforce Diversity and Health Equity, IDEA-C efforts are guided by a novel Institute-wide committee, a series of staff-led working groups, and support from external experts in

organizational change. One key activity of IDEA-C is implementing NIDDK's Racial and Ethnic Equity Plan (REEP). In 2021, NIH launched efforts to identify and address structural racism and to promote equity in its activities and put in place a requirement for each Institute and Center to establish an actionable REEP. The NIDDK REEP is structured around a set of goals to advance equity across the NIDDK workplace, workforce, and research areas. The goals will be monitored for progress and updated as needed to reflect new opportunities. Guiding implementation of the REEP is the application of a "Racial and Ethnic Equity Lens" to NIDDK's workforce, structures, and systems.

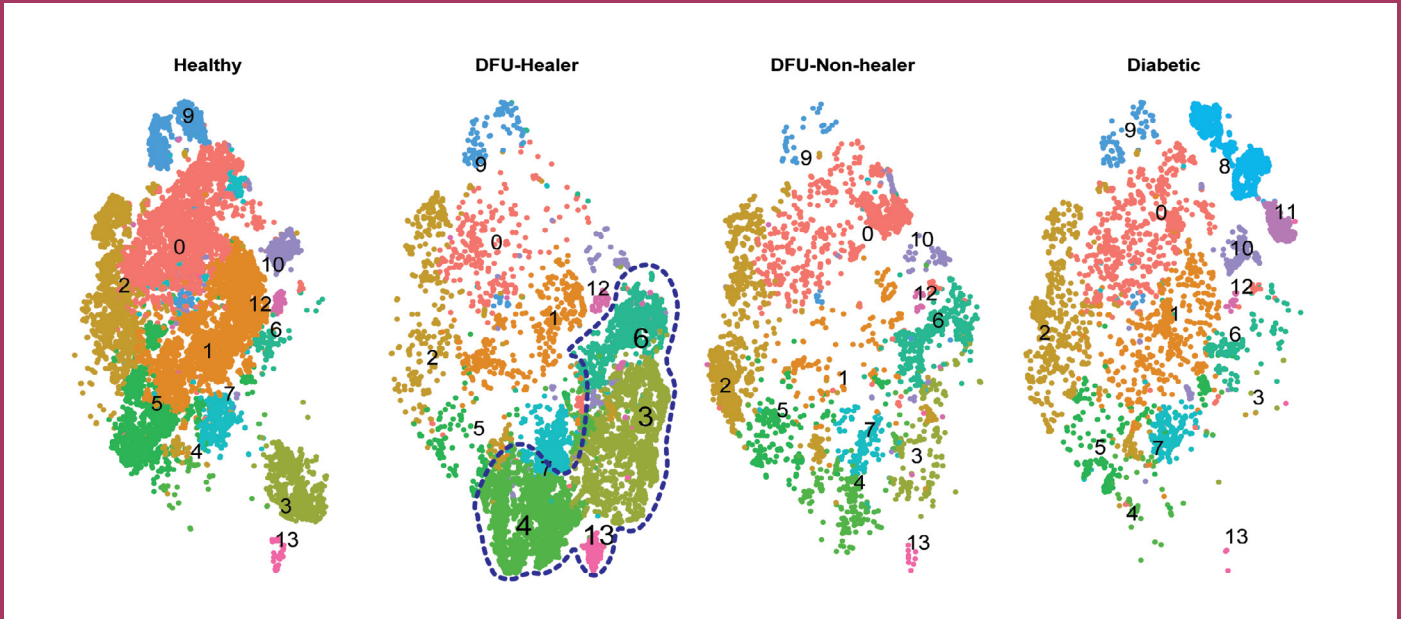
NIDDK recognizes that its efforts to bolster research on health disparities and health equity are dependent upon a workforce that has the necessary expertise and tools and reflects the diversity of the American public.

NIDDK is also actively engaged in NIH-wide efforts, including the UNITE initiative, to develop and implement strategies to increase diversity in the biomedical sciences

and break down barriers of structural racism. The NIH-Wide Strategic Plan for Diversity, Equity, Inclusion, and Accessibility articulates NIH's vision for embracing, integrating, and strengthening diversity, equity, inclusion, and accessibility in the NIH workforce, its structure and culture, and the research it supports. Guided by this vision, NIH will enhance its ability to serve an increasingly diverse U.S. population.

CONTINUOUS IMPROVEMENT TOWARD TRANSFORMATIVE CHANGE

These strengthened efforts require the full participation of NIDDK leadership and staff as the Institute grows, adapts, and evolves to reach our goals. They also demand rigorous evaluation and a continuous review and improvement process. NIDDK will assess and monitor these efforts and share findings with our stakeholders through this annual report and other venues. NIDDK is poised to act to eliminate health disparities, advance health equity, enhance diversity in the NIDDK and broader biomedical research workforces, and create transformative change in the lives of all who are affected by diseases and conditions within the NIDDK mission.



As described in this chapter, scientists used cutting-edge technologies to perform a single-cell analysis of over 174,000 cells from the skin of four groups of people. The first group comprised individuals without diabetes (labeled “Healthy” in the figure above). The other three groups were people with diabetes who either had diabetic foot ulcers (DFUs) that healed within 12 weeks (“DFU-Healer”), had non-healing DFUs (“DFU-Non-healer”), or had no DFUs (“Diabetic”). This figure visualizes a map of the molecular characteristics of fibroblasts found in the skin of each group of individuals. Fibroblasts are a type of cell that play a major role in wound healing, and the scientists identified 14 distinct subsets of fibroblasts, represented by the different colors in the figure. Specifically, they discovered that “HE-Fibros,” a previously undescribed subset of fibroblasts, were abundant in wound beds of DFU-Healers, whereas the wound beds of DFU-Non-healers did not contain as many HE-Fibros. This finding is illustrated by the increased number of cells in the lassoed area under “DFU-Healer” and fewer cells in the equivalent position under “DFU-Non-healer.” Found only in the foot, these unique HE-Fibros promoted wound healing in DFUs by remodeling cellular structures and promoting inflammation associated with healing.

Image provided by Dr. Aristidis Veves, Harvard University, and Dr. Manoj Bhasin, Emory University. Originally published in Theocharidis G, Thomas BE, Sarkar D,...Bhasin M. Single cell transcriptomic landscape of diabetic foot ulcers. Nat Commun 13: 181, 2022. Reprinted under the terms of the Creative Commons CC-BY license.

Diabetes, Endocrinology, and Metabolic Diseases

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

Diabetes is a debilitating disease that affects an estimated 37.3 million people in the United States—or 11.3 percent of the total population—and is the eighth leading cause of death.¹ Although overall rates of diabetes-related complications have declined substantially in recent years, disease burden remains significant, as the number of people with diabetes is still very high.² Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial cost for diagnosed diabetes in the United States in 2017—including costs of medical care, disability, and premature death—was \$327 billion.³ Effective therapy can prevent or delay diabetic complications, but 23 percent of U.S. adults with diabetes are undiagnosed and therefore not receiving therapy.¹

Diabetes affects an estimated 37.3 million people in the United States—or just over 1 in every 10 people.¹ Another 96 million U.S. adults have “prediabetes,” which puts them at elevated risk of developing type 2 diabetes.¹ The estimated total financial cost for diagnosed diabetes in the United States in 2017 was \$327 billion.³

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, type 2 diabetes, and gestational diabetes, a form of diabetes that develops during pregnancy but in many cases resolves after pregnancy. There are also rare forms of diabetes, known as monogenic diabetes, which are associated with specific genes.

In addition to increasing the risk for complications of vision loss, kidney failure, and amputation, diabetes doubles the risk for heart disease, many forms of cancer, some forms of dementia, hearing loss, erectile dysfunction, urinary incontinence, and many other common diseases.²

Type 1 diabetes affects approximately 5 percent of adults diagnosed with diabetes and the majority of children and youth diagnosed with diabetes.¹ It most often develops during childhood but may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the insulin-producing β (beta) cells of the pancreas. Thus, people with type 1 diabetes require lifelong insulin administration to regulate their blood glucose levels.

¹ Centers for Disease Control and Prevention. National Diabetes Statistics Report website. <https://www.cdc.gov/diabetes/data/statistics-report/index.html>. Accessed October 12, 2022.

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

³ American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 41: 917-928, 2018.

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. These results underscore the importance of pursuing research to develop novel technologies to help people with type 1 diabetes manage their blood glucose levels with less burden, including 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 U.S. Food and Drug Administration (FDA)-approved diabetes management technologies, including artificial pancreas devices that automatically link glucose monitoring and insulin delivery. Researchers are also working to further develop and enhance β -cell replacement therapies, such as islet transplantation, that potentially will eliminate the need for insulin injections, toward the ultimate goal of a cure for type 1 diabetes.

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

Type 2 diabetes is the most common form of the disease, affecting about 90 to 95 percent of people diagnosed with diabetes in the United States.⁴ 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. The percentage of adults with diagnosed diabetes in the United States was highest among racial and ethnic minority populations, including American Indian and Alaska Native persons, non-Hispanic Black people, and people of Hispanic origin.¹ 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.⁵

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 β -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 96 million U.S. adults who have "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.¹ 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 who make lifestyle changes to lose weight by adopting a healthy diet and increasing physical activity can dramatically reduce their risk of developing type 2 diabetes. To a more limited degree, the safe and well-tolerated drug metformin can also help prevent or delay type 2 diabetes.

Type 2 diabetes is increasingly being diagnosed in children and adolescents, disproportionately affecting youth from racial and ethnic minority populations in the United States. NIDDK-supported research has shown that type 2 diabetes is more aggressive and difficult to treat in youth compared to adults.

Previously called "adult-onset" diabetes because it is predominantly diagnosed in older individuals, type 2 diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects youth from racial and ethnic minority populations in the United States. Results from NIDDK-supported research have shown that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because those with early disease onset are at especially high risk for developing complications. In addition, increasing rates of type 2 diabetes may lead to more people who enter pregnancy with diabetes, and diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or development of gestational diabetes during pregnancy—is associated with an increased risk of blood glucose abnormalities in offspring. Thus, the rising rates of diabetes and prediabetes could contribute to a

⁴ Centers for Disease Control and Prevention. What is Diabetes? website. <https://www.cdc.gov/diabetes/basics/diabetes.html>. Accessed October 12, 2022.

⁵ Kim C, et al. Gestational diabetes and the incidence of type 2 diabetes: A systematic review. *Diabetes Care* 25: 1862-1868, 2002.

cycle of ever-growing rates of diabetes, in addition to increasing risks for pregnancy complications. 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 most common forms of diabetes, type 1 and type 2, are associated with variations in multiple genes. Some rare forms of diabetes, called monogenic diabetes, result from mutations in a single gene. Neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. Many cases of monogenic diabetes may be incorrectly diagnosed, which may complicate management. There are also unusual forms of diabetes that differ from known types, called “atypical diabetes.” People with atypical diabetes may be diagnosed with and treated for type 1 or type 2 diabetes, but not have a history or signs consistent with their diagnosis. In addition, individuals may have a condition called latent autoimmune diabetes in adults (LADA). Finally, more recently, type 3c diabetes, a form of diabetes that may appear after pancreatitis, has been described. It is critical to discover and define rare and atypical forms of diabetes, which could lead to better diagnoses, improved treatments, and potential prevention of these diseases.

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

TESTING NEW TYPE 1 DIABETES THERAPIES

New Oral Therapy for Type 1 Diabetes Can Delay Disease Progression and Lower Insulin Requirements for at Least 2 Years: A small clinical trial has highlighted a new possible oral therapy to delay type 1 diabetes progression, as well as a potential new biological marker to monitor disease progression. In type 1 diabetes, the immune system launches a misguided attack against the insulin-producing β (beta) cells in the pancreas. Novel therapies to protect β -cells from this attack are urgently needed. Similarly, easily monitored markers of β -cell health are needed to warn of the earliest stages of type 1 diabetes and to predict and track disease severity.

Previous NIDDK-supported research suggested that verapamil might slow diabetes progression. Verapamil is an oral medication approved by the U.S. Food and Drug Administration (FDA) over 30 years ago to treat high blood pressure. In a small clinical trial, 24 male and female volunteers recently diagnosed with type 1 diabetes were treated with insulin and either verapamil or an inactive placebo. In 2018, scientists reported that people taking verapamil for 1 year had better insulin responses, used less insulin, and had fewer incidents of low blood glucose (sugar) than did people taking a placebo, all with no adverse effects. These results suggested that verapamil could safely improve overall β -cell function and might prevent β -cell loss.

Now, new research has detailed a year-long extension of this trial. In the trial’s second year, the verapamil-treated group was split into two subgroups: one continued taking verapamil, while the other stopped. Those who used verapamil for 2 years maintained their β -cell health and continued to need reduced levels of insulin compared to the group that never took verapamil. However, those who stopped the drug after 1 year saw their β -cell health decline and their insulin needs rise, demonstrating that verapamil’s benefits required continuous use. Researchers also found that levels of a protein called chromogranin A (CHGA) in the blood may be a promising biological marker for poor β -cell health. Specifically, they found that CHGA blood levels were elevated in people with type 1 diabetes compared to people without the disease. CHGA levels dropped substantially in people who took verapamil, but remained high in those who took the placebo, suggesting that CHGA levels reflect changes in β -cell health in response to verapamil treatment. Thus, CHGA levels might be a simple way to track type 1 diabetes initiation, progression, and/or response to treatment.

A small clinical study has found that the oral medication verapamil may help preserve β -cell health in those newly diagnosed with type 1 diabetes.

These findings may lead to new options to diagnose, treat, and monitor type 1 diabetes. Future studies will be needed to better characterize both verapamil’s safety and effectiveness, as well as CHGA’s usefulness as a marker of β -cell health.

Xu G, Grimes TD, Grayson TB,...Shalev A. Exploratory study reveals far reaching systemic and cellular effects of verapamil treatment in subjects with type 1 diabetes. Nat Commun 13: 1159, 2022.

RESEARCH TOWARD IMPROVING TREATMENT OF TYPE 2 DIABETES

Study Demonstrated Two Diabetes Drugs Are More Effective Than Others in Long-term Treatment: A

large clinical trial comparing four commonly used blood glucose (sugar)-lowering medications found that glargine and liraglutide were more effective than sitagliptin or glimepiride at achieving and maintaining blood glucose levels within the recommended range when added to treatment with metformin. The study also examined each drug's side effects and impact on development of diabetes-related cardiovascular disease over an average of a 5-year period.

People with diabetes who keep their blood glucose levels in the near-normal range have a much lower risk of developing diabetes complications. Metformin is the first-line treatment, but, over time, people with type 2 diabetes may need another glucose-lowering drug, and there is no consensus on which drug to choose. Launched in 2013, NIDDK's Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) study was designed to directly compare four U.S. Food and Drug Administration (FDA)-approved, glucose-lowering drugs' long-term effectiveness. The study enrolled 5,047 participants from diverse racial and ethnic groups who had type 2 diabetes, were already taking metformin, and did not have established cardiovascular complications. Participants were randomly assigned to take one of four drugs: glargine, sitagliptin, liraglutide, or glimepiride.

After an average of 4 years, the researchers found that, in combination with metformin, all four drugs had a beneficial effect, but glargine and liraglutide were best at keeping blood glucose levels in the recommended range. However, they found that it was difficult to maintain the recommended glucose levels in nearly three-quarters of all participants over 4 years, showing type 2 diabetes' aggressive nature. In terms of side effects, severe hypoglycemia (dangerously low blood glucose) was uncommon but affected more participants receiving glimepiride, and gastrointestinal symptoms were more common in those receiving liraglutide. None of the drugs had robust effects on lowering the risk of cardiovascular disease over an average of 5 years, but the researchers found that participants taking liraglutide were least likely to experience any cardiovascular disease overall compared to the other groups.

The GRADE study findings confirm the usefulness of glargine and liraglutide, in combination with metformin, in the treatment of people with type 2 diabetes and help health care providers make evidence-based recommendations when guiding long-term management of type 2 diabetes.

The GRADE study closes important gaps in knowledge regarding the use of glucose-lowering drugs in people who are already taking metformin and confirms the usefulness of glargine and liraglutide in the treatment of people with type 2 diabetes. Unfortunately, a now-available class of diabetes drug called SGLT2 inhibitors was not FDA-approved at the launch of GRADE recruitment and was not included in the study, so questions remain as to how SGLT2 inhibitors would perform against the four drugs tested in the trial. The study also demonstrated a need for more effective treatments for long-term management of type 2 diabetes. NIDDK stands uniquely poised to support comparative effectiveness trials like GRADE to help people with type 2 diabetes and their providers make evidence-based treatment decisions that lead to better health.

Nathan DM, Lachin JM, Balasubramanyam A,...Younes N; for the GRADE Study Research Group. Glycemia reduction in type 2 diabetes—glycemic outcomes. [N Engl J Med](#) 387: 1063-1074, 2022.

Nathan DM, Lachin JM, Bebu I,...Younes N; for the GRADE Study Research Group. Glycemia reduction in type 2 diabetes—microvascular and cardiovascular outcomes. [N Engl J Med](#) 387: 1075-1088, 2022.

New Insights into Body Fat Tissue and Weight Gain Induced by Type 2 Diabetes Drugs:

Studying two forms of a master molecular regulator of body fat tissue, PPAR γ , researchers discovered that, in mice, one form is associated with weight-gain side effects of a type 2 diabetes drug—a finding with implications for new treatment strategies. PPAR γ is central to fat tissue development in mice and humans and is involved in other biological processes related to diabetes and metabolism. It is also the target of type 2 diabetes drugs called thiazolidinediones (TZDs), which activate PPAR γ to improve blood glucose (sugar) levels but lead to unwanted weight gain. The two forms of PPAR γ in mice and humans, PPAR γ 1 and PPAR γ 2, differ slightly in structure. While there were hints of other differences from earlier research, specific functional distinctions were not clear. Hoping for new insights that could lead to improved therapies, a team of researchers set out to study these two forms of PPAR γ more closely.

For their research, the scientists designed a series of experiments and generated male mice that were deficient in one or the other form of PPAR γ to identify any differences. Because PPAR γ is known to control the activity of many genes, the researchers examined gene regulation in the mice and found that PPAR γ 1 and PPAR γ 2 regulate distinct sets of genes in various body fat tissues. They also identified other functional differences between PPAR γ 1 and PPAR γ 2. Most intriguingly, when the researchers gave a TZD drug to mice deficient in PPAR γ 1, they discovered that the mice had improved blood glucose levels without the usual drug-induced weight gain. Although deficient in PPAR γ 1, these mice still had PPAR γ 2, so the researchers concluded that PPAR γ 2 is sufficient for the drug's benefits, while PPAR γ 1 must be responsible for the weight-gain side effect.

This research in mice brings to light previously unknown features of fat tissue and new understanding of weight gain caused by some type 2 diabetes drugs. If further studies show that PPAR γ 1 and PPAR γ 2 function similarly in humans, researchers may be able to develop drugs that specifically target one of PPAR γ 's forms to treat diabetes with fewer side effects.

Hu W, Jiang C, Kim M,...Lazar MA. Isoform-specific functions of PPAR γ in gene regulation and metabolism. *Genes Dev* 36: 300-312, 2022.

RESEARCH ON DIABETES COMPLICATIONS

New Insights into Relationships Between Genetic Risk Factors for Type 2 Diabetes and Metabolic Conditions:

A new study found that groups of genetic variations that increase the risk of type 2 diabetes may also influence the risk of developing associated metabolic conditions. Type 2 diabetes increases people's risk of developing serious and often life-threatening complications, such as cardiovascular disease and kidney failure. Because there is so much variability in whether or not individuals with type 2 diabetes develop these clinical outcomes, better understanding of genetic risk factors and the associated complications could help advance personalized patient care and improve prevention and treatment approaches.

In previous research, scientists used data from a large-scale cohort study to identify genetic variations that predispose an individual to type 2 diabetes and were able to group them into several subgroups based on the type of genetic mechanisms that led to the disease. For instance, within the group of genetic

variations that affect the body's glucose (sugar) uptake and increase insulin resistance, the scientists identified three subgroups, or "clusters," that also increase people's risk for obesity, lipodystrophy (a disorder that affects how the body accumulates and stores fat), and disrupted liver lipid metabolism. In this new study, the research team analyzed individual-level genetic data from a total of 454,193 participants, including 25,015 individuals with type 2 diabetes, in 13 cohort studies to determine whether these clusters were also associated with other clinical outcomes such as high blood pressure, coronary artery disease, and reduced kidney function. Even though all clusters included genetic variations that increase type 2 diabetes risk, there were differential associations with cardiovascular disease risk and kidney function. For example, coronary artery disease risk was decreased in the disrupted liver lipid metabolism cluster, whereas the risk was higher in the lipodystrophy cluster. Clusters for obesity and lipodystrophy were both associated with higher blood pressure, and the disrupted liver lipid metabolism cluster was associated with reduced kidney function.

Although not yet ready for use in a clinical setting, knowing whether and how someone with type 2 diabetes genetic risk factors could be predisposed to cardiovascular diseases or metabolic conditions could one day be a useful tool for not only predicting disease risk and informing patient management, but also classifying participants for clinical studies. Further research to clarify relationships between type 2 diabetes genetic risk, cardiovascular risk, and metabolic function will also provide insight into complex biological mechanisms underlying type 2 diabetes and may even lead to new targets for drug development.

DiCorpo D, LeClair J, Cole JB,...Udler MS. Type 2 diabetes partitioned polygenic scores associate with disease outcomes in 454,193 individuals across 13 cohorts. *Diabetes Care* 45: 674-683, 2022.

Type 2 Diabetes Prevention Strategies May Not Provide Protection Against Cardiovascular Diseases in Adults:

New findings from the Diabetes Prevention Program Outcomes Study (DPPOS) show that weight reduction through lifestyle changes or taking metformin, a medication that controls high blood glucose (sugar) levels to treat type 2 diabetes, may not provide additional protection against cardiovascular diseases in people with diabetes or at high risk of diabetes (prediabetes).

The Diabetes Prevention Program (DPP) was a landmark trial that transformed the way we approach type 2 diabetes prevention. Launched in 1996, the

randomized controlled clinical trial recruited a diverse cohort of people at high risk for type 2 diabetes and demonstrated that the disease can be effectively prevented or delayed through lifestyle interventions (moderate physical activity aimed at reducing weight) or with metformin. Even though the trial was completed in 2001, the ongoing DPPOS continues to follow most DPP participants, and the data show that lifestyle changes or metformin treatment continues to provide long-term benefits in preventing or delaying type 2 diabetes even after two decades. Because people with type 2 diabetes are at increased risk for cardiovascular events such as heart attacks and strokes, the DPPOS researchers sought to determine whether lifestyle changes or metformin can also prevent or delay cardiovascular episodes. In this new analysis, they found that, surprisingly, neither lifestyle interventions nor metformin had a significant impact, either beneficial or unfavorable, on the incidence of cardiovascular events despite the improvement of cardiovascular risk factors in the lifestyle intervention group. One of the reasons behind this result could be that more time is needed for these interventions to show a beneficial effect on cardiovascular health. Other potential explanations include the DPPOS participants receiving a less intensive lifestyle intervention than in DPP, as well as their extensively using out-of-study medications, including those that lower blood lipid (fat) levels and blood pressure. These medications may have diluted the differences between study groups. This suggests that even though metformin and lifestyle intervention reduce the risk of type 2 diabetes, they may not be effective against cardiovascular disease when blood glucose, lipids, and blood pressure are well controlled.

Continuing to investigate the effects of metformin and lifestyle interventions on cardiovascular health will help optimize diabetes prevention and care and may provide important clues to cardiovascular disease prevention. Further research is needed to better understand and clarify the long-term effects of these interventions.

Goldberg RB, Orchard TJ, Crandall JP,...Temprosa M; on behalf of the Diabetes Prevention Program Research Group. *Effects of long-term metformin and lifestyle interventions on cardiovascular events in the Diabetes Prevention Program and its outcome study.* *Circulation* 145: 1632-1641, 2022.

Early and Intensive Control of Blood Glucose Is Associated with Reduced Risk of Diabetic Foot Ulcers in People with Type 1 Diabetes: New findings from a long-standing observational study show, for the first

time, that risk of diabetic foot ulcers (DFUs) is decreased by controlling blood glucose (sugar) levels early and intensively in individuals with type 1 diabetes. DFUs commonly occur in people with diabetes and can lead to lower extremity amputation, which is associated with high mortality. Prevention, if possible, is the best course of action, as current treatment options are limited. Identifying DFU prevention strategies is critical to improve the health and quality of life of people with type 1 diabetes.

Previous studies have suggested a link between high blood glucose levels and the risk of DFUs and lower extremity amputations in people with type 1 diabetes. However, questions remained as to whether intensive control of blood glucose could affect the risk of DFUs or amputations. Fortunately, NIDDK's Diabetes Control and Complications Trial (DCCT) and its ongoing observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, provided a rare and exciting opportunity to answer these questions. Completed in 1993, DCCT was the first randomized controlled trial to show that intensive treatment to keep blood glucose levels as near to normal as safely possible can reduce risk for several diabetic complications, including retinopathy (a form of eye disease), neuropathy (nerve damage), and kidney disease. The intensive treatment involved more frequent insulin administration and blood glucose monitoring than was conventional at the time. EDIC has continued to study the health of the majority of the DCCT participants for nearly 3 decades and has shown additional benefits of the intensive treatment. In this new analysis, researchers found that those whose blood glucose levels were intensively managed during the DCCT were less likely to develop DFUs starting at an average of 17 years from when the DCCT began. Additional analysis revealed several risk factors that put individuals at greater risk of DFUs: higher average glucose levels (as measured by hemoglobin A1c [HbA1c]), older age, albuminuria (having too much albumin in urine, which is a sign of kidney disease), cardiovascular autonomic neuropathy (damage to nerves in the heart and blood vessels), and retinopathy.

Diabetic foot ulcers can now be added to the list of diabetic complications that may be preventable through early and intensive control of blood glucose levels in people with type 1 diabetes.

This study suggests that controlling blood glucose levels intensively and early in the disease course is beneficial for people with type 1 diabetes to reduce long-term risk of DFUs, confirming the importance of early intervention to prevent diabetic complications. Further research on the risk factors identified may help predict who is at increased risk of DFUs and lower extremity amputations and guide appropriate prevention strategies in a timely manner.

Boyko EJ, Zelnick LR, Braffett BH,...de Boer IH; for the DCCT/EDIC Research Group. Risk of foot ulcer and lower-extremity amputation among participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 45: 357-364, 2022.

A Comprehensive Map of Cells from Diabetic Foot Ulcers Reveals Factors Critical for Successful Wound Healing:

Researchers used state-of-the-art technologies to develop a detailed and comprehensive view of diabetic foot ulcers (DFUs) at the cellular and molecular level and revealed elements that promote successful wound healing. DFUs are a devastating complication of diabetes with limited treatment options. Even though most foot ulcers heal with appropriate management, recurrence is common after initial healing and, in worst cases, leads to lower extremity amputations, significantly affecting quality of life and putting a huge financial burden on the health care system. Improved knowledge about how wound healing occurs in DFUs is needed to identify novel treatment approaches that promote healing in a timely manner and prevent further complications.

By studying differences between diabetic foot ulcers that heal and those that do not, researchers discovered a subset of cells that promote successful wound healing.

In new research, scientists used cutting-edge technologies to perform a large-scale, single-cell analysis of over 174,000 cells from the foot, forearm, and blood to examine the cells from men and women with DFUs that healed within 12 weeks versus those with non-healing DFUs. They observed major differences in the types of cells found in different sites of the body and in different DFUs. Specifically, they discovered that a previously undescribed subset of fibroblast cells, which they called “HE-Fibros,” were abundant in wound beds of healing DFU samples. Found only in the foot, these unique cells promoted wound healing by firmly attaching to the structures between cells, remodeling

those structures, and communicating with immune cells to promote inflammation associated with healing. In contrast, non-healing DFUs did not contain as many HE-Fibros and instead showed signs of dysregulated chronic inflammation associated with impaired healing. Additionally, healing DFUs and non-healing DFUs showed types of inflammation and immune signatures that were significantly distinct from each other. For instance, immune cells called M1 macrophages, which promote inflammation and wound healing, were largely present in healing wounds, whereas the majority of the macrophages found in non-healing wounds were M2 macrophages, which suppress inflammation.

Exactly how DFUs form and heal is still not completely understood, but these new data identify specific cells that are important for wound healing in DFUs and provide insights into the roles they play in inflammation, as well as how they might interact with other cells to encourage an environment favorable to wound healing. Further studies of these cellular and molecular signatures will not only help identify the “foot at risk” of chronic ulcers or amputations, but also provide a recipe for successful wound healing in DFUs, which may lead to new treatment approaches.

Theocharidis G, Thomas BE, Sarkar D,...Bhasin M. Single cell transcriptomic landscape of diabetic foot ulcers. *Nat Commun* 13: 181, 2022.

STUDYING LINKS BETWEEN STRUCTURAL RACISM AND DIABETES HEALTH DISPARITIES

Effects of Historic Redlining Persist To Elevate Risk of Death from Diabetes: A recent study investigated the effects of historic residential redlining practices on current health outcomes, focusing on death rates from diabetes and premature death due to diabetes. The study showed significantly worse health outcomes in those who lived in “redlined” areas that were previously graded as less desirable, compared to those who did not, with this negative impact on health persisting for decades. Formalized in 1934 by the Federal Housing Administration and prohibited later in 1968, residential redlining was the systemic practice of denying various services, such as credit access and insurance, to residents of neighborhoods—populated primarily by racial and ethnic minority groups—that were graded as “declining” and “hazardous” in maps created by the Home Owners’ Loan Corporation (HOLC). Recent data show persistent effects of structural racism and inequities, such as

redlining, on various health outcomes, including mental health, preterm birth, and COVID-19 outcomes.

In new research, scientists sought to determine whether people with chronic medical needs and high medical cost burden, such as people with diabetes, are disproportionately and negatively impacted by historic redlining. Their analysis combined three sets of data—a digitized copy of the HOLC map of Seattle, Washington; census data; and data on mortality rate and years of life lost (an estimate of the average years a person would have lived if they had not died prematurely). They found that mortality rate and years of life lost in general were significantly higher in areas with exposure to worse HOLC grading, showing clinically meaningful differences in health outcomes. However, these differences were much bigger when they examined mortality and years of life lost specifically due to diabetes, showing an approximately 50 percent increase in the rate of diabetes mortality in areas with a 1-unit-higher HOLC grade (e.g., those with a “hazardous” rather than a “declining” grade); similar results were observed for years of life lost. Results also showed persistence of these differences over the course of 25 years from 1990 to 2014, even though redlining was formally prohibited in 1968.

The historic and persistent effects of redlining may put individuals with diabetes at an elevated risk of early death and demonstrate the long-term negative impact of structural racism on health outcomes. This finding highlights the urgent need for targeted interventions that will stop perpetuating inequities in order to reduce diabetes health disparities.

Current residents in areas with previous exposure to redlining are more likely to experience social risk factors such as poverty, discrimination, and poor educational attainment and employment opportunities. While this study does not establish redlining as a direct cause of increased diabetes mortality, it is the first study to show that redlining, as a surrogate for structural racism, can be a critical link between structural racism and diabetes disparities. It also highlights the important role that our living environment and social factors play in health and diabetes care, while underscoring the urgent need to identify and implement targeted interventions that will stop perpetuating inequities in order to close the gap on diabetes health disparities.

Linde S, Walker RJ, Campbell JA, and Egede LE. Historic residential redlining and present-day diabetes mortality and years of life lost: The persistence of structural racism. *Diabetes Care* 45: 1772-1778, 2022.

UNDERSTANDING CELL SIGNALING AND COMMUNICATION

A Novel Protein Complex May Influence Diabetes Development:

Scientists discovered a new complex of proteins that regulate the function of insulin-producing β (beta) cells and may influence the development of type 1 and type 2 diabetes. Hormones—signaling molecules that act on distant tissues and organs—regulate many physiological and behavioral processes, so elucidating their roles is critical to understanding health and disease. A previously identified hormone, fatty-acid-binding protein 4 (FABP4), has been shown to be released by fat cells (adipocytes) during times of starvation as these cells break down their stored fat for use as energy for the body, and FABP4 levels have been strongly associated with cardiometabolic disease. FABP4’s exact role, however, has been unclear.

In this new study, scientists discovered that FABP4 joins with two other proteins—adenosine kinase and nucleoside diphosphate kinase—to form a novel complex they named “Fabkin.” To determine the role of Fabkin, the scientists used two mouse models of diabetes. In a model of type 1 diabetes, they observed that Fabkin increased both shortly before and during disease development, suggesting that it may have a role in β -cell failure and disease pathogenesis. Interestingly, blocking Fabkin preserved β -cell mass and function, protecting against development of type 1 diabetes. In a mouse model of type 2 diabetes, blocking Fabkin improved control of blood glucose (sugar) and prevented the disease. To determine whether Fabkin had a role in diabetes in humans, the investigators looked at its levels and found that serum Fabkin was increased in individuals with new-onset type 1 diabetes compared to individuals without diabetes. In older people with type 1 diabetes with various durations of disease, serum Fabkin correlated with levels of hemoglobin A1c (HbA1c; a measure of blood glucose levels over time), suggesting that it is associated with control of blood glucose levels. Additional experiments to understand the underlying mechanisms of how Fabkin exerts its effects suggested that the hormone complex couples energy levels with a metabolic response to regulate the function of β -cells.

This important discovery of Fabkin and its novel mechanism to integrate energy status with regulation of metabolism has revealed a promising new therapeutic target to combat metabolic diseases, including type 1 and type 2 diabetes. Further research on Fabkin and its impacts on human health and disease will be required to capitalize on these exciting results.

Prentice KJ, Saksi J, Robertson LT,...Hotamisligil GS. A hormone complex of FABP4 and nucleoside kinases regulates islet function. *Nature* 600: 720-726, 2021.

New Insights on Cell-to-cell Communication—miRNA “Zip Codes”: Researchers have identified short genetic sequences on microRNAs (miRNAs) that help determine which miRNAs are retained by the cell that produced them and which are released to affect other cells. This knowledge provides important new insights into cell-to-cell communication and could inform the development of therapies for diseases associated with miRNA dysfunction. miRNAs are very short RNA molecules involved in regulating gene activity and play a role in both health and disease; miRNA dysfunction has been linked to type 2 diabetes, obesity, and other diseases. miRNAs may be retained by their parent cell or released in exosomes—small cellular delivery packages that transfer miRNAs and proteins from one cell to another. However, the mechanisms by which cells determine which miRNAs go where are not understood.

To address this gap in knowledge, scientists examined miRNAs in exosomes secreted by different types of mouse cells grown in the laboratory, including fat cells (adipocytes), liver cells, and other cells, finding that each cell type secreted different miRNAs in their exosomes. Additionally, some miRNAs were more likely to be found in exosomes, while others were mostly retained by the cell that produced them, suggesting a mechanism of miRNA sorting. To understand how the sorting occurred, the scientists studied whether specific genetic sequences in miRNAs determined whether they were packaged into exosomes or retained by cells—was there a “zip code” telling the cell where miRNAs should go? Indeed, experiments identified several short sequence motifs associated with miRNAs either being released in exosomes (called EXOmotifs) or retained by cells (called CELLmotifs); interestingly, each of the cell types studied used different sequence motifs, suggesting that there is no one universal exosome “addressing” system. The scientists next confirmed the importance of these motifs by showing that genetically modifying an miRNA’s sequence motif “zip code” changed its location.

For example, adding an EXOmotif to one of the cellular miRNAs promoted its release into exosomes. This redirection of miRNAs led to changes in gene activity in the recipient cells, suggesting that altering these sequence motifs to change the location of miRNAs could be used to affect downstream cellular activity.

These results provide new understanding about how cells sort miRNAs and communicate with one another. Further understanding of the mechanisms underlying miRNA sorting could facilitate new approaches for miRNA-based therapies for a variety of diseases.

Garcia-Martin R, Wang G, Brandão BB,...Kahn CR. MicroRNA sequence codes for small extracellular vesicle release and cellular retention. *Nature* 601: 446-451, 2022.

Cellular Aberrations Associated with Insulin Resistance in People Without Diabetes: Researchers have discovered a large network of cellular alterations in people with insulin resistance but without diabetes. Insulin resistance is a major risk factor for the development of metabolic syndrome and type 2 diabetes, and the impact of insulin resistance on metabolic syndrome is well studied. However, many people without diabetes have insulin resistance, and the molecular determinants underlying this remain elusive.

In this study, researchers generated myocytes—a type of muscle cell that absorbs glucose (sugar) in response to insulin—from blood samples of 20 individuals without diabetes but with a range of insulin sensitivities. Ten individuals had insulin resistance (I-res), while the others had insulin sensitivity (I-sen), and both groups were equally divided between men and women. Individuals with I-res had elevated blood glucose levels compared to their I-sen counterparts, and an assessment of insulin-stimulated glucose uptake by the laboratory-grown myocytes showed this was significantly impaired in I-res cells compared to I-sen cells. Next, the team analyzed the spectrum of cellular signaling changes among these samples. The results indicated large differences in molecular signatures in cells based on I-res status and that many of the alterations in these I-res cells overlapped with alterations observed in cells from individuals with type 2 diabetes in a previous study by the same group. Many of these alterations were found in biological pathways not previously known to be involved in insulin signaling. Moreover, the researchers found striking molecular differences between cells from men and women, many of which occur in diabetes and could contribute to sex-specific differences in physiology and disease.

These findings indicate critical points of regulation of cellular processes in insulin resistance that can potentially serve as novel sites for future therapeutic development. Further research is needed to clarify how sex-specific differences in molecular signatures affect normal physiology and the risk of metabolic disease between men and women.

Haider N, Lebastchi J, Jayavelu AK, ...Kahn CR. Signaling defects associated with insulin resistance in nondiabetic and diabetic individuals and modification by sex. *J Clin Invest* 131: e151818, 2021.

ADVANCING PARATHYROID DISEASE DIAGNOSIS AND TREATMENT

Case Studies Identify New Autoimmune Form of Parathyroid Hormone Impairment: A recent case study has identified how a misguided autoimmune reaction to the parathyroid hormone type 1 receptor (abbreviated PTHR or PTH1R) can cause parathyroid hormone (PTH) resistance, a condition that can cause serious disruptions of the body's mineral levels. Normally, PTH helps control calcium and phosphorus levels. PTH resistance occurs when the body fails to respond to PTH, causing high calcium levels and low phosphorus levels in the blood.

Most cases of PTH resistance are congenital, due to genetic mutations or gene-related effects on one of the signaling proteins that mediates PTH activity. However, the PTH resistance of two women referred to the National Institutes of Health Clinical Center did not fit this pattern, prompting researchers, including those with the NIDDK Intramural Research Program, to dig deeper into the cause of their symptoms. Though these two women demonstrated classic signs of PTH resistance—high calcium levels, low phosphorus levels, and other common symptoms such as muscle cramps, tingling, and numbness—these symptoms had started later in life, and the women did not have genetic traits known to cause PTH resistance. Additionally, the women had elevated PTH levels that were difficult to correct with standard medication regimens. The scientists tested the women's blood to look for autoimmune irregularities and found that both women had high levels of antibodies directed against PTH1R, which were impairing the receptor's ability to bind PTH. Further tests also found that the women had higher-than-usual levels of an immune cell type sometimes seen in other autoimmune diseases.

Together, these results identified how autoimmunity against PTH1R can lead to PTH resistance. Further

research will be needed to determine how common this cause of PTH resistance is, and, since both people in this case study were Black women, whether it is affected by ancestry or biological sex. These findings could also have important implications for PTH resistance treatment, suggesting that people with an autoimmune-associated form of the condition may benefit from immune-suppressing therapies.

Mandl A, Burbelo PD, Di Pasquale G, ...Weinstein LS. Parathyroid hormone resistance and autoantibodies to the PTH1 receptor. *N Engl J Med* 385: 1974-1980, 2021.

Novel Computational Pipeline Approach Leads to Discovery of Possible New Treatments for the Endocrine Disorder Hyperparathyroidism: Scientists recently used a new strategy to identify, screen, and test possible new drugs to treat hyperparathyroidism by targeting the parathyroid hormone type 1 receptor (abbreviated PTHR or PTH1R) protein. Overactive PTHR signaling can result in hyperparathyroidism, an endocrine disorder in which the parathyroid gland makes too much parathyroid hormone. This hormone is vital for maintaining normal calcium and vitamin D levels and for proper bone turnover. However, excess parathyroid hormone works through its receptor, PTHR, to cause elevated calcium levels in the blood, which can lead to health problems such as bone thinning and kidney stones.

Seeking new ways to treat hyperparathyroidism, researchers devised a computational pipeline approach to identify and screen for compounds to affect PTHR's function. Using a series of computer models and simulations, researchers predicted how various parts of the PTHR protein interact with each other. This approach identified specific sites on PTHR that were "druggable" (i.e., where a small molecule could bind and change the receptor's shape and function). Scientists then used another set of simulations to screen a library of compounds virtually, looking for those predicted to bind well to the identified sites on PTHR. This computational strategy identified several promising compounds, and one of these compounds, Pitt12, was tested in both cells grown in the lab and in male mice. In both sets of experiments, Pitt12 inhibited the effects of parathyroid hormone, possibly by disrupting PTHR's interactions with other signaling proteins. In mice, Pitt12 also reduced blood calcium levels, indicating that this compound might be useful in preventing the elevated calcium levels associated with hyperparathyroidism. Preliminary experiments also suggested that Pitt12's

inhibitory effects on PTHR did not seem to extend to other similar receptors tested. Such specificity would be desirable in a therapeutic, though additional experiments will be needed to determine Pitt12's suitability for further drug development.

Researchers devised a new computational pipeline to identify and screen for compounds to treat the disorder hyperparathyroidism.

In addition to identification of Pitt12, this study also provided broadly valuable information on PTHR. This data could inform work on drugs targeting this receptor for other purposes, such as treating bone and mineral disorders. The researchers' new computational pipeline approach could also be adapted to identify small molecules targeting receptors other than PTHR, and thus could improve the drug development process for a wide variety of diseases.

Sutkeviciute I, Lee JY, White AD,...Villardaga J-P. Precise druggability of the PTH type 1 receptor. Nat Chem Biol 18: 272-280, 2021.

Research on Type 2 Diabetes in Youth

Type 2 diabetes affects many millions of adults in the United States, but it has also been increasing in children and young adults. The SEARCH for Diabetes in Youth (SEARCH) study, a joint effort supported by NIDDK and the Centers for Disease Control and Prevention, revealed that while type 2 diabetes is still uncommon in young people, its numbers have been rising steadily as a result of the obesity epidemic, especially among racial and ethnic minority populations and populations with low socioeconomic status.

Children with type 2 diabetes are at higher lifetime risk than adults of developing serious diabetes complications such as blindness, kidney failure, diabetic foot ulcers, strokes, and heart attacks because their likelihood increases with duration of diabetes. According to the SEARCH study, almost three out of four teenagers and young adults with type 2 diabetes already have at least one complication or associated health condition. What makes these statistics truly devastating is that these young people are experiencing debilitating and life-threatening complications during what should be the most productive period of their lives.

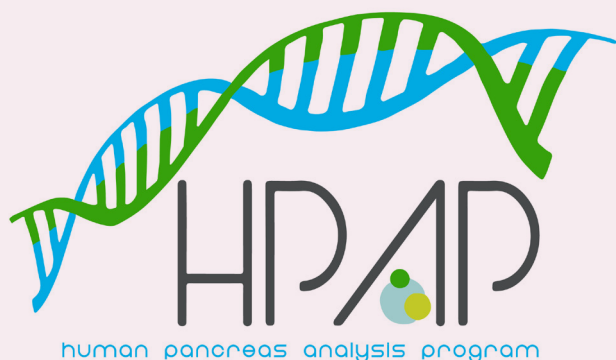
Unfortunately, we now also know that some of the medications most commonly used to treat type 2 diabetes in adults are either not as effective in controlling blood glucose (sugar) or have not been well studied in young people with the disease. For example, the NIDDK-supported Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial has shown that neither the most commonly used adult type 2 diabetes drug, metformin, nor a lifestyle intervention program was sufficient to control the disease in young people. TODAY also demonstrated that insulin resistance (an impaired response to insulin that both precedes and accompanies the disease) was greater and loss of insulin-producing β (beta) cell function occurred much more rapidly in youth-onset type 2 diabetes than when the disease arises during

middle age. These findings have been reinforced by similar results from another NIDDK-funded research effort, the Restoring Insulin Secretion (RISE) Consortium, again highlighting the urgent need to identify better treatment options for young people with type 2 diabetes.

To address this growing public health challenge, NIDDK continues to support and stimulate research to shed more light on the mechanisms underlying youth-onset type 2 diabetes and to determine what makes it so difficult to treat. TODAY2, an ongoing observational study, is providing long-term follow-up data on the progression of type 2 diabetes and various complications in participants from the TODAY trial. Data from TODAY2 may help identify and understand the unique factors that accelerate type 2 diabetes progression in youth so that researchers can leverage that knowledge to slow down or stop progression of the disease.

Another research area of particular interest is prevention. Given how aggressive and difficult to treat the pediatric form of the disease is, it is crucial to find effective prevention methods and better ways to detect the earliest warning signs of the disease so that treatment can begin before significant disease progression has occurred. Therefore, NIDDK issued a funding opportunity announcement in 2021 to create a clinical consortium to further study the disease in youth. The consortium will aim to recruit a large, diverse cohort of young people at risk for diabetes and gather data that may improve our ability to predict those with highest risk of developing the disease and increase our understanding of the factors that drive progression to type 2 diabetes in youth. This knowledge may one day help guide future development of effective prevention and treatment approaches to reduce the burden type 2 diabetes places on young people with the disease.

Human Pancreas Analysis Program— New Insights into Diabetes



Diabetes occurs when the body's blood glucose (sugar) levels are too high. Glucose is the body's main source of energy and comes from the foods we eat. Normally, the hormone insulin, which is made by the pancreas, acts in tissues of the body to promote glucose absorption from the blood for use as fuel. In type 1 diabetes, the body's immune system launches a misguided attack on the insulin-producing cells of the pancreas, destroying them and leading to a rise in blood glucose levels. The onset of type 1 diabetes can be predicted using autoimmune and genetic markers. However, approaches to prevent or modify disease development are needed. Progress in this area could be greatly facilitated by a deeper understanding of the physical and functional organization of the human pancreatic environment and the interactions between the pancreas and the immune system at the cellular and molecular level.

To fill this knowledge gap, in 2016 NIDDK established the Human Pancreas Analysis Program (HPAP), an integral component of the Human Islet Research Network (HIRN). HPAP's initial aims were to procure pancreata from people with and without type 1

diabetes to conduct extensive cellular analyses and to generate integrated molecular signatures of the human pancreas at various stages of disease progression, providing information on type 1 diabetes risk and development.

In addition to performing in-depth characterizations of the pancreatic tissue ecosystem, an overarching goal of HPAP investigators is to accumulate, analyze, and distribute high-value datasets to the diabetes research community through a searchable database called PANC-DB. The latest version of PANC-DB, called version 2.0, was released in May 2022, and it provides researchers with an intuitive search interface and the ability to perform interactive analyses and comparative studies of diverse datasets. PANC-DB 2.0 offers new and improved capabilities enabling the diabetes research community to explore HPAP data more effectively while also providing a model for open-access data sharing.

Based on the success of HPAP's original focus on human type 1 diabetes, NIDDK announced in 2018 an expansion of HPAP to include the study of pancreata recovered from tissue donors with type 2 diabetes and related metabolic disorders. Type 2 diabetes develops when the body becomes resistant to the effects of insulin and the pancreas loses the capacity to produce enough insulin to keep blood glucose at a healthy level. The goal of this HPAP expansion is to better understand the molecular mechanisms responsible for pancreatic cell dysfunction in type 2 diabetes by studying pancreatic tissue from people with the disease using a range of experimental approaches and technologies.

FEATURE

These two efforts are now referred to as HPAP-T1D and HPAP-T2D, and they are integrated in the HIRN consortium. Many of the HPAP investigators are involved in both of these programs, which greatly facilitates shared data management and comparison of the pathophysiology of these two types of diabetes. Both the HPAP-T1D and the HPAP-T2D teams collect tissues from diverse donor populations to explore differences in how these diseases manifest in and affect populations with different backgrounds.

Data produced and new biological insights gained through HPAP's efforts will help advance the common goals of diabetes researchers to improve understanding of disease origins and progression and may ultimately lead to new strategies to reverse or prevent disease.

Understanding the Pancreas, Inside and Out: Efforts in Pancreatic Disease

This Feature also appears in the “Digestive Diseases and Nutrition” chapter.

The pancreas is a key player in many diseases, including diabetes and digestive diseases such as pancreatitis. Understanding the various roles of the pancreas in human health and disease—and how pancreatic diseases interact with each other—is therefore an important NIDDK research goal. In addition to supporting a robust investigator-initiated research portfolio on pancreatic diseases, NIDDK also continually seeks to identify and encourage study in areas of new opportunity. From establishing research consortia to encouraging dialogue between scientists with complementary expertise, NIDDK uses a multi-pronged approach to facilitate and pursue the most compelling research, with the long-term goal of reducing the burden of disease and improving public health.

The pancreas is an elongated gland behind the stomach, close to the first part of the small intestine, and it has two main functions, called the “endocrine” and “exocrine” functions. The pancreatic endocrine functions are carried out by structures called islets, which make the hormones insulin and glucagon that help regulate the body’s blood glucose (sugar) levels. Meanwhile, the pancreatic exocrine cells make digestive enzymes that break down food in the intestine. When either of these functions is compromised, serious disease can result. In type 1 diabetes, for instance, the body loses the ability to make insulin due to a misguided autoimmune attack on the pancreatic islets, leading to a lifelong need to take insulin. Also, any disruptions of the carefully orchestrated steps needed to safely produce and secrete digestive enzymes can cause inflammation of the pancreas (pancreatitis). Pancreatitis has many underlying causes, and this disease can be either

acute (short term) or chronic (long lasting). Both forms of pancreatitis can lead to complications, including damage to the pancreas and other organs.



PROMOTING COLLABORATION TO UNDERSTAND THE PANCREAS AS A WHOLE

Traditionally, diseases related to endocrine and exocrine pancreatic functions—such as diabetes and pancreatitis, respectively—have been treated by different medical specialists and studied by different researchers. Increasingly, however, scientists are finding that intricate and crucial crosstalk occurs between the pancreas’s endocrine and exocrine functions as the body co-regulates digestion and metabolism. This crosstalk can also be seen in how disruptions in one function can adversely affect the other, such as when diabetes arises after chronic or acute pancreatitis. However, the mechanisms underlying these relationships and how they affect both health and disease are not fully understood.

To encourage discussion and investigation of the connections between the endocrine and exocrine pancreatic functions, NIDDK hosted a workshop on this topic in June 2022. This workshop, titled “Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases,” brought together researchers from the endocrine and exocrine

FEATURE

pancreas research communities to share new findings and expertise. Scientific presentations highlighted cutting-edge research on pancreas anatomy and physiology, as well as the latest perspectives on the links between endocrine and exocrine pancreatic disease. Researchers also discussed available tools for holistic analysis of the pancreas and identified knowledge gaps and key steps needed to support further study of its interdependent functions. The workshop's chairs closed the session with a plan to summarize and submit the workshop's proceedings for publication.

INVESTIGATING LINKS BETWEEN TYPE 1 DIABETES AND PANCREATITIS

Another NIDDK effort to shed light on the links between different pancreatic diseases is the Type 1 Diabetes in Acute Pancreatitis Consortium or T1DAPC. Formed in 2020, the Consortium's purpose is to study type 1 diabetes and other forms of diabetes that occur during or after one or more episodes of acute pancreatitis. The T1DAPC is composed of 10 clinical centers and one data coordinating center, which will support the T1DAPC's main clinical effort: the Diabetes RElated to Acute pancreatitis and its Mechanisms (DREAM) study.

DREAM's main goal is to understand the connections between pancreatitis and diabetes. High blood glucose during acute pancreatitis can sometimes last only a few weeks before getting better, or it can persist and lead to a diabetes diagnosis. Diabetes can also appear a year or more after the acute pancreatitis has resolved. Little is known, however, about how often or why diabetes occurs in these situations. The DREAM study is designed to answer some of these questions, helping researchers better understand what types of diabetes develop after acute pancreatitis and who is at risk. The DREAM study began recruiting participants in fall 2021 and is expected to continue recruiting through summer 2024.



FACILITATING NEW CLINICAL TRIALS IN PANCREATITIS

There are currently no U.S. Food and Drug Administration (FDA)-approved drugs to treat recurrent acute and chronic pancreatitis. Thus, there is an urgent need to develop effective therapies for these diseases, as well as a growing interest in best practices for pancreatitis clinical trials. To help address these needs, in July 2022, NIDDK—with additional support from the National Pancreas Foundation and participation of the FDA—held a 1-day workshop on clinical trials in recurrent acute and chronic pancreatitis.

This workshop covered a range of topics centered on the opportunities and challenges of designing and conducting patient-focused pancreatitis clinical trials. Presentations by researchers, as well as NIDDK and FDA staff, discussed considerations for designing successful trials, from identifying appropriate participant populations to defining suitable outcome measurements. Also covered were topics such as integrating patient perspectives, resolving ethical considerations, and forming successful public-private partnerships. Participants were also informed about currently available opportunities for investigators, including early-stage investigators. The final panel discussion focused on identifying knowledge gaps and ways to move the field forward. NIDDK developed a summary of the workshop for publication, and ideas gained from the workshop will help inform future NIDDK research directions.

FEATURE

MOVING PANCREATIC DISEASE RESEARCH FORWARD

As researchers study the pancreas's various roles in disease, their findings continue to highlight previously unappreciated connections between digestive and metabolic health. As described above, NIDDK is taking a holistic approach to advancing the study of pancreatic diseases, seeking to improve public health by promoting collaborative research, supporting important clinical trials, and encouraging the development of new treatments for pancreatic diseases.

Advancing Research on Artificial Pancreas Devices for Type 1 Diabetes Treatment

In type 1 diabetes, the insulin-producing β (beta) cells of the pancreas are destroyed by a misguided immune system attack. People with the disease must measure blood sugar (glucose) levels throughout the day and night and administer insulin to survive. 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 can complicate keeping blood sugar within the range recommended to reduce the risk of long-term complications such as blindness and heart, kidney, and nerve disease.

A major goal of NIDDK-supported research has been to develop technologies, such as artificial pancreas devices (also called closed-loop systems or bionic pancreas), that help people manage their type 1 diabetes and keep their blood sugar levels in a healthy range while lowering the risk of hypoglycemia. Recent progress was reported from an NIDDK-supported clinical trial testing the iLet[®] Bionic Pancreas, a closed-loop system that requires minimal input from the user. Such research advances have relied on the contributions of dedicated volunteers with type 1 diabetes participating in clinical trials testing new and emerging technologies for managing blood sugar levels. (See inset for the story of a participant in the iLet[®] Bionic Pancreas clinical trial.)

RESEARCH TO DEVELOP CLOSED-LOOP TECHNOLOGIES

Historically, people with type 1 diabetes have administered insulin through multiple daily injections or through an insulin pump, and most people with the disease continue to use those management strategies today. In more recent years, scientists have made significant progress on developing closed-loop technologies that aim to automate type 1 diabetes management. These systems consist of a continuous glucose monitor (CGM) that measures blood sugar levels, an insulin pump, and a computer algorithm on the device itself or through a smartphone app that calculates the amount of insulin needed based on the CGM's data and instructs the pump to deliver it. These features of closed-loop technology enable people with type 1 diabetes to achieve recommended blood sugar levels without the enormous burden associated with older methods of type 1 diabetes management—thus improving their health and quality of life.

In 2016, the U.S. Food and Drug Administration (FDA) approved Medtronic's MiniMed[™] 670G, making it the first commercially available closed-loop system in the United States. In 2019, the FDA approved a second closed-loop device, the Tandem Control-IQ[™] system. More recently in 2022, the FDA approved the Omnipod[®] 5 Automated Insulin Delivery System. NIDDK-supported research contributed to the early development or testing of these devices.

PERSONAL PERSPECTIVE

Many other closed-loop systems are now under development and being tested in clinical trials, as it is important to give people with type 1 diabetes—who have diverse needs and range in age from very young children to older adults—a variety of available devices so they can choose one that best fits their needs.

DEVELOPING AND TESTING A BIONIC PANCREAS DEVICE

The iLet® Bionic Pancreas (abbreviated here as Bionic Pancreas) was first developed by researchers at Boston University and Massachusetts General Hospital with support from NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program), which NIDDK administers.

One feature of the Bionic Pancreas is that it requires minimal input from the user. For example, to initiate the device, users input only their body weight. Another example is that the Bionic Pancreas does not require counting carbohydrates, which affect blood sugar levels more than other foods do. Instead, it only requires that people input the meal type (breakfast, lunch, or dinner) and whether the carbohydrates at that meal are “usual for me, more, or less.” The device’s computer algorithms, which were designed to adapt to users’ needs, then calculate the insulin dosing.

A randomized controlled clinical trial conducted at 16 sites across the United States and supported by the Special Diabetes Program tested a Bionic Pancreas device that delivers insulin. (Another version of the Bionic Pancreas, not tested in this trial, delivers both insulin and its counteracting hormone, glucagon.) An important aspect of the trial was that it specifically included participants from groups who can be underrepresented in clinical research, including individuals from racial and ethnic minority populations, people with low income and education levels, and people with high hemoglobin A1c (HbA1c)

levels (a measure of average blood sugar levels) that put them at increased risk for developing long-term complications.

The researchers assigned over 300 participants, aged 6 to 79 years, to an intervention group that used the Bionic Pancreas or to a control group in which participants practiced their usual care by using their own diabetes management strategies (e.g., insulin injections, insulin pump, or a commercially available closed-loop system). After the 13-week trial, the researchers reported that both children and adults using the Bionic Pancreas showed improvements in HbA1c levels compared to participants in the control group. This is an encouraging result, as improved HbA1c levels over time have been shown to correspond with fewer diabetes complications. Trial results also showed that Bionic Pancreas users spent more time with their blood sugar levels in the recommended target range. Importantly, these benefits were achieved without increasing the occurrence of hypoglycemia. These exciting results suggest that the Bionic Pancreas outperformed the control group’s usual care.

HOPE THROUGH RESEARCH

NIDDK continues to support research to improve and test closed-loop 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 racial and ethnic minority populations, children, adolescents and young adults, older adults, pregnant women, and people who have frequent, severe episodes of hypoglycemia. Research is also ongoing toward improving technology adoption in individuals from underrepresented backgrounds with type 1 diabetes. Continued research could give people with type 1 diabetes a range of available devices to address their unique management needs.

Lauryn's Story



Lauryn participated in an NIDDK-supported clinical trial testing an iLet® Bionic Pancreas

When Lauryn was in eighth grade, she listened to a lesson on diabetes given at her medical magnet middle school in her hometown of Jacksonville, Florida. This information helped her when, a couple of weeks later, she started experiencing the symptoms of type 1 diabetes that she had just learned about. “I had frequent urination, I was thirsty, and I was falling asleep in class,” Lauryn recalls. “Normally, I never fall asleep in class.” Because of her lesson, she was confident that she had type 1 diabetes, even before her diagnosis was confirmed.

Adjusting to life with type 1 diabetes as an adolescent “was definitely rough,” Lauryn says. She remembers how tough it was for her to always think about when

to take insulin and how much to take depending on what she was eating. Another challenge for Lauryn was that when her blood sugar levels fell, she felt terrible. Because she feared having low blood sugar, “I’d try to keep my [blood] sugar on the higher side and not take as much insulin as I needed to,” she admits. As a result, her hemoglobin A1c (HbA1c) levels were about 9 percent, while the recommended level is below 7 percent.

Lauryn was not alone—most teenagers and young adults with type 1 diabetes have higher than recommended HbA1c levels. This worrisome trend underscores the importance of research to identify strategies to help young people manage their disease and improve their short- and long-term health.

“It was probably one of the best things that has happened.... It introduced me to an easier life,” says Lauryn, talking about how participating in a Bionic Pancreas clinical trial showed her a less burdensome approach to managing her type 1 diabetes.

Lauryn’s opportunity to contribute to that research came in the summer of 2021 when she was 20 years old. She got a phone call from one of her health care providers at Nemours Children’s Health, Jacksonville. He encouraged her to join a new clinical trial being done at Nemours—one of 16 participating U.S. sites—that was testing an iLet® Bionic Pancreas device (Bionic Pancreas). Until then, Lauryn had only used multiple daily insulin injections for managing her type 1 diabetes, but she was interested in trying a system with an insulin pump. “I thought it would make life easier, so I didn’t have to do injections all the time,” she says. Lauryn signed up for the 13-week trial and was happy she was randomly selected for an arm of the trial that would test the Bionic Pancreas.

PERSONAL PERSPECTIVE

Lauryn feels that joining the trial was the right choice. “It was probably one of the best things that has happened” since her type 1 diabetes diagnosis, she says. “It introduced me to an easier life.” Lauryn explained that one big advantage of being on the new device was that it greatly reduced the number of needed injections. With the Bionic Pancreas, she only had to change the needle at her insulin infusion site once every 3 days—a dramatic decrease from the six insulin injections each day she was administering before the trial.

Another major benefit was that her HbA1c levels drastically improved by the end of the trial—decreasing from about 9 to 7 percent. When asked if the HbA1c improvement made her feel better, she responds, “I felt like it did. I wasn’t as tired, and I was more active.” Another plus was that she used less insulin while on the Bionic Pancreas. Although the insulin and other supplies she used as part of the trial were paid for by the research study, paying for insulin and other diabetes management supplies is a challenge for her and her mom. Not only was she able to further type 1 diabetes research through her participation in the trial, but she also says she benefitted from the helpful break from the costs of managing her diabetes.

Lauryn notes that there were some aspects of the device that did not work well for her. For example, she disliked the wire that delivered insulin because it got caught on things. She also did not feel that the feature that eliminated carbohydrate counting worked well for her all the time, though she did like it in some instances. Such research participant feedback is important because it helps scientists improve devices to enhance patient satisfaction.

“I wasn’t as tired, and I was more active,” says Lauryn, speaking about how she felt after her hemoglobin A1c levels dramatically improved during her participation in a clinical trial.

Overall, Lauryn appreciated that the Bionic Pancreas helped improve her health while reducing the burden of managing her type 1 diabetes. Importantly, it also introduced her to a new way of managing her diabetes other than injecting insulin. As a result, at the end of the trial when she had to return the Bionic Pancreas to the researchers, she decided to start using a commercially available insulin pump. At the time of this interview, Lauryn’s health insurance had stopped covering her commercial pump, so she was back to using insulin injections. “I’m trying to stay as healthy as I can until I get back on the pump,” she says.

An unexpected benefit of the trial was the bond that Lauryn developed with the research team. “I really enjoyed working with them,” she says. Lauryn particularly bonded with a Senior Clinical Research Coordinator at Nemours whom she worked with very closely during the trial, and the Coordinator has become a mentor. “She’s an endocrinologist, and I want to be a reproductive endocrinologist, so there’s a lot of things I could learn from her. That was a great aspect of doing the trial,” Lauryn says.

Now a 21-year-old senior in college, Lauryn is majoring in chemistry/pre-med with a minor in physics. She plans to attend medical school, pursue that goal of becoming a reproductive endocrinologist, and work as a physician on a military base. When she’s not busy studying, she enjoys going to theme parks or watching videos of them—she loves their atmosphere and the feeling they give of being away from the real world.

“I would encourage everyone to try a clinical trial at least once,” Lauryn says. She explains that research is important to her because “we need to know if things will work or if things won’t work.” In particular, she thinks it was important for her to participate in the Bionic Pancreas clinical trial as a person of color. “For me to have done the trial, I feel like it will show other people who look like me: ‘I can do it too. I can be healthy and have diabetes,’” she says. “It’s about helping my culture, helping my community, and showing them there are other people out there

PERSONAL PERSPECTIVE

just like me with diabetes living a healthy life, living a normal life.... I'm definitely glad that I did the trial."

Lauryn thinks it was important for her to participate in the Bionic Pancreas clinical trial as a person of color. "For me to have done the trial, I feel like it will show other people who look like me: 'I can do it too. I can be healthy and have diabetes.'"

In the true spirit of a person with a calling to help others, Lauryn has also spent time online sharing

her experiences of living with type 1 diabetes and educating others about the disease. She says that when she was first diagnosed, she felt alone. "I didn't see a lot of people like me with diabetes, but then I realized there *are* a lot of people out there like me with diabetes." She shares her experiences with others to help them realize that they aren't alone.

Through her participation in the Bionic Pancreas clinical trial and her sharing of her personal experiences of living with type 1 diabetes, Lauryn is making a positive impact on the lives of other people with the disease. And at 21, she is just getting started.

Contributing to Research on Gestational Diabetes Mellitus

Pregnancy can be a joyous time. But it also places significant stress on the body. During pregnancy, virtually every organ system works harder to support the developing fetus, and the resulting physiological changes can induce adverse metabolic conditions in the pregnant person. For example, hormones produced by the placenta can prevent the body from using insulin effectively, which can cause sugar (glucose) to build up in the blood instead of being absorbed by cells. In some cases, blood sugar levels can rise during pregnancy to an extent that results in the diagnosis of a condition called gestational diabetes mellitus (GDM). GDM is a form of diabetes that is distinct from type 1 or type 2 diabetes, as it develops during pregnancy and usually resolves after pregnancy. However, GDM is known to confer short- and long-term health risks to pregnant people and their children, including babies with high birth weight, delivery complications, and a greater risk of developing type 2 diabetes and obesity. Traditional approaches to diagnosing GDM include a screening test 24 to 28 weeks into pregnancy, but research suggests that this may be too late to counteract some of the lasting adverse impacts of GDM. The NIDDK-supported study Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) aims to address critical questions about GDM screening and diagnosis, toward improving the health of mothers and their children. (See inset for the story of a GO MOMs participant.)

SETTING THE STAGE—THE HAPO STUDY

In 2008, the landmark NIH-funded Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study released findings of health issues associated with blood sugar levels during pregnancy that were above

normal (hyperglycemia) but not high enough to meet the traditional definition of GDM. In this prospective, observational study, the HAPO researchers studied a racially and ethnically diverse cohort of more than 23,000 pregnant women and their babies and found that elevated maternal blood sugar levels below those that would qualify as GDM were associated with multiple adverse outcomes for mother and child. These complications included high birth weight for the infants and the need for caesarean delivery. Because the HAPO participants' blood sugar levels, though elevated, did not meet the traditional diagnostic criteria for GDM, they were not treated for the disease.

In 2010, HAPO results led an international panel of experts to recommend new diagnostic criteria for GDM. However, these criteria were not widely used in the United States, largely due to findings from an NIH-convened expert panel that pointed out knowledge gaps regarding best treatment strategies using these alternate criteria and the need for more research. Additionally, the uncertainty regarding long-term health impacts of elevated blood sugar levels below the traditional threshold for GDM remained.

PAVING THE WAY FOR CONTINUED RESEARCH ON GDM—THE HAPO FOLLOW-UP STUDY

Realizing the critical insights that could be gleaned from further study of HAPO participants, researchers began the HAPO Follow-up Study (HAPO FUS), funded by NIDDK with additional support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. HAPO FUS enrolled more than 4,800 mother-child pairs from the original HAPO study and collected additional data 10 to 14

PERSONAL PERSPECTIVE

years post-delivery to better understand the long-lasting effects of elevated maternal blood sugar levels. Mothers were evaluated for type 2 diabetes and prediabetes, and children were assessed for overweight and obesity using body mass index (a ratio of weight to height), body fat percentage, and waist circumference. Their blood sugar levels were also evaluated. In 2019, HAPO FUS researchers reported that the adverse outcomes of even modestly elevated blood sugar levels during pregnancy extend more than a decade. Among participating mothers whose pregnancies during HAPO met, in retrospect, the alternate criteria for GDM (although not traditional criteria), more than half of these women developed type 2 diabetes or prediabetes. Among participating children, the researchers found that the likelihood of developing obesity was significantly greater among those born to mothers whose pregnancies were affected by GDM based on the alternate criteria. Moreover, those children were also more likely to develop insulin resistance, a risk factor for type 2 diabetes.

THE PROMISE OF FUTURE RESEARCH—GO MOMS

The HAPO FUS findings are important because they demonstrate that elevated maternal blood sugar levels below those traditionally defined as GDM are associated with long-term adverse health effects for mothers and children. However, knowledge gaps and research opportunities remain regarding how blood sugar metabolism changes across the entire course of pregnancy and if screening for and treating GDM earlier in pregnancy could reduce these health risks.

To address these important questions and build upon previous research, in 2021, NIDDK established the GO

MOMs study to improve GDM screening and diagnosis by better understanding blood sugar levels throughout pregnancy. The study, which is taking place at 9 sites throughout the United States and is ongoing, aims to enroll more than 2,000 women without diabetes in their first trimester of pregnancy and is using continuous glucose monitoring (CGM) technology to map blood sugar levels throughout pregnancy. CGM devices measure blood sugar levels every 5 minutes. Participants are asked to wear the device for 10 days at four different times during their pregnancy to provide the researchers with a picture of how blood sugar levels are changing over time. The study also uses oral glucose tolerance tests—a measure of how well a person's body is processing sugar—as a tool to diagnose GDM. By understanding more about blood sugar levels during pregnancy, the hope is that researchers can identify potential early indicators of GDM and pinpoint the best times to screen for and treat it. Because GDM disproportionately affects those from racial and ethnic minority populations, another important goal of the study is to recruit diverse participants so that results are applicable across affected groups.

The importance of GO MOMs is underscored by recent data showing that rates of GDM are rising in the United States, climbing 30 percent between 2016 and 2020.¹ Additionally, as other NIDDK-supported studies have shown the devastating impacts of type 2 diabetes in youth (see Feature in this chapter), GO MOMs and other future research could improve the health of future generations to come.

¹ Gregory ECW, et al. *Trends and characteristics in gestational diabetes: United States, 2016–2020*. Centers for Disease Control and Prevention. *National Vital Statistics Reports*; vol. 71 no. 3, 2022.

Angelica's Story



Angelica, pictured here with her son, participated in an NIDDK-supported clinical study to better understand how blood sugar levels change during pregnancy

Thirty-two-year-old Angelica is a teacher in the Chicago Public School system, and she recently graduated with a master's degree in English as a Second Language, to complement her first master's degree in Urban Education. "I'm the type of person who has to stay busy all the time!" she says. For the first 8 years of her career, Angelica taught seventh graders before transitioning out of the classroom and into a leadership role managing her school's bilingual program. After spending this first part of her career helping children, she decided the time was right to have a little one of her own, and she became pregnant with her first child in the summer of 2021.

At Angelica's first pre-natal doctor's appointment, medical staff approached her about enrolling in the Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) study at Northwestern University. Diabetes runs in her family, and Angelica started thinking about the impact that gestational diabetes (GDM), if she were to develop it, could have on her and her baby's health. She wanted to do whatever she could to navigate her pregnancy as healthfully as possible. "Pregnancy can be scary. But the more information we have, the more we can advocate for the little humans inside of us. This is a service to my little one," Angelica says. She also acknowledged a heartbreaking reason she wanted to participate in this study—her partner of 8 years recently passed away from stage 4 cancer. He was a staunch proponent of research and had recognized the importance of people participating in clinical studies to advance medicine. In honor of him, she made the commitment to join GO MOMs. Angelica had advocated for her partner's health throughout his treatment, and now she wanted to do the same for their baby. And so, her journey through pregnancy and the GO MOMs study began.

"Studies like GO MOMs empower us as pregnant women to have access to information, resources, and support that allow us to advocate for our little ones throughout the entire pregnancy," says Angelica.

As a standard part of the study protocol, Angelica traveled to the study site at Northwestern several times throughout her pregnancy to be fitted with a continuous glucose monitor. A continuous glucose monitor measures blood sugar levels every 5 minutes. The device used in this study is about the size of a large coin, and it adheres to the body for 10 days. After 10 days, she simply returned it to the study site by mail for analysis or she dropped it off at one of her

PERSONAL PERSPECTIVE

scheduled appointments. Angelica said these study site visits were always very quick and hassle-free. While the monitor did fall off twice, requiring her to return to have another one put on, she says she didn't mind because she knew how important this information gathering was to the success of the study. Also, as part of the protocol, she had two separate oral glucose tolerance tests—one test early on and one later in the pregnancy. This test required her to drink a sugary beverage and measured how well her body processed the ingested sugar. While Angelica didn't care for the taste of the drink much at all, during the final test she felt her baby move. "It was so rewarding knowing I was doing this to protect the health of my baby," she shared.

"They were great at making me feel important. I felt they genuinely cared about me and my little human," says Angelica, referring to the GO MOMs study staff.

Throughout her participation, only the study staff had access to the blood sugar data, and Angelica did not see the test results. Test results were only released to a participant if the results showed that she developed GDM. Thankfully, Angelica had a smooth pregnancy and never developed GDM. In May 2022, she delivered a healthy baby boy. Study staff were at the hospital to record her newborn baby's physical measurements including birth weight, length, and skinfolds (a fast, non-invasive method to explore infant nutritional status).

In describing her experience with study staff, Angelica says "they were great at making me feel important.

I felt they genuinely cared about me and my little human ... there was a strong relationship built over a short amount of time." She added that many people don't enjoy going to the doctor, "but I loved going to all of my GO MOMs appointments. When my participation ended at delivery, I thought 'I'm really going to miss you!'"

Reflecting upon her experience in this study, Angelica says she realizes how fortunate she was to have had access to this type of research that many others do not. "Studies like GO MOMs empower us as pregnant women to have access to information, resources, and support that allow us to advocate for our little ones throughout the entire pregnancy," she remarked. Results from GO MOMs are expected to shed critical new light on how blood sugar levels change throughout pregnancy, toward improving GDM diagnosis and treatment.

"It was so rewarding knowing I was doing this to protect the health of my baby," says Angelica, speaking about her participation in the GO MOMs study.

Angelica is back to work now and plans to take a couple of years off from furthering her education to enjoy being a mom. But her ambition knows no bounds. In the future, she plans to pursue doctoral studies and achieve her dream of becoming a school principal. As both a dedicated educator and a research participant in the GO MOMs study, Angelica has already had a tremendous impact on future generations.



NIH OBESITY RESEARCH
TASK FORCE SYMPOSIUM:
**THE GLOBAL IMPACT
OF OBESITY**

September 9, 2022

WEBINAR

The trans-NIH Obesity Research Task Force was established to accelerate progress in obesity research across NIH, given the importance of the obesity epidemic as a major public health problem and its relevance to the missions of most of the NIH Institutes, Centers, and Offices. The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, Dr. Griffin P. Rodgers; the Director of the National Heart, Lung, and Blood Institute, Dr. Gary H. Gibbons; and the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Dr. Diana W. Bianchi. The Task Force holds two seminars each year, covering a broad range of topics. On September 9, 2022, the Task Force convened a symposium on the global impact of obesity where six distinguished scientists highlighted their research from around the world. A summary of this seminar is featured in this chapter.

Obesity

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

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment (social determinants of health) such as a lack of healthy, affordable food and places to exercise in many communities; sedentary jobs; and other conditions that influence what, when, and how much people eat. Diet, activity, and aspects of our environment also may modify 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.

Individuals who have obesity may develop devastating health problems, face reduced life expectancy, and experience stigma and discrimination.

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 for children and adults in health care, home, community, and other settings using a variety of approaches and technologies, surgical interventions, and combinations of strategies. In parallel, NIDDK-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches.

Nearly 42 percent of U.S. adults and nearly 20 percent of children and adolescents have obesity.^{1,2}

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

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

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

² For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).

PEDIATRIC OBESITY PREVENTION RESEARCH

Parenting Program for Obesity Prevention in Firstborn Children Benefits Siblings:

In a recent study, researchers found that a responsive parenting intervention shown to help new parents prevent childhood obesity in their firstborn children also had beneficial spillover effects on the growth of their second-born children years later. The study, called SIBSIGHT, followed an earlier clinical trial—Intervention Nurses Start Infants Growing on Healthy Trajectories (INSIGHT). For the INSIGHT intervention, nurses delivered information in the home to first-time parents, including education on infant feeding, sleep, and play, and responding to the child's needs. The intervention resulted in healthier body weights of the young children, compared to those in a control group whose parents received information about safety.

For the SIBSIGHT study, the researchers recruited INSIGHT participants who had a second child, including those who had received the responsive parenting intervention and those from the control group. The SIBSIGHT study was only observational; that is, the participants did not receive any further training on responsive parenting when their second children were born, even though it had been an average of 2.5 years since the birth of their first children. Monitoring the growth of 117 second-born infants based on body mass index (BMI), a measure of weight relative to height, the researchers found that at age 1 year, second-born children whose parents received the intervention with their first child had a significantly lower BMI, by 0.36 units, compared to those whose families were in the control group. This weight-related benefit of the intervention for second children was similar to that observed in the firstborn children at the same age. Because the study participants were mostly White, middle-income families, further research would be needed to determine the benefits to children from other backgrounds.

A responsive parenting intervention shown to help new parents prevent childhood obesity in their firstborn children also had beneficial effects on the growth of their second-born children years later.

This study demonstrates that an intervention of responsive parenting for obesity prevention in firstborn children has a continuing benefit for second-born children. The findings provide hope that a parenting strategy,

taught once when first children are infants, could help with setting those children and their future siblings on a healthy growth trajectory starting early in life.

Savage JS, Hochgraf AK, Loken E,...Paul IM. INSIGHT responsive parenting educational intervention for firstborns is associated with growth of second-born siblings. Obesity 30: 183-190, 2022.

STUDYING OUTCOMES OF BARIATRIC SURGERY FOR OBESITY TREATMENT

Weight Loss from Bariatric Surgery Compared to Nonsurgical Care for People with Severe Obesity:

Researchers found that bariatric surgical procedures, including gastric bypass surgery and sleeve gastrectomy, led to significantly more weight loss than nonsurgical care for people with severe obesity—information that could help with treatment decisions. Although past research demonstrated that bariatric surgery leads to substantial weight loss, only a few long-term studies compared weight loss from nonsurgical care to that from surgery, and there has been less information on sleeve gastrectomy, though it is currently the most common bariatric procedure.

To better understand the effects of surgery, researchers analyzed electronic medical records and other data from women and men of diverse race and ethnicity with severe obesity in a large health care system, including 13,900 people who had sleeve gastrectomy (SG), 17,258 who had Roux-en-Y gastric bypass (RYGB), and 87,965 people who did not have surgery. Those in the nonsurgical group received usual medical care, which in general did not include specific obesity treatment. On average, 1 year after surgery, people in the RYGB group had lost 28 percent of their weight, and those who had SG lost 23 percent of their weight. At a similar time point, those in the nonsurgical group had lost 0.2 percent of their weight. Longer-term follow-up data were available for a majority of the people. At 5 years, the people who had surgery regained some weight, but those who had RYGB still maintained an average 22 percent weight loss, and those in the SG group still maintained 16 percent weight loss, or approximately 60 pounds and 43 pounds lost, respectively. Some regained enough weight to be within 5 percent of their initial weight, however, including 1 of every 10 people who had SG and 1 in 27 who had RYGB. Those who didn't have surgery had lost approximately 2 percent of their weight, or about 6 pounds. At 10 years, those who had RYGB were still on average 20 percent below their

pre-surgical weight, and those in the nonsurgical group had lost approximately 5 percent of their weight. (There were not enough data to analyze weight loss 10 years after SG.)

Researchers found that, compared to nonsurgical care for people with severe obesity, bariatric surgical procedures—including gastric bypass surgery and sleeve gastrectomy—led to substantially greater weight loss that was maintained for years, based on 10 years of follow-up data for gastric bypass surgery and 5 years of data for sleeve gastrectomy.

This study provides important information that people with severe obesity and their health care providers can use when considering bariatric surgery. The findings also suggest a need for additional care for people who experience weight regain after surgery. Future research could explore other long-term effects of bariatric surgery on health.

Arterburn DE, Johnson E, Coleman KJ,...Haneuse S. Weight outcomes of sleeve gastrectomy and gastric bypass compared to nonsurgical treatment. *Ann Surg* 274: e1269-e1276, 2021.

IDENTIFYING A LINK BETWEEN EXERCISE AND FOOD CONSUMPTION

An Exercise-induced Molecule Reduces Obesity in Mice:

Scientists discovered that a molecule produced during exercise by various mammals, including people, can reduce food consumption and obesity in mice.

Exercise is a powerful tool that can help protect against obesity and obesity-associated diseases such as type 2 diabetes and cardiometabolic disease. Physical activity results in many molecular changes in the body, but the extent to which each molecular alteration contributes to health benefits, including obesity prevention, is not well understood. A team of researchers analyzed blood samples from male mice before and after an intense bout of exercise running on a treadmill and looked for molecules that increased following exercise. The researchers found the largest increase was in a compound called *N*-lactoyl-phenylalanine, or Lac-Phe, which is a molecule of unknown function. Interestingly, the team found similar increases in Lac-Phe in blood samples following exercise in thoroughbred racehorses

and humans, suggesting exercise-induced production of Lac-Phe is not unique to mice. When the researchers gave an injection of Lac-Phe to obese mice on a high-fat diet, the mice reduced their food intake by half over 12 hours even though circulating levels of the molecule fell to baseline within 1 hour, suggesting long-lasting benefits. Obese mice treated with Lac-Phe for 10 days lost weight and had lower blood glucose (sugar) levels than obese mice that did not undergo treatment. In contrast, Lac-Phe treatment had no effect on food consumption in lean mice on a normal diet. Previous research has shown that Lac-Phe is synthesized by the enzyme CNDP2, found in many cell types including immune cells and cells that line the surfaces of organs. In the current study, the researchers confirmed in cultured cells that Lac-Phe production requires this enzyme, and that Lac-Phe is secreted from the cells. CNDP2 requires the molecule lactate to generate Lac-Phe. Lactate is produced in the body during strenuous exercise, causing the burning sensation in exhausted muscles. In the cultured cells, increasing the lactate supply increased Lac-Phe production. Lastly, the research team examined mice that were genetically engineered to lack CNDP2 and were thus deficient in Lac-Phe; these mice had increased food intake and weight gain while on a daily exercise regimen, compared to mice with CNDP2.

Scientists discovered that a molecule produced during exercise by various mammals, including people, can reduce food consumption and obesity in mice.

Taken together, these results suggest that regular exercise increases production of Lac-Phe, which helps to regulate food intake and body weight. More research is needed to unmask how Lac-Phe may be acting in the brain to suppress feeding and obesity, which may provide new therapeutic opportunities to capture the benefits of physical activity for human health.

Li VL, Yang H, Contrepois K,...Long JZ. An exercise-inducible metabolite that suppresses feeding and obesity. *Nature* 606: 785-790, 2022.

INSIGHTS INTO FAT TISSUE-BRAIN COMMUNICATION

A Direct Line of Communication Identified Between Fat Tissue and the Brain: Researchers have discovered sensory nerve cells that send messages from fat tissue to the brain in mice. This finding challenges the conventional notion that circulating hormones in the blood are the sole messengers sending information related to stress and metabolism between fat tissue and brain cells.

In mammals, fat tissue stores energy (calories) and releases this energy when the body needs it. Fat tissue also regulates hormones and signaling molecules that update the brain on fullness, hunger, and metabolism. Disruption of these critical functions can contribute to several diseases including diabetes, obesity, and fatty liver disease. Researchers have known that nerve cells contact fat tissue. However, they suspected that they were part of a network of nerves responsible for the body's "fight-or-flight" response that activates fat-burning pathways during stress and physical activity—not sensory nerve cells that carry data directly to the brain. Until now, a lack of suitable laboratory tools and techniques prevented scientists from identifying the function of nerve cells contacting fat tissue. The team of researchers leading this study developed new techniques to overcome these obstacles.

First, they used an imaging technique they had recently developed that turned fat tissue transparent so they could visualize the nerve cells that extend into the

tissue. Surprisingly, in experiments in male mice, they discovered that nearly half of the nerve cells were not part of the fight-or-flight response network, but rather connected to an area of the brain where sensory cells originate. Next, the team used a genetic tool, developed previously and that they optimized, to analyze the function of the sensory nerve cells by selectively removing these cells within the fat tissue. The experiments demonstrated that destroying sensory input from fat tissue to the brain in mice results in elevated body temperatures and the generation of "beige fat," a type of fat tissue that breaks down other fat molecules to produce heat. These results suggest that the two types of nerve cells extending into fat tissue, cells in the fight-or-flight network and sensory cells, have opposing functions: the former act as a "gas pedal" for burning fat, and the latter act as the "brake". When the brake was removed, a response reminiscent of fight-or-flight was activated (fat-burning, body temperature increase).

These findings fill an important knowledge gap on how the brain regulates different fat tissue functions, highlighting the importance of this newly discovered avenue of brain-body communication. Future research could lead to new therapeutic strategies to treat obesity and other metabolic diseases.

Wang Y, Leung VH, Zhang Y,...Ye L. *The role of somatosensory innervation of adipose tissues.* *Nature* 609: 569-574, 2022.

Symposium Held To Explore the Global Impact of Obesity

The epidemic of obesity in adults and children is not limited to the United States. Obesity prevalence is increasing globally and can co-exist with malnutrition and chronic undernutrition. Given the global impact of obesity, the research community recognizes the need to accelerate development of new and innovative prevention and treatment strategies, close knowledge gaps with the goal of translation into more effective patient care, and explore lessons the United States and international communities can learn from each other toward developing creative and integrated approaches to obesity prevention and treatment. To that end, six leading scientists highlighted their research from around the world at a September 2022 virtual symposium organized as part of the NIH Obesity Research Task Force Seminar Series. The research presented was supported by NIDDK and other NIH Institutes.

Dr. Francesco Branca of the World Health Organization presented on the topic of the dual burden of malnutrition (DBM). DBM, defined as the simultaneous manifestation of both undernutrition (micronutrient deficiencies, underweight, childhood stunted growth) and overweight/obesity, affects most low- and middle-income countries. DBM can occur at the country, household, and individual levels. While progress has been made worldwide toward exclusive breastfeeding of infants as well as reductions in childhood stunted growth, increases in overweight/obesity continue. Dr. Branca outlined opportunities for action to address DBM globally including scaling up health services; redesigning social safety nets and educational programs; and expanding agricultural development to make nutritious foods available, affordable, and appealing.

Dr. Lara Dugas of Loyola University presented her research on sleep timing, gut microbiota, and

cardiometabolic risk. The Modeling the Epidemiologic Transition Study (METS) has six sites worldwide in low-, middle-, and high-income countries, including in Africa, Caribbean countries, and the United States. Through self-reporting methods, METS researchers tracked sleep timing and dietary habits in study participants. The longest sleep durations and highest dietary fiber intake were reported in Ghana, while the shortest sleep durations and lowest dietary fiber intake were reported in the United States. Longer sleep durations are associated with a lower prevalence of obesity and cardiometabolic risk. High-fiber intake is associated with a rich and diverse gut bacterial ecosystem.

Dr. Marcella Nunez-Smith of Yale University presented her research on obesity and cardiometabolic disease in understudied Eastern Caribbean populations with a high burden of chronic disease morbidity and mortality. The objectives of the Eastern Caribbean Health Outcomes Research Network (ECHORN) cohort study are to expand clinical research to include these minority populations, address the need for regional research infrastructure, and increase regional capacity to translate research into policy and practice. ECHORN consists of several initiatives including diabetes, hypertension, and childhood obesity subprojects. All data collected through the ECHORN cohort study are publicly available to the research and policy communities on a data-sharing platform.

Dr. Franco Sassi of the Imperial College Business School presented on The Science and Technology in childhood Obesity Policy (STOP) project in European countries. The STOP project aims to develop a measurement framework for epidemiological surveillance, establish new evidence on childhood obesity determinants and impacts of policies and interventions, and design toolkits for policy

FEATURE

implementation. New STOP analyses have provided evidence in support of fiscal and regulatory policies, social marketing interventions, physical education and physical activity interventions, and food reformulation programs. In ongoing efforts, a primary care-led, family-based approach for addressing obesity in children under the age of 5 is currently being tested in a randomized controlled trial in several countries.

Dr. William Dietz of the Milken Institute of Public Health at George Washington University presented an overview of the global syndemic (concurrent epidemics) of COVID-19, obesity, food and nutrition insecurity, and climate change. Dr. Dietz highlighted the impact of many contributing factors, such as increased greenhouse gas emissions that affect weather and food production, food costs, transportation systems, structural racism and related social determinants of health, physical inactivity, and other factors. The COVID-19 pandemic resulted in increased hospitalization, severity of infection, and death in people with chronic diseases such as obesity, diabetes, and cardiovascular disease and in people of color. The pandemic also led to food and nutrition insecurity secondary to food supply chain failures and job loss. Moreover, COVID-19 lockdowns resulted in dramatic increases in childhood obesity. Dr. Dietz put forth his suggestions to address this syndemic with actions to build and strengthen resilient, sustainable,

plant-based food systems that shift reliance away from ultra-processed foods; address physical activity; and many other actions to help combat obesity, diabetes, and COVID-19 mortality.

Dr. Jonathan Wells of University College London presented his research on the evolution of human adiposity (excess fat tissue) and obesity. His talk explored how body fat tissues are regulated, how they develop over the life course, what biological functions they serve, and how they may have evolved. There is substantial evidence that human adiposity is not merely a buffer against the threat of starvation but is also a resource for meeting the energy (calorie) costs of growth, reproduction, and immune function. However, human metabolism is sensitive to environmental cues. Readily available, inexpensive, and palatable ultra-processed foods, as well as economic forces such as product placement, television advertising, and celebrity endorsements, could be contributing to the current obesity epidemic.

The seminar included a lively discussion among speakers and participants on current challenges and opportunities. Continued research could reveal better strategies to prevent and treat obesity on a global scale, thereby preventing many adverse health outcomes.

Workshop on Housing and Obesity: Gaps, Opportunities, and Future Directions for Advancing Health Equity



November 14–15, 2022



Workshop Held To Explore the Relationship Between Housing Insecurity and Obesity

Many important aspects of our health are shaped by the environment and conditions in which we live. A serious health challenge across the United States is the rise in housing insecurity, including inability to afford rent and utilities, experiencing frequent moves, living in low-quality housing or overcrowded conditions, and residing in under-resourced neighborhoods. Studies have implicated housing insecurity as an important risk factor for obesity (along with its comorbidities like diabetes) due to obstacles such as limited availability of healthy and affordable food, lack of safe green spaces to encourage physical activity, mental stress, and inadequate means of transportation for health care visits. Housing insecurity is also rooted and sustained in historical systemic racism and is a driver of present-day residential segregation, disparities in home ownership, housing inequality, and wealth inequalities. These challenges underscore housing insecurity as a barrier to health equity and a critical social determinant of health.

As part of ongoing efforts to advance health for all people, NIDDK, along with other NIH Institutes and Centers, the Centers for Disease Control and Prevention, and the U.S. Department of Housing and

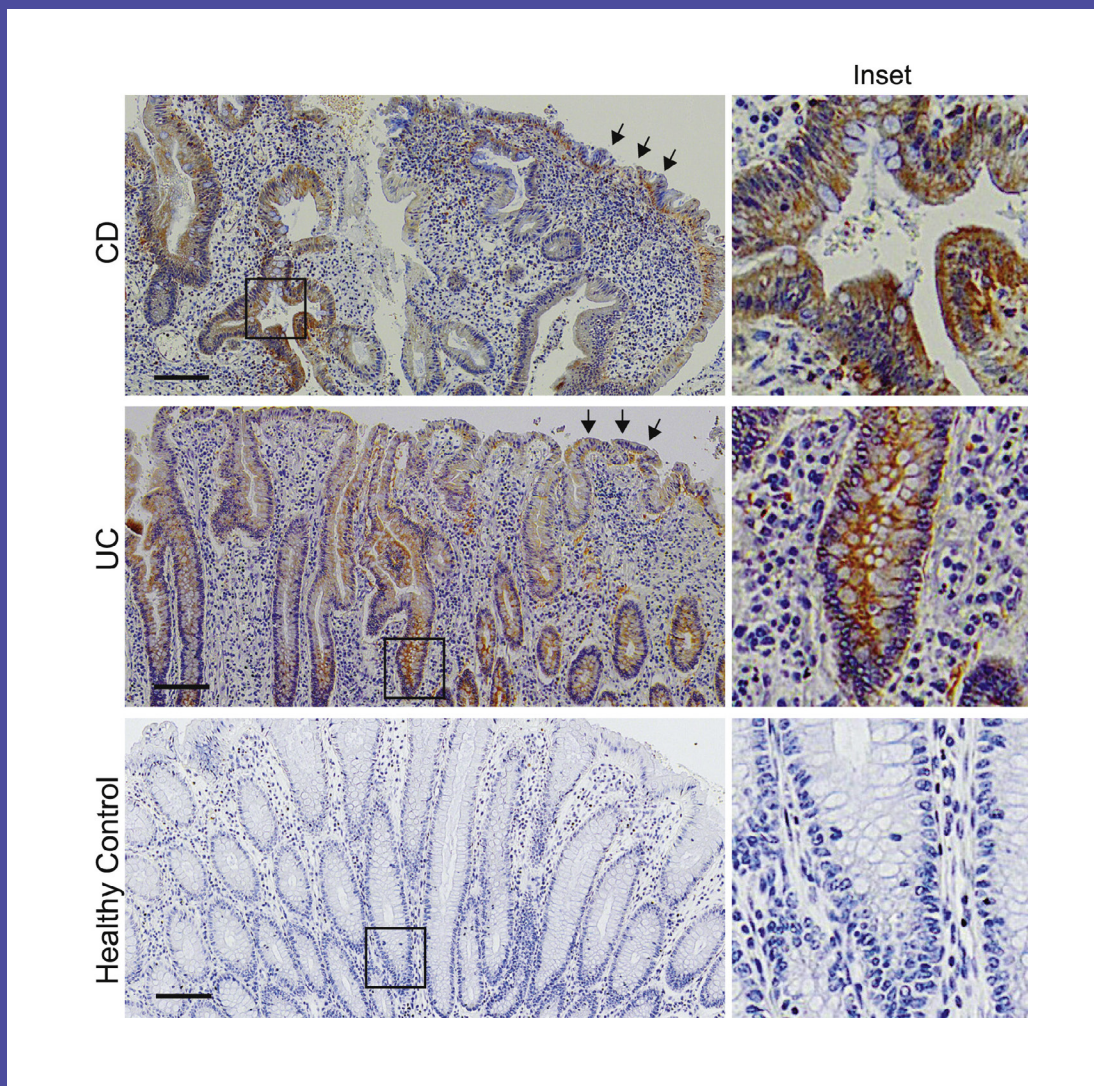
Urban Development, co-sponsored a multi-agency workshop to explore the role of housing insecurity in obesity-related health disparities, review the evidence for housing-related interventions to overcome these disparities, and identify future research directions to advance health equity. The overall goal of the workshop was to accelerate research on the role of housing insecurity—including housing affordability, quality, and stability—on behaviors and pathways that increase risk for obesity-related health disparities across the lifespan. The workshop also aimed to propel research on interventions to address housing insecurity.

The meeting brought together a diverse group of researchers, leaders, and experts from a range of disciplines, including housing and the neighborhood environment, obesity, health disparities, health equity, public health, and other relevant fields. The participants discussed existing research that links housing policies and programs with obesity, methods for housing and obesity research, and interventions that address housing as a social need and a core social determinant of health. The workshop also included discussions to identify critical research questions

FEATURE

and opportunities for creating research partnerships and collaborations across federal, regional, and local housing programs.

This workshop serves as an integral component of NIDDK's endeavors to achieve health equity by advancing understanding of social determinants of health, both as causes of disease and as targets for intervention. A summary of the workshop will be made available to the public.



Intestinal lesions caused by inflammatory bowel disease (IBD) are typically slow to heal, contributing to the chronic nature of the disease. One way to treat IBD would be to help the gut repair itself, but scientists must first understand how the lesions mend and why recovery can be so slow. As highlighted in this chapter, researchers discovered a surprising role for a protein called gasdermin B (GSDMB) in the healing of IBD lesions. The above images are microscopic views of intestinal tissue from people with a form of IBD: either Crohn's disease (CD, top panels) or ulcerative colitis (UC, middle panels). The brown color represents GSDMB, which is present at high levels in the inflamed tissue of people with IBD compared to people without IBD (healthy controls, bottom panels). Higher levels of GSDMB were found in places where lesions are healing (arrows in top and middle panels), suggesting that GSDMB helps repair wounds. The researchers also showed that people with IBD are more likely to have defects in GSDMB—knowledge that could aid development of new therapies to encourage intestinal healing.

Image courtesy of Dr. Theresa Pizarro, Case Western Reserve University. Reprinted from Cell, Volume 185, Issue 2, Rana N, Privitera G, Kondolf HC, Bulek K, Lechuga S, De Salvo C, Corridoni D, Antanaviciute A, Maywald RL, Hurtado AM, Zhao J, Huang EH, Li X, Chan ER, Simmons A, Bamias G, Abbott DW, Heaney JD, Ivanov AI, Pizarro TT, GSDMB is increased in IBD and regulates epithelial restitution/repair independent of pyroptosis, Pages 283-298.e17, Copyright 2022, with permission from Elsevier.

Digestive Diseases and Nutrition

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

Digestive diseases can exact a significant toll on individuals across the lifespan, resulting in a lower quality of life, years lost due to premature death, and costs associated with hospitalization and pharmaceutical and surgical interventions. The burden of digestive diseases in the United States is substantial: based on recent data, it is estimated that digestive disease is the primary diagnosis in a total of 66.4 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments in the United States each year.¹ Similarly, analyses with 2019 national inpatient samples identified 4.0 million hospitalizations with a primary diagnosis of digestive diseases and 16.7 million hospitalizations with a primary or secondary diagnosis of digestive diseases.² In addition, analyses focusing specifically on the clinical and economic burden of emergency department visits identified 18.7 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling \$121.8 billion in 2019.³

Annual estimates of the burden of digestive diseases list these diseases as the primary diagnosis in 66.4 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments.¹

Inflammatory bowel disease (IBD), an umbrella term for chronic and painful intestinal diseases that include Crohn's disease and ulcerative colitis, is marked by damaging intestinal inflammation that can cause rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. IBD often strikes early in life, with a peak age of onset in adolescence or young adulthood.

Treatment frequently requires prolonged use of multiple drugs and may require surgical removal of the affected portion 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 predict the best course of treatment and catalyze the design of novel, more personalized 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.

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

¹ Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). <http://www.cdc.gov/nchs/ahcd/index.htm>. Accessed October 12, 2022.

² Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS). <http://www.hcup-us.ahrq.gov/nisoverview.jsp>. Accessed October 12, 2022.

³ Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS). <http://www.hcup-us.ahrq.gov/nedsoverview.jsp>. Accessed October 12, 2022.

Diseases of the stomach and intestines also include peptic ulcer disease, which is typically caused by infection with the bacterium *Helicobacter pylori* or use of nonsteroidal anti-inflammatory drugs. Peptic ulcer disease is common and, if left untreated, could raise the risk of stomach cancer. Other stomach and intestinal disorders include functional GI disorders, which can cause 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 have 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 caustic stomach acids rise up into the esophagus, is a common functional GI 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—a potentially devastating disease still on the rise in the United States. Gastroparesis, another type of functional GI disorder, is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. There are two major forms of gastroparesis: one is a complication of diabetes, and the other is of unknown cause, making treatment difficult. Current therapies for gastroparesis are directed toward helping people manage this chronic condition so they can be as comfortable and active as possible. Another disorder that poses a major public health burden is fecal incontinence, or impaired bowel control. Fecal incontinence is more common in older adults, but 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 aim 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 GI disorders, which will lead to improvements in diagnosis and management.

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. This damages the small intestine and interferes with its ability to absorb nutrients from foods, resulting in chronic diarrhea, bloating, anemia, and, in children, slower growth and short stature. The only current treatment for celiac disease is maintenance

of a strict gluten-free diet, which is difficult for many people. 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.

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

The microbes that inhabit the GI tract—also known as the intestinal microbiome—are important factors in maintaining 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, and because pancreatitis is difficult to detect in its early stages, many cases are advanced by the time they are diagnosed. Research has elucidated genetic and other factors contributing to pancreatitis that may lead to ways to treat or prevent this disorder.

The liver performs many critical metabolic functions within the digestive system, including processing and distributing nutrients such as fats. Serious adverse health effects can occur when the liver is functionally compromised by disease, which sometimes leads to

scarring. Severe scarring (cirrhosis) could result in complete liver failure (end-stage liver disease). Some liver diseases primarily affect children, such as biliary atresia (a progressive inflammatory liver disease), while others generally affect adults, such as nonalcoholic fatty liver disease (NAFLD) or its more severe form, nonalcoholic steatohepatitis. In recent years, however, NAFLD in the United States has been increasingly diagnosed in children as well, concurrent with rising rates of overweight and obesity. NAFLD is also associated with health disparities: while the disease occurs in people of all races and ethnicities, in the United States it is more likely to affect those of Hispanic ethnicity than those from other ethnic groups. 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. When liver disease reaches the end stage, the only effective treatment is a liver transplant. Because the number of livers available for transplant from deceased donors is limited, sometimes a healthy living person will donate part of their liver. 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.

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

The number of Americans with overweight or obesity 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 obesity, 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 to understand dietary needs in health and disease. NIDDK staff works collaboratively with representatives from across NIH, including in NIH's Office of Nutrition Research, to advance nutrition research efforts.

IMPORTANT ROLES OF BILE ACIDS IN HEALTH AND DISEASE

How Gut Bacteria Use a Bile Acid To Keep Inflammation

in Check: Using cultured cells, mouse models, and human samples, scientists have discovered how certain bacteria might suppress gastrointestinal inflammation by modifying a bile acid in the gut. The human gastrointestinal tract is teeming with trillions of bacteria that can aid digestion and influence health and disease. To prevent undue inflammation in the gut—like what occurs in inflammatory bowel disease (IBD)—it is important to understand how gut bacteria coexist with the immune system, which must strike a delicate balance between tolerating friendly bacteria and attacking disease-causing microbes. It has been shown previously that 3-oxolithocholic acid (3-oxoLCA), a chemical compound derived from a liver bile acid, may help suppress gut inflammation by preventing T cells (a class of cells involved in immune responses) from developing into inflammation-promoting “T helper” cells. It was unclear exactly how 3-oxoLCA was being produced from bile acids, however, and whether it plays a role in preventing gut inflammation. Knowing these important details could lead to the development of new treatments for IBD.

Using fecal samples from volunteers, a team of scientists was able to identify several species of gut bacteria that can break down the bile acid lithocholic acid

(LCA) to generate the compounds that suppress T cell activation. They found that these bacteria—with at least some working in concert—can modify LCA to generate 3-oxoLCA and the abundant bile acid derivative isolithocholic acid (isoLCA), both of which could prevent T cells from transforming into specific types of inflammation-promoting T helper cells. Likewise, male and female mice colonized with these bacteria could convert LCA into 3-oxoLCA and isoLCA, and these mice also had lower levels of inflammation-promoting T helper cells. Importantly, the researchers analyzed samples from men and women and found that people with IBD had lower levels of LCA-converting bacteria—and lower levels of 3-oxoLCA and isoLCA—compared to people without IBD. They also had more markers of inflammation-promoting T helper cells. This suggests that high levels of LCA-derived compounds produced by certain gut bacteria may help prevent IBD by suppressing the gut's immune response. Altogether, these results offer a deeper understanding of how microbes can control the immune system in the gut to prevent inflammation, and they offer new approaches to develop potential therapies for IBD by promoting immune tolerance.

Paik D, Yao L, Zhang Y,...Devlin AS. Human gut bacteria produce T_H17 -modulating bile acid metabolites. *Nature* 603: 907-912, 2022.

Identifying the Distinguishing Features of Bile Acid Diarrhea: New research has provided much-needed insight into the nature of a particularly distressing form of chronic diarrhea, setting the foundation for improved ways to diagnose and treat it. Irritable bowel syndrome (IBS)—a debilitating group of symptoms involving recurring abdominal pain and changes in bowel movements—affects millions of people in the United States and can severely impact quality of life. Women are twice as likely to develop IBS than men. A common symptom is chronic diarrhea, called “IBS with diarrhea” or IBS-D. About a third of people with IBS-D have a more severe form of diarrhea, called bile acid diarrhea, caused by too much bile acid in the large intestine (colon). Bile acids are produced by the liver and released into the small intestine to aid in fat metabolism, then later reabsorbed in the colon for reuse. Little is known about the underlying causes of bile acid diarrhea, and many of the tests for it can be unreliable or inaccessible for many people. Also, new targeted therapies are needed because many people have difficulty adhering to current treatments, which are limited to unpleasant-tasting medicines that bind bile acids in the gut and prevent them from affecting the functions of the colon.

Researchers recently set out to identify defining characteristics of bile acid diarrhea that could lead to new ways to diagnose and treat the disorder by undertaking an in-depth analysis of chronic diarrhea in a group of 205 adults diagnosed with IBS-D, more than three-quarters of whom were women. To understand what differentiates bile acid diarrhea from other types of diarrhea, they compared people with the disorder to those who have IBS-D without bile acid diarrhea. The people with bile acid diarrhea experienced faster movement of stool through their large intestines, consistent with their more severe symptoms. Bile acid diarrhea was also associated with changes in the gut microbiome; in particular, the microbiomes of people with bile acid diarrhea were less diverse and had different compositions of bacteria than those from people without the disorder. The researchers also found several genes that were more active in people with bile acid diarrhea, including those involved in regulating inflammation and the permeability of the intestinal wall, pointing to a possible role for intestinal damage as a contributor to the symptoms of this disorder.

Scientists have gained important biological insights into what sets a form of diarrhea with high intestinal bile acid levels apart from less severe forms of chronic diarrhea, offering potential new ways to diagnose and treat this distressing condition.

This study suggests that, at least in people diagnosed with IBS-D, there are fundamental, biological differences that set bile acid diarrhea apart from other types of diarrhea. The findings offer new potential markers—clinical, bacterial, and genetic—that can be used to help detect this disorder in people with chronic diarrhea. They also provide hints of the underlying causes of bile acid diarrhea, offering possible new pathways to facilitate diagnosis and treatment.

Camilleri M, Carlson P, BouSaba J,...Busciglio I. Comparison of biochemical, microbial and mucosal mRNA expression in bile acid diarrhoea and irritable bowel syndrome with diarrhoea. *Gut* doi:10.1136/gutjnl-2022-327471, 2022.

CAUSES AND EFFECTS OF NONALCOHOLIC FATTY LIVER DISEASE

Since 2002, scientists in the Nonalcoholic Steatohepatitis Clinical Research Network have dedicated their time and energy to studying nonalcoholic fatty liver disease

(NAFLD), one of the most common (and rising) forms of liver disease, for which no approved medical treatment is available. Over the past two decades, the Network has made many important contributions to the field, including developing a scoring system for diagnosing the disease and its progression, assessing genetic and other risk factors, and testing multiple candidate therapies. Its past clinical studies have been conducted in partnership with other NIH Institutes, including the National Cancer Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, as well as with industry partners. Two recent advances out of the Network continue its tradition of adding new knowledge of this disease in both children and adults that can be applied to clinical care.

Genetic Risk Factors and Disease Severity in Children with Nonalcoholic Fatty Liver Disease:

Results of a study on NAFLD in children, including those from a highly affected ethnic population, show that some genetic variants increase risk of disease, particularly its more severe form. NAFLD has become the most common form of chronic liver disease in children. In its early stages, the disease can involve fat accumulation in the liver, followed in some children by inflammation and tissue damage, placing them at risk for more severe outcomes, such as liver cirrhosis and the need for a liver transplant. NAFLD occurs in people of all races and ethnicities, but in the United States the disease is more likely to affect those of Hispanic ethnicity than those from other ethnic groups, such as non-Hispanic Black persons. While it often tracks with other forms of metabolic disease, such as obesity and diabetes, questions remain as to why only some individuals with these metabolic diseases develop NAFLD. Studies with adult participants have shown that genetic variations appear to underlie some of this risk, but evidence in children is more limited.

A group of scientists in the Nonalcoholic Steatohepatitis Clinical Research Network studied more than 800 girls and boys who were diagnosed with NAFLD at varying stages, based on microscopic evaluation of liver biopsies. The majority of the children were of Hispanic ethnicity. Scientists analyzed DNA from blood samples given by the children and their parents to identify genetic variants associated with increased risk for developing NAFLD. Among several genetic variants identified, one in the *PNPLA3* gene showed the strongest association with disease. Children who inherited this genetic variant from both parents, the majority of whom were of Hispanic ethnicity, developed more severe disease at a younger age and at a lower level of overweight. The *PNPLA3*

variant is also linked to NAFLD in people who develop the disease later in life, but in this study, it was found to be associated with patterns of fatty liver disease that are primarily seen only in children, suggesting that this variant can affect the livers of people differently across the lifespan. The researchers further evaluated disease stage of the liver samples against a selection of genetic variants, including the *PNPLA3* variant, to pinpoint which were likely to contribute to severe disease. They found some variants were associated with early fat accumulation in the liver, while others occurred in tandem with inflammation and tissue damage.

Studies in children and adults with nonalcoholic fatty liver disease have linked genetic risk factors and outcomes to disease stage, with severe, later-stage disease associated with a higher risk of complications and death. These findings can inform clinical care for this disease, which is increasingly common in the United States and around the globe.

This study enhances understanding of genetic risk factors for NAFLD and its severity in children, who show some unique features of the disease compared to adults. Because the majority of study participants were of Hispanic ethnicity, these findings are particularly valuable for this at-risk population. Insights from this study can help explain differences in NAFLD risk, disease severity, and treatment response, providing foundational knowledge needed for therapeutic development and improving clinical care for these children.

Goyal NP, Rosenthal SB, Nasamran C,...Schwimmer JB; for the NASH Clinical Research Network. Nonalcoholic fatty liver disease risk and histologic severity are associated with genetic polymorphisms in children. *Hepatology* doi:10.1002/hep.32570, 2022.

Tracking Outcomes in Adults with Nonalcoholic Fatty Liver Disease: A study following people with NAFLD has shown a direct link between disease stage and outcomes, with severe, later-stage disease associated not only with a higher risk of liver-related complications and death, but also with complications in other organ systems. NAFLD, in which fatty deposits form in the liver, affects a large and increasing portion of the population in the United States and around the world. It is often found with other chronic metabolic diseases, such as obesity and type 2 diabetes. In its more severe form of nonalcoholic steatohepatitis, inflammation and fibrosis (scarring and

tissue damage) can occur. More detailed knowledge of disease outcomes could help inform clinical care and design clinical research on new treatments.

This study by investigators in the Nonalcoholic Steatohepatitis Clinical Research Network followed a cohort of adult women and men with nonalcoholic fatty liver disease who were mostly White and of European ancestry. The researchers analyzed participants' liver biopsies to assess disease stage based on how much fibrosis was present and tracked major outcomes, including complications in the liver and other organs. They found that risk of death and liver-related complications that compromised organ function, including liver cancer, increased in those individuals with more severe stages of fibrosis, such as cirrhosis. Almost all individuals with later-stage fibrosis showed evidence that they had the more severe form of NAFLD, nonalcoholic steatohepatitis. Late-stage disease was also associated with signs of complications in other organ systems throughout the body, including more type 2 diabetes and hypertension, as well as reduced kidney function.

These findings linking outcomes to disease stage add to the evidence base for determining prognosis and informing clinical care for NAFLD. Identifying these direct relationships between disease stage and clinical outcomes is important for providing more options to test new therapeutic approaches. Applying the results of this study to the general population is limited, however, by the lack of diversity in the study population. Thus, more research is needed to collect data in additional populations and determine whether these results are broadly generalizable.

Sanyal AJ, Van Natta ML, Clark J,...Tonascia J for the NASH Clinical Research Network. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 385:1559-1569, 2021.

INVESTIGATING HOW GUT CELLS SENSE AND COMMUNICATE WITH THEIR ENVIRONMENTS

How a Gut “Feeling” Helps Digestion: Research using a mouse model provided insight into how cells sense the chemical and physical properties of gut contents to regulate digestion. As food moves through the gastrointestinal (GI) tract, digestive organs break the food—using motion and digestive juices—into parts

small enough for the body to absorb and use for energy, growth, and cell repair, while moving waste down and out of the body. These digestive activities require the cells lining the GI tract to be able to sense the chemical and physical properties of the contents and translate these properties into signals to modulate the function of and transit through the gut. Previous studies identified a subset of enteroendocrine cells (EECs) in the GI tract that have Piezo2, a protein which is also found in a type of skin cell responsible for the sense of touch. In the GI tract, these cells interact closely with the contents of the gut, but it was unknown if and how these cells might act as sensors to “touch” and “feel” gut contents and affect gut function in response.

Using genetic techniques, the scientists identified the EEC Piezo2 cells in the mouse gut and investigated their role. When the EEC Piezo2 cells were stimulated, the scientists observed an increase in the frequency of gut contractions, suggesting that these cells had a role in moving the gut. When the Piezo2 protein was missing from these cells, the scientists were no longer able to affect contraction frequency. To further study the role of EEC Piezo2 cells, the scientists observed digestion in mice genetically altered to be missing Piezo2. In comparison to mice with the protein, mice lacking Piezo2 were unable to regulate motility in response to gut contents. Instead, small-sized indigestible beads, given by mouth to the animals, moved right through and were not distributed appropriately throughout the gut. Additionally, it took longer for these mice to move large-sized waste pellets through their GI tract. Collectively, these results indicate that the subpopulation of EEC cells with Piezo2 is critical to the mechanosensory system of the mouse GI tract to sense gut contents and regulate GI motility in response.

Disruption of gut motility in humans can lead to abdominal pain and changes in bowel movements, such as constipation or diarrhea, and has been implicated in disorders of the GI like irritable bowel syndrome. Further research is needed to explore whether EEC Piezo2 cells are present and act similarly to detect gut contents in humans, whether these cells are disrupted in GI diseases, and if stimulation of these cells can contribute to improvements of symptoms. This discovery provides a new avenue to explore and could help development of novel strategies to treat people with GI disorders.

Treichel AJ, Finholm I, Knutson KR,...Beyder A. Specialized mechanosensory epithelial cells in mouse gut intrinsic tactile sensitivity. Gastroenterology 162, 535-547.e13, 2022.

The Sweet Spot: How a Gut Sensory Cell Determines Preference for Sugar Over Artificial Sweetener:

Researchers have discovered how gut sensory cells discern nutritive sugars from non-caloric artificial sweeteners to guide an animal's preference for sugar.

It has been known for decades that animals and humans generally prefer sugar to artificial sweeteners, that sweet-sensing taste buds on the tongue are not essential to drive sugar intake, and that this preference for sugar relies on feedback from the gut. But how the gut steers such preferences has remained elusive. The current study builds upon research from the same team who previously identified a direct line of communication between neuropod cells (sensory cells in the gut) and the brain that allows for sensing and rapid signaling of information about food intake. Here, they delved deeper to determine whether this gut-to-brain pathway can discriminate between nutrient stimuli, and if so, which neural mechanisms underlie this differentiation. Using lab-grown “mini-organs” derived from mouse and human cells to represent the small intestine, the researchers showed that real sugar stimulated neuropod cells to release a chemical neurotransmitter called glutamate that is relayed to the brain, while artificial sweetener triggered the release of a different neurotransmitter, ATP, likely activating a different gut-brain pathway.

Next, the scientists aimed to determine whether neuropod cells are necessary for the animals' sugar preference by using a technique called optogenetics to control the activity of the cells with light. To do this, the scientists first developed a novel, flexible fiber-optic cable adapted to the unique biological conditions of the gut. They were then able to turn the neuropod cells “on” and “off” in the guts of genetically engineered, live mice. The mice exposed to a wavelength of light that silences neuropods lost their preference for consuming sugar over sweetener, while mice exposed to a neutral wavelength of light did not, suggesting that neuropod cells are essential for the gut to send signals to the brain that help the animal discriminate between sugar and artificial sweeteners. Moreover, when the researchers inhibited glutamate signaling with a drug delivered to neuropod cells in the gut, sugar preference was reduced, indicating that glutamate signaling from neuropod cells enables mice to discern sugar from sweetener.

Taken together, these results demonstrate the sensory role of neuropod cells in the gut and show that they can differentiate among different stimuli similar to other sensory cells (e.g., taste buds on the tongue detecting

different flavors or retinal cells in eyes detecting different colors). This study lays the foundation for future research to determine how other nutritional stimuli, such as fats and proteins, are sensed by the gut and transmitted to the brain to influence food choices. It also raises the possibility that interventions could eventually be developed to help people reduce sugar intake.

Buchanan KL, Rupprecht LE, Kaelberer MM,...Bohórquez DV. The preference for sugar over sweetener depends on a gut sensor cell. Nat Neurosci 25: 191-200, 2022.

Chatty Neighboring Cells Promote Eosinophilic

Esophagitis: Messages exchanged among a network of “talkative” immune and esophageal cells may be important in determining whether people with eosinophilic esophagitis (EoE) go on to develop a more severe form of the disease. EoE is a chronic disease, often associated with food allergies and marked by immune cell infiltration and impaired functioning of the esophagus, including difficulty swallowing food and drink. In some people, but not others, the disease progresses to tissue damage, inflammation and esophageal narrowing, and ulcers, at which point treatment is less effective. It is important to understand what causes the disease to progress—and why it only progresses in some people—so researchers could develop new ways to stop it before it becomes harder to treat.

To this end, the Consortium of Eosinophilic Gastrointestinal Disease Researchers, funded in part by NIDDK, set out to uncover the exact mechanisms at work behind progression of EoE. To do this, they analyzed esophageal biopsies from children and adults with EoE at 11 study sites. They compared biopsies from those whose disease had progressed to esophageal damage and narrowing with another group whose disease had not progressed. Progressive EoE was more common in adults, women, and in people with a longer duration of EoE. An analysis of possible genetic factors associated with disease progression, using a diagnostic panel of 94 gene products typically linked to EoE, showed that biopsies from those with progressive EoE showed lower activity in a gene called *TSPAN12*, specifically within endothelial cells (cells that line blood vessels) in the esophagus. To explore how this reduced *TSPAN12* activity could play a role in EoE progression, the investigators pivoted to a cell model grown in a culture dish. They found an elaborate “social” cell network in which an inflammatory chemical called IL-13 from immune cells caused nearby endothelial cells

to lose their *TSPAN12* activity, which then signaled to neighboring fibroblasts (cells that form connective tissue) to lay down more scar tissue, similar to progressive EoE. Returning to the clinical context, the researchers observed that treatment with an antibody that blocks IL-13 in people with EoE restored esophageal *TSPAN12* activity.

This study uncovers some of the unique disease processes at work in the progressive form of EoE. Knowledge of these pathways can help point to more personalized approaches to therapy and prevention of disease progression.

Shoda T, Wen T, Caldwell JM,...Rothenberg ME; Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) Investigators Group. Loss of endothelial *TSPAN12* promotes fibrostenotic eosinophilic esophagitis via endothelial cell-fibroblast crosstalk. *Gastroenterology* 162: 439-453, 2022.

Gut Bacteria Utilize Dietary Fiber To Release Beneficial Nutrient with Positive Effects on Metabolism:

Researchers have demonstrated that certain human gut microbes can mine dietary fiber to extract a beneficial nutrient that otherwise would remain inaccessible to the human body.

Many factors—including population growth, climate change, and societal disruptions caused by the COVID-19 pandemic—have focused attention on food production and the massive amount of waste generated during food manufacturing. Fiber byproducts such as peels, rinds, and seeds discarded from fruits and vegetables have potential nutritive value and may be an untapped source of biomolecules that promote human health. Here, a team of researchers first studied groups of male mice harboring common human gut microbes as well as “germ-free” mice that were raised and maintained without any microbes. The mice were fed a high-fat, low-fiber diet, characteristic of what many people in the United States and other developed countries eat, with or without supplementation of fiber from oranges. The researchers discovered that when mice were fed orange fiber, a molecule called *N*-methylserotonin was released in high abundance—but this only happened in mice that harbored the collection of human gut microbes. Testing dozens of different human gut bacteria and utilizing innovative laboratory analyses, they identified a bacterial species that can produce enzymes that act like molecular scissors to break down the fiber and release the nutrient. When the researchers added *N*-methylserotonin to the drinking water of germ-free mice on a high-fat, low-fiber diet without any fiber supplementation, the mice had reduced body fat, improved sugar metabolism in the liver,

and more rapid gut motility, suggesting beneficial effects of this biomolecule. Importantly, in a small, all-female, human study, the researchers showed that people who consumed orange fiber snacks had increased levels of *N*-methylserotonin in their stool samples compared to people who ate pea-fiber containing snacks, indicating the release of this molecule occurs in humans and is fiber specific. Moreover, the study participants who ate the orange snacks also had increased levels of gut microbial genes that produce enzymes that break down fibers entrapping *N*-methylserotonin and allow for its release.

Although more research is needed to better understand the actions of *N*-methylserotonin in humans, this study highlights the relationships between food science, nutrition, and the microbiome. It also identifies a potential framework for establishing affordable and sustainable sources of dietary fiber—and nutrients within these—by utilizing food production byproducts that would otherwise be discarded. These results indicate potential therapeutic applications such as supplementing the human diet with select fibers for personalized nutrition.

Han ND, Cheng J, Delannoy-Bruno O,...Gordon JI. Microbial liberation of *N*-methylserotonin from orange fiber in gnotobiotic mice and humans. *Cell* 185: 2495-2509, 2022.

FACTORS INVOLVED IN INFLAMMATORY BOWEL DISEASE

Identifying Defects in Wound Healing in Inflammatory Bowel Disease: Researchers revealed an unexpected function for a protein in the proliferation (increase in number) and locomotion of intestinal cells, pointing to its possible role in promoting intestinal healing in people with inflammatory bowel disease (IBD). IBD is a painful disorder of the gut that is caused by a complicated interaction among genetics, gut microbes, the immune response, and environmental factors. A hallmark of IBD is damage to the intestinal lining in the form of lesions that are slow to heal, contributing to the chronic nature of the disease. One way to potentially alleviate symptoms of IBD and reduce inflammation would be to accelerate intestinal healing, which requires an understanding of why the lesions persist.

Scientists have uncovered a possible role for a protein in the healing of intestinal lesions, which could lead to the development of new therapies for inflammatory bowel disease.

New research has moved scientists closer to understanding this puzzle. Scientists were studying a protein called gasdermin B (GSDMB) that was initially suspected to be involved in controlling microbial infections by causing infected cells to self-destruct. They found high levels of GSDMB in the inflamed lesions of people with IBD, suggesting that GSDMB could play an important role in the disease. To investigate further, the scientists studied a human intestinal cell line that produces GSDMB. They uncovered a surprising function for this protein: rather than playing a role in the cells' destruction, it helped the cells multiply and move. These actions are essential during injury healing, when cells fill a wound by multiplying and moving into the damaged area. To test this idea, the scientists made an artificial "wound" in the laboratory by scraping a gap through a layer of cells and observing how well the remaining cells were able to fill the empty space. Unlike cells with functional GSDMB, cells that were missing GSDMB were not able to multiply and move into the wound. The scientists found that GSDMB's important role in cell growth and movement is accomplished by propagating signals that stimulate proliferation and engage cellular machinery critical for mobility. Importantly, cells with variations of GSDMB found in some people with IBD were not able to heal the artificial wound. This means defects in GSDMB could play a significant role in preventing wound healing in IBD. More research could build upon these findings and might lead to therapies that overcome or bypass defects in GSDMB, offering new potential avenues for treatment of IBD.

Rana N, Privitera G, Kondolf HC, ...Pizarro TT. GSDMB is increased in IBD and regulates epithelial restitution/repair independent of pyroptosis. *Cell* 185: 283-298, 2022.

UNDERSTANDING AND TREATING INTESTINAL INFECTIONS

Improving Microbe-based Therapy for *C. diff* Infections:

New research has uncovered details of what happens during fecal microbiota transplantation (FMT) when it is used as a treatment for *Clostridium difficile* (*C. diff*) infections, offering insight into potentially safer and improved microbe-based therapies. Changes or disruptions in the gut's microbiome—the diverse community of bacteria, viruses, and fungi that naturally inhabit the intestines—are associated with *C. diff* bacterial infections, a disease that causes severe diarrhea and colitis. One treatment proven to be successful is FMT, whereby gut microbes from a healthy donor's stool

sample are introduced into the recipient's large intestine to help reestablish a more functional gut microbiome. Despite a success rate of over 90 percent of people cured after a single treatment, many questions remain about how FMT works. For example, it is unclear how long the donor bacterial strains remain in the recipient following transplantation. Knowing whether the donated microbiota persist could help predict whether the *C. diff* infection is likely to return. It would also be important to know which donated strains are necessary for clearing the infection so a more defined therapeutic cocktail can be designed that avoids the transfer of unnecessary strains or disease-causing bacteria.

*Researchers tracked the engraftment and persistence of individual bacterial strains after fecal microbiota transplantation, which could aid the development of simpler and safer treatments for *C. diff* infections.*

To address these questions, researchers supported by NIDDK and the Crohn's and Colitis Foundation analyzed gut microbiomes and identified bacterial strains from 13 people before and after undergoing FMT as a treatment for recurrent *C. diff* infections. They also analyzed the microbiomes from the seven healthy donors who provided the FMT samples and developed a new statistical method to track the transfer of strains from donors to recipients during the study period of up to 5 years after FMT. This enabled the researchers to determine which strains successfully colonized and persisted in the recipients following transplantation, and which strains correlated with successful outcomes (*i.e.*, no relapses of *C. diff* infections). They found that, in people who experienced no relapses, over two-thirds of donor strains were retained for at least 5 years following FMT, while less than one-quarter of the recipient strains were retained (some additional strains were derived from food or the environment). The researchers also identified the bacterial strains that appear to be necessary for such a long-term engraftment. This suggests that a stable, near-permanent colonization of donor microbiota from FMT, driven by certain bacterial strains, is a reliable predictor for a successful outcome.

This research underscores the value of microbe-based therapy as an effective and potentially long-term treatment for *C. diff* infections. It also paves the way for the design of streamlined, synthetic therapies that consist only of certain bacterial strains and avoid the

transfer of unnecessary microbes, thereby providing an attractive and safer alternative to FMT.

Aggarwala V, Mogno I, Li Z,...Faith J. *Precise quantification of bacterial strains after fecal microbiota transplantation delineates long-term engraftment and explains outcomes.* *Nat Microbiol* 6: 1309-1318, 2021.

Cellular Response to Bacteria May Explain Why Infection Sometimes Causes Stomach Cancer:

Researchers have uncovered a promising clue as to why some people with *Helicobacter pylori* (*H. pylori*) infections may be more likely to develop stomach cancer: they may carry a genetic variation that causes cells in the stomach to respond more strongly to the bacteria.

About one-third of the U.S. population—and more than half of the world’s population—is infected with *H. pylori*, a species of bacteria that can cause gastritis, a type of chronic inflammation in the stomach. In the United States, the rate of *H. pylori* infection is higher in immigrants from areas where the infection is more common, such as in Asia and Central or South America. Most people with gastritis do not have symptoms, but the lingering inflammation could eventually produce ulcers and other changes to the stomach wall. In fact, infection with *H. pylori* is the leading known cause of stomach cancer, a disease with a typically poor prognosis because it is usually discovered in its late stages when it is difficult to treat. It is unclear, however, why *H. pylori* infections are more likely to cause stomach cancer in some people but not others.

Researchers sought to answer this question by examining how cells in the stomach interact with the *Helicobacter* bacteria during an infection. In a laboratory model that used cultured cells from mice or humans, they found that cells from the stomach responded to the infection by producing a chemical called interferon alpha (IFN α). This chemical signal was found to then convert

nearby immune cells into “immune suppressor cells,” which could potentially dampen the stomach’s immune response and create an environment that is favorable for cancer development and growth. Using a mouse model of *Helicobacter*-induced stomach cancer, the researchers showed that blocking IFN α prevented the formation of these immune suppressor cells and the cells that are the precursors to stomach cancer. The researchers also looked at samples from almost 200 men and women in China and Vietnam with gastritis (with or without *H. pylori*) and found that some people had a variation in a gene involved in the cellular response to *H. pylori* infections. If the people with this genetic variant also harbored *H. pylori*, their stomachs had higher levels of IFN α , more immune suppressor cells, and a higher incidence of cancer than those with a more common genetic variant.

Some people with H. pylori infections may be more likely to develop stomach cancer because they have a genetic variation that could cause cells in the stomach to respond more strongly to the bacteria.

These studies provide a possible reason why some people with *H. pylori* infections are more likely to develop stomach cancer: they have a genetic variation that causes a more robust response to the infection, leading to a stronger suppression of the local immune response that typically keeps cancer cells in check. This finding suggests that people who have this genetic variation may benefit from more clinical surveillance to detect the disease early, when it is more likely to respond to treatment.

Ding L, Chakrabarti J, Sheriff S,...Merchant JL. *Toll-like receptor 9 pathway mediates Schlafen⁺-MDSC polarization during Helicobacter-induced gastric metaplasias.* *Gastroenterology* 163: 411-425, 2022.

Liver Network Aims To Transform Treatment



Liver Cirrhosis Network

NIDDK has launched a new Liver Cirrhosis Network to conduct clinical and translational research, working toward expanding treatment options and transforming clinical care for this potentially life-threatening condition.

Cirrhosis describes a condition in which the liver has been inflamed and damaged by chronic disease, resulting in scarring and loss of function over time. Many forms of chronic liver disease can cause cirrhosis, such as viral hepatitis (mainly chronic hepatitis B or C viral infections), nonalcoholic fatty liver disease, disease from excessive alcohol consumption, autoimmune liver diseases, and genetic types of disease such as hemochromatosis. Cirrhosis places people at much greater risk of developing complications, including hepatocellular carcinoma, a type of liver cancer. And the risk of cirrhosis and its complications is not distributed equally, with some racial and ethnic groups in the United States bearing a greater burden.

Treatment of the underlying cause of chronic liver disease can halt cirrhosis progression, ideally before the liver is irreparably damaged and a transplant is required. Scientists are also trying to develop treatments that can repair the liver damage that has already occurred, to restore liver function and avoid these potentially severe outcomes. Reversing damage in liver cirrhosis is crucial, with rates rising in the United States and a growing gap in the number of organs available for transplant relative to those in need.

Meeting this urgency with action, NIDDK put plans in motion for the Liver Cirrhosis Network with a request for public input from members of the scientific and industry communities, asking them to share information on new approaches to diagnosis and therapy, as well as perspectives on clinical research opportunities. This input helped to inform NIDDK's

release of funding opportunity announcements in 2020, requesting applications for scientific proposals. Since that time, NIDDK has been establishing partnerships with other NIH Institutes on this endeavor to synergize with their efforts relating to chronic liver disease. In 2021, the Network was established with scientists at 11 sites located at universities across the country, including 10 clinical centers and a scientific data coordinating center. These sites are working in collaboration with a diverse population of adult study participants, some of whom belong to groups that have been underrepresented in past studies despite being at higher risk for cirrhosis.

Plans for future research include an observational study that will collect a vast constellation of data from study participants, including clinical, behavioral, genetic, metabolic, microbiome, biomarker, and social determinants of health data, as well as information on risk factors in racial and ethnic groups that experience a disproportionate burden of cirrhosis. This information will help researchers understand what drives the progression of cirrhosis from multiple causes, including nonalcoholic and alcoholic forms of fatty liver disease as well as hepatitis B and C, and in the presence of comorbidities such as obesity and HIV infection. These insights can, in turn, point to possible treatment approaches. One type of therapy, in particular, will be studied through a randomized controlled trial. Network sites will test whether statins—drugs commonly taken for high cholesterol—can safely prevent cirrhosis progression. The goal of each of the Network's studies is to usher in a new era of cirrhosis management, with a wider array of effective treatment options beyond liver transplantation.

For additional information on the Liver Cirrhosis Network, please visit its website at: www.lcnstudy.org.

Inflammatory Bowel Disease Genetics Consortium: Unearthing Genetic Factors Underlying Chronic Gut Inflammation

Millions of people in the United States are affected by inflammatory bowel disease (IBD), the collective term for a group of debilitating digestive disorders that include Crohn's disease and ulcerative colitis. IBD is characterized by chronic, painful inflammation in the gastrointestinal tract, with symptoms that include diarrhea, bleeding, and loss of appetite. People with IBD also have a high lifetime risk of complications that require surgical interventions, contributing to a substantial loss in quality of life. Uncovering the underlying causes of the inflammation has been extremely difficult, although it appears to result from complicated interactions between multiple genetic and environmental factors, including disruptions in the community of microorganisms inhabiting the gut.

The NIDDK IBD Genetics Consortium (IBDGC) was established in 2002 to identify genetic factors involved in IBD susceptibility. In collaboration with the International IBD Genetics Consortium, the IBDGC has identified over 250 regions of the human genome that are associated with risk of IBD. In some cases, researchers have even been able to pinpoint specific genes within these regions and uncover how certain variations in these genes could play roles in IBD (by skewing the immune system and intestinal tissue towards an inflammatory state, for example). The current phase of the IBDGC, launched in 2022, is continuing to encourage studies that will identify and characterize individual genes within these regions of the genome, providing a deeper understanding of the disease and new targets for treatments.

Reflecting a bias that is common among early genetic studies, most participants in large IBD genetic studies have been people with European ancestry, who were also believed to be more at risk for developing the disease than other ancestral lineages. In recent studies, the IBDGC and its collaborators have expanded the scope of genetic studies to include participants from a more diverse array of ancestries, providing a clearer picture of how genetics intersect with disease risk across all populations. For example, it is now recognized that African Americans are at increased risk for developing severe disease that could require hospitalization, which may reflect ancestry-specific genetic factors, along with disparities in diagnosis and access to health care. Recent research from the IBDGC has found that genetic risk factors for IBD overlap between people of African and European ancestries, but the degrees of risk conveyed by some shared genetic variants are different between the two populations, providing valuable and wide-ranging insight into the complicated nature of IBD risk factors for all people. More research that includes diverse populations is needed to help understand the factors that affect risk for IBD; identifying these unique risk factors could help tailor treatments for people with the disease. The current phase of the IBDGC will address this need by utilizing the Consortium's multiple research centers to recruit participants from populations currently underrepresented in IBD genomic studies, including African American and Hispanic persons. Importantly, genetics represent only one component of IBD risk, and understanding the genetic contributions can help

FEATURE

explain how other factors contribute to IBD risk as well, such as environmental and socioeconomic influences.

The IBDGC is an excellent example of how NIDDK-sponsored research is revealing critical insights into a complicated disease through foundational discoveries. The goals of the current phase—continuing to identify genetic risk regions, identifying specific genes and genetic variants involved in IBD susceptibility across diverse populations, and understanding how these variants influence the development of IBD—will build upon the Consortium’s previous successes. The overall objective of the IBDGC remains the same: to improve the health and quality of life of all people with IBD by enhancing management and treatment of this potentially devastating disease.

For additional information on the Inflammatory Bowel Disease Genetics Consortium, please visit its website at: www.ibdgc.org.

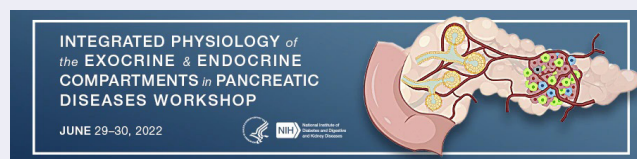
Understanding the Pancreas, Inside and Out: Efforts in Pancreatic Disease

This Feature also appears in the “Diabetes, Endocrinology, and Metabolic Diseases” chapter.

The pancreas is a key player in many diseases, including diabetes and digestive diseases such as pancreatitis. Understanding the various roles of the pancreas in human health and disease—and how pancreatic diseases interact with each other—is therefore an important NIDDK research goal. In addition to supporting a robust investigator-initiated research portfolio on pancreatic diseases, NIDDK also continually seeks to identify and encourage study in areas of new opportunity. From establishing research consortia to encouraging dialogue between scientists with complementary expertise, NIDDK uses a multi-pronged approach to facilitate and pursue the most compelling research, with the long-term goal of reducing the burden of disease and improving public health.

The pancreas is an elongated gland behind the stomach, close to the first part of the small intestine, and it has two main functions, called the “endocrine” and “exocrine” functions. The pancreatic endocrine functions are carried out by structures called islets, which make the hormones insulin and glucagon that help regulate the body’s blood glucose (sugar) levels. Meanwhile, the pancreatic exocrine cells make digestive enzymes that break down food in the intestine. When either of these functions is compromised, serious disease can result. In type 1 diabetes, for instance, the body loses the ability to make insulin due to a misguided autoimmune attack on the pancreatic islets, leading to a lifelong need to take insulin. Also, any disruptions of the carefully orchestrated steps needed to safely produce and secrete digestive enzymes can cause inflammation of the pancreas (pancreatitis). Pancreatitis has many underlying causes, and this disease can be either

acute (short term) or chronic (long lasting). Both forms of pancreatitis can lead to complications, including damage to the pancreas and other organs.



PROMOTING COLLABORATION TO UNDERSTAND THE PANCREAS AS A WHOLE

Traditionally, diseases related to endocrine and exocrine pancreatic functions—such as diabetes and pancreatitis, respectively—have been treated by different medical specialists and studied by different researchers. Increasingly, however, scientists are finding that intricate and crucial crosstalk occurs between the pancreas’s endocrine and exocrine functions as the body co-regulates digestion and metabolism. This crosstalk can also be seen in how disruptions in one function can adversely affect the other, such as when diabetes arises after chronic or acute pancreatitis. However, the mechanisms underlying these relationships and how they affect both health and disease are not fully understood.

To encourage discussion and investigation of the connections between the endocrine and exocrine pancreatic functions, NIDDK hosted a workshop on this topic in June 2022. This workshop, titled “Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases,” brought together researchers from the endocrine and exocrine

FEATURE

pancreas research communities to share new findings and expertise. Scientific presentations highlighted cutting-edge research on pancreas anatomy and physiology, as well as the latest perspectives on the links between endocrine and exocrine pancreatic disease. Researchers also discussed available tools for holistic analysis of the pancreas and identified knowledge gaps and key steps needed to support further study of its interdependent functions. The workshop's chairs closed the session with a plan to summarize and submit the workshop's proceedings for publication.

INVESTIGATING LINKS BETWEEN TYPE 1 DIABETES AND PANCREATITIS

Another NIDDK effort to shed light on the links between different pancreatic diseases is the Type 1 Diabetes in Acute Pancreatitis Consortium or T1DAPC. Formed in 2020, the Consortium's purpose is to study type 1 diabetes and other forms of diabetes that occur during or after one or more episodes of acute pancreatitis. The T1DAPC is composed of 10 clinical centers and one data coordinating center, which will support the T1DAPC's main clinical effort: the Diabetes RElated to Acute pancreatitis and its Mechanisms (DREAM) study.

DREAM's main goal is to understand the connections between pancreatitis and diabetes. High blood glucose during acute pancreatitis can sometimes last only a few weeks before getting better, or it can persist and lead to a diabetes diagnosis. Diabetes can also appear a year or more after the acute pancreatitis has resolved. Little is known, however, about how often or why diabetes occurs in these situations. The DREAM study is designed to answer some of these questions, helping researchers better understand what types of diabetes develop after acute pancreatitis and who is at risk. The DREAM study began recruiting participants in fall 2021 and is expected to continue recruiting through summer 2024.



FACILITATING NEW CLINICAL TRIALS IN PANCREATITIS

There are currently no U.S. Food and Drug Administration (FDA)-approved drugs to treat recurrent acute and chronic pancreatitis. Thus, there is an urgent need to develop effective therapies for these diseases, as well as a growing interest in best practices for pancreatitis clinical trials. To help address these needs, in July 2022, NIDDK—with additional support from the National Pancreas Foundation and participation of the FDA—held a 1-day workshop on clinical trials in recurrent acute and chronic pancreatitis.

This workshop covered a range of topics centered on the opportunities and challenges of designing and conducting patient-focused pancreatitis clinical trials. Presentations by researchers, as well as NIDDK and FDA staff, discussed considerations for designing successful trials, from identifying appropriate participant populations to defining suitable outcome measurements. Also covered were topics such as integrating patient perspectives, resolving ethical considerations, and forming successful public-private partnerships. Participants were also informed about currently available opportunities for investigators, including early-stage investigators. The final panel discussion focused on identifying knowledge gaps and ways to move the field forward. NIDDK developed a summary of the workshop for publication, and ideas gained from the workshop will help inform future NIDDK research directions.

FEATURE

MOVING PANCREATIC DISEASE RESEARCH FORWARD

As researchers study the pancreas's various roles in disease, their findings continue to highlight previously unappreciated connections between digestive and metabolic health. As described above, NIDDK is taking a holistic approach to advancing the study of pancreatic diseases, seeking to improve public health by promoting collaborative research, supporting important clinical trials, and encouraging the development of new treatments for pancreatic diseases.

Coordinating Research on New Treatment for Rare Childhood Liver Disorder

Alagille syndrome is a rare liver disorder typically diagnosed in infancy. People with Alagille syndrome have fewer bile ducts in the liver, resulting in elevated levels of bile acids, which causes severe itching, liver injury, and other potentially serious developmental issues throughout the body. Decades of research supported by NIDDK have contributed to understanding, diagnosis, and therapy for this condition, including the recent development of a new treatment that is potentially life changing for children with Alagille syndrome and their families. (See inset for a perspective on this research from a study coordinator.)

ABOUT ALAGILLE SYNDROME

As newborns or soon after, children with Alagille syndrome usually show early signs of the disorder, such as jaundice (yellowing of the eyes and skin), poor growth, and pale, loose stools. But a defining feature of Alagille syndrome is the severe, chronic, debilitating itching, called pruritus, which greatly limits their quality of life and is extremely distressing for the child and their family. The intense, constant discomfort of the itching compromises every aspect of these young lives, disrupting sleep and school, and resulting in skin damage from repeated scratching. The disorder results from an inherited deficiency in the number of bile ducts that develop inside the liver. These ducts are essential for delivering bile from the liver to the gallbladder for storage until it is released into the intestine to aid in fat digestion. Bile components are later reabsorbed further down the intestinal tract and returned to the liver. The insufficient number of bile ducts causes a back-up of bile in the liver, called cholestasis, which may cause damage to the organ.

Other organ systems are also affected, such as the heart, eyes, face, skeleton, kidneys, and blood vessels.

Investigators supported by NIDDK and other Institutes at NIH have made great strides in identifying the genetic risk factors and disease processes underlying Alagille syndrome. Based on this research, new genetic tests were developed to assist in the diagnosis of this disorder. Also building on discoveries of the disease processes, a number of therapeutic approaches have been used over the years to alleviate the severe itching of Alagille syndrome, through improving bile flow, removing bile, or blocking substances that cause the itching sensation. Yet, these treatments do not always provide reliable, long-term relief for the insatiable itch. Other approaches are more invasive, such as bile duct surgery or liver transplantation. As with other rare diseases, clinical research on Alagille syndrome to test new treatments is often challenging, due to the limited number of patients seen at any one medical facility.

CLINICAL STUDIES OF ALAGILLE SYNDROME

In 2008, NIDDK formed the Childhood Liver Disease Research Network, or ChiLDReN, combining and expanding upon existing pediatric liver disease consortia and studies. The goals of the new Network were to facilitate the understanding of many rare, cholestatic liver diseases in children and discovery of new diagnostic and treatment options, and to help train the next generation of investigators specializing in pediatric liver diseases. The Network's sites currently include a data coordinating center and 16

PERSONAL PERSPECTIVE

clinical centers located across the United States and Canada. ChiLDReN's research focusing on Alagille syndrome has included ongoing studies tracking the course of the disorder, as well as studies increasing understanding of disease mechanisms, identifying risk factors, and testing new treatments.

An important interventional clinical trial conducted through the Network, called ITCH, evaluated a new drug called maralixibat for its ability to safely and effectively relieve severe itching in children with Alagille syndrome. The drug works by inhibiting reabsorption of intestinal bile acids, leading to their excretion. Launched in 2014, ITCH demonstrated that certain doses of the drug improved children's itching severity as reported by their caregivers, compared to placebo. Combined results from another ChiLDReN study conducted from 2015 to 2020 (IMAGINE II) and a study from the United Kingdom showed that maralixibat treatment could safely and durably improve the children's severe itching and quality of life. The ITCH clinical trial was supported by NIDDK and by NIH's National Center for Advancing Translational Sciences, and the ITCH and IMAGINE II clinical trials also involved a public-private partnership between NIDDK and the pharmaceutical company that owned maralixibat. These studies and others funded by the pharmaceutical company provided the data necessary to gain approval from the U.S. Food and Drug Administration (FDA) in late 2021 for maralixibat as the first dedicated treatment for pruritus associated with Alagille syndrome.

ONGOING DISCOVERIES

NIDDK continues to support research on the disease processes and clinical care of children with Alagille syndrome, as the new maralixibat treatment and other available therapeutics do not work for everyone. Since the ChiLDReN Network's establishment, it has added another study that is using noninvasive imaging to monitor liver disease over time in children with Alagille syndrome. In other ongoing research, Network investigators are testing new treatments for this disorder and also engaging in basic research to explore the functions of specific genes and proteins in the disease, which can inform new diagnostic and treatment approaches. Individual investigators outside of ChiLDReN are also advancing research on Alagille syndrome. For example, current NIDDK-funded projects are using animal models to test innovative treatment approaches that could potentially rebuild the system of bile ducts in the liver and avoid the need for transplantation.

The collective impact of these NIDDK-funded research efforts, carried out by individuals involved in ChiLDReN and outside the Network, serves to further knowledge of Alagille syndrome and other forms of pediatric cholestatic liver disease, forming the basis for improved tests and treatments.

To learn more about the Childhood Liver Disease Research Network's studies, including ITCH and IMAGINE II, see: <https://childrennetwork.org/Clinical-Studies>.

PERSONAL PERSPECTIVE

Jessi's Experience as an ITCH and IMAGINE II Study Coordinator



Jessi served as a coordinator for NIDDK-supported studies of the Childhood Liver Disease Research Network; photo courtesy of Children's Hospital of Philadelphia

Clinical research studies are truly a team effort, relying on the contributions of study participants, study coordinators, doctors, nurses, medical facilities, patient support organizations, and sponsors like NIDDK, other NIH collaborators, and partners in the pharmaceutical industry. Some of the essential, unsung heroes of this team effort are the study coordinators, also called research coordinators, who facilitate the participation of children and their families while ensuring the highest-quality science.

Jessi, 43, a native and current resident of Philadelphia with a master's degree in public health, has been involved in clinical research at the Children's Hospital of Philadelphia, or CHOP, throughout her entire career. When not busy with her work, she enjoys staying active—biking, running, doing yoga, and spending time with her husband and two daughters, including having picnics in the city's many parks and taking trips outside the area for fruit picking.

Currently, Jessi serves as a Senior Director of Research, providing strategic day-to-day support to CHOP's Chief Scientific Officer. But a large part of her formative career development was spent as a study coordinator, and later coordinator supervisor, working with her site from the ground up to build their participation in the Childhood Liver Disease Research Network (ChiLDRen), and its ITCH and IMAGINE II studies of Alagille syndrome treatment, testing a new drug to relieve the pruritus (severe itching) associated with the disease.

Jessi's motivation for being involved in clinical research studies is clear: "We're really concerned about the lives of these children and ways to improve them—that's such a gratifying mission to stand behind."

"When I started my career at CHOP 20 years ago, it was as a research coordinator," recalls Jessi. She began work at the CHOP's Fred and Suzanne Biesecker Pediatric Liver Center on a study collecting information on children with cholestatic liver diseases, where she had her first interactions with children with Alagille syndrome and their families. The Center attracted many of these families due

PERSONAL PERSPECTIVE

to the renown of its investigators who helped to identify some of the key genetic variants associated with Alagille syndrome. Jessi observes, “At CHOP, it doesn’t feel like it’s such a rare disease. Our site has been a key center for patients with Alagille syndrome all around the world.”

Based on her experience, Jessi was tapped to be the first study coordinator for her site’s team within NIDDK’s multi-center Biliary Atresia Research Consortium or “BARC.” The predecessor of the modern-day ChiLDReN Network, BARC later merged with another NIDDK consortium called the Cholestatic Liver Disease Consortium or “CLiC.” “Everyone likes to joke, ‘BARC and CLiC got married and then they had ChiLDReN,’” quips Jessi.

As part of the research team, Jessi worked on a number of NIDDK-sponsored BARC, CLiC, and ChiLDReN studies of children with liver diseases due to cholestasis (or limited bile flow from the liver), including Alagille syndrome. An early, ongoing study in which CHOP participated was on the progression of liver diseases in children over time, including rare cholestatic liver diseases such as Alagille syndrome. Later, Jessi served as the study coordinator for the ITCH interventional trial testing the new drug maralixibat as a treatment for pruritus in children with Alagille syndrome. ITCH presented some new challenges through its design as an NIDDK-supported partnership with the pharmaceutical industry. “Although this was an NIDDK-funded study, it had a lot of the complexity and organization that a traditionally industry-sponsored study may have in terms of the interaction and coordination with multiple units and parts,” notes Jessi.

From early on, families with children affected by Alagille syndrome expressed interest in joining the study. “We had families who were very eager when they heard about this as a possible study because the pruritus that these families experience can really be so debilitating and compromise quality of life and day-to-day activities,” says Jessi. She describes the struggles these families go through, trying one drug

after another that only provides limited or waning relief. “For many of them, they’ve gone through all that we have available to offer, so there was a lot of excitement in the patient community to know that there were potentially new treatments available to treat the itching.”

In addition to coordinating study conduct and data collection among the CHOP team, NIDDK, data coordinating center, and industry partner, Jessi and the other study coordinators also helped facilitate other day-to-day tasks in running the study. These included screening potential participants and attending each of their study visits—about 10 visits per year over the multiple years of the study for each of the two families who participated at the CHOP site in ITCH, and later in IMAGINE II. In between study visits, she assisted with collecting data entered by parents into electronic diaries and scheduling the families’ upcoming visits. Coordinators also attended meetings of the Steering Committees overseeing the studies and helped address practical concerns. “One of the interesting things about the ChiLDReN Network is the way it involves everyone in effect, not only the participants and our PI [principal investigator] leaders, but that there is a real emphasis on involving the coordinators,” she observes. As Jessi grew more experienced, she transitioned from her role as a coordinator for ITCH to one managing a group of coordinators for the follow-on study of IMAGINE II.

“The research coordinator for ITCH and IMAGINE is maybe like the conductor of an orchestra,” says Jessi, who has served as a coordinator for studies of the Childhood Liver Disease Research Network.

“The research coordinator for ITCH and IMAGINE is maybe like the conductor of an orchestra,” says Jessi. The work of the “conductor” is multi-dimensional, seamlessly blending the efforts of three instrumental functions—interactions with patients and their families, fulfilling regulatory requirements at the

PERSONAL PERSPECTIVE

institutional level, and performing administrative duties that interact with the data coordinating center and industry partner. “The research coordinator is really at the nexus of the family participation in the study, coordinating everything on their behalf, while at the same time, adhering to the protocol.... It’s a fine dance,” she says.

The coordinator provides a high level of “concierge-type service,” says Jessi, to reduce participants’ burden, while still allowing the study to collect the highest-quality data. For example, CHOP study coordinators accommodated travel plans and provided translation services to overcome language barriers for one participating family, and helped another participant family who had a newborn child by being flexible with appointment scheduling and mailing treatments. “We’re really grateful for the participation of families in these studies,” Jessi says. “That is one of the high-value components of serving in this role ... the relationship that is established with these research participants.... that’s probably one of the things that those of us in clinical research at the coordinator level can find so valuable and rewarding is that we are directly having an impact on care.”

“The relationship that is established with these research participants ... that’s probably one of the things that those of us in clinical research at the coordinator level can find so valuable and rewarding,” remarks Jessi, a coordinator for groundbreaking studies testing a new treatment for the rare pediatric liver disease of Alagille syndrome.

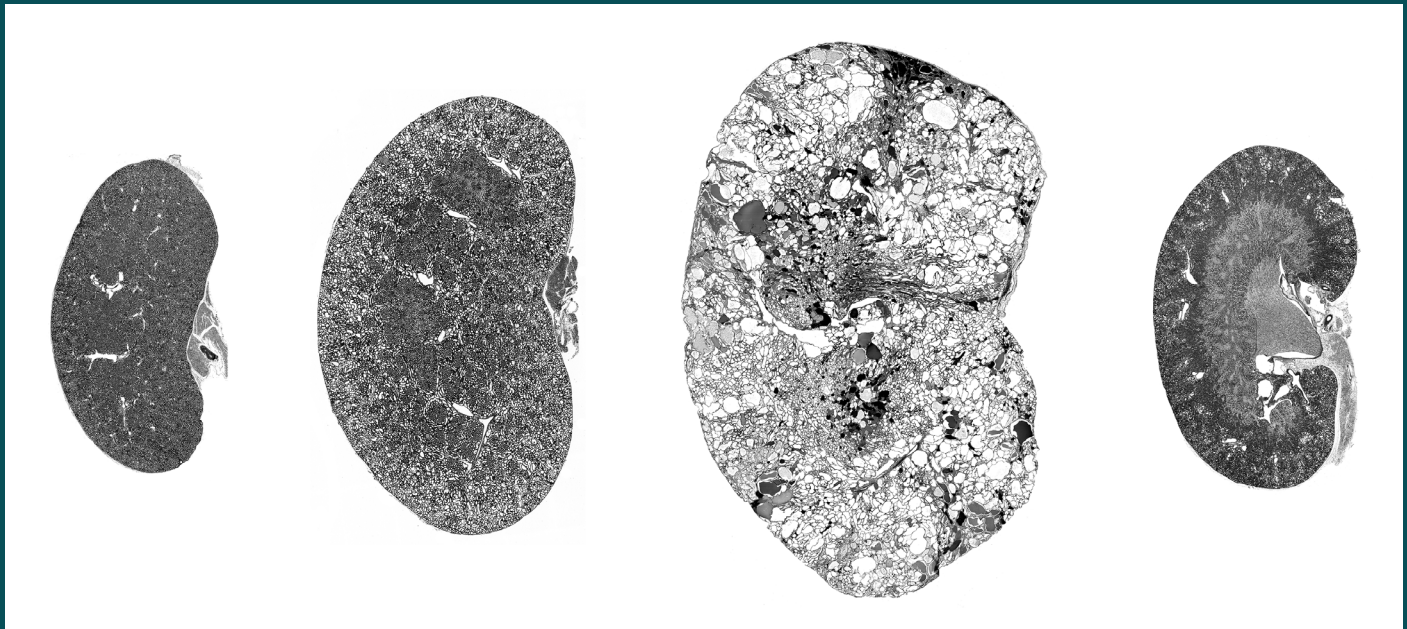
When asked about whether others should consider getting involved in clinical research, her answer is a “resounding yes.” She adds that “there’s a real value in facilitating or participating in research ... from a participant perspective, from a physician perspective, and also from the perspective of the non-physician research team members.” Jessi’s motivation for being

involved in clinical research is clear: “We’re really concerned about the lives of these children and ways to improve them—that’s such a gratifying mission to stand behind.”

Jessi’s commitment to caring for children and families affected by disease is also evident in her choice of activities outside of CHOP. She has been involved with the local chapter of the American Liver Foundation and with the Alagille Syndrome Alliance, serving on committees and planning patient education events.

In her new role supporting CHOP’s Chief Scientific Officer, she has the opportunity to make an even broader impact on a wide range of childhood diseases. But Jessi has not forgotten her roots as an experienced study coordinator and draws upon them often to inform her current work. “There are many days that I do miss that opportunity to have that interface at the patient or clinic level,” Jessi says. Still, she feels that her 20 years worth of experience with the practical aspects of clinical research at CHOP, largely as part of the CHILDRen Network studies, is an integral part of the value she brings to her current role.

Looking back on Jessi’s impressive performance as an “orchestra conductor,” coordinating this groundbreaking research while optimizing participants’ study experiences, one can only say “Bravo!”



A

B

C

D

As described in this chapter, researchers have found that in mice, kidney damage caused by polycystic kidney disease (PKD) can largely be reversed by turning on the normal version of a gene that was initially faulty. PKD is a form of chronic kidney disease that reduces kidney function and may lead to kidney failure. PKD causes many fluid-filled cysts to grow in the kidneys; unlike the usually harmless simple kidney cysts that can form in the kidneys later in life, PKD cysts can change the shape of the kidneys, including making them much larger. The most common form of PKD is autosomal dominant polycystic kidney disease (ADPKD), which results from mutations in the human *PKD1* or *PKD2* gene. In a new study, scientists induced PKD in mice by inactivating either of the corresponding mouse genes—*Pkd1* or *Pkd2*—specifically in the kidney. As illustrated in the image, mice with inactivated *Pkd1* developed enlarged kidneys containing the characteristic cysts that worsened over time, here shown at 13 weeks (B) and 16 weeks of age (C); these results were in stark contrast to non-cystic kidneys from mice with the normal *Pkd1* gene (A). However, when the researchers later used a genetic technique to reactivate the *Pkd1* gene, the cysts resolved, and the kidney damage was largely reversed (D). These findings may lay the foundation for developing gene therapy approaches to treat people with ADPKD.

Image provided by Dr. Stefan Somlo, Yale University. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, [Nature Genetics](#), Renal plasticity revealed through reversal of polycystic kidney disease in mice, Dong K, Zhang C, Tian X, Coman D, Hyder F, Ma M, and Somlo S, Copyright © 2021.

Kidney, Urologic, and Hematologic Diseases

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

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

An estimated 37 million American adults have impaired kidney function—also called chronic kidney disease (CKD).¹ 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. CKD can also result from other factors, as noted below.

An estimated 37 million American adults have chronic kidney disease.¹

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 2019, over 809,000 patients in the United States and its territories were living with ESRD.² Over 569,000 had previously received either hemodialysis or peritoneal dialysis, and over 239,000 were living with a kidney transplant.² 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. ESRD prevalence in 2019 was about 3.3 times greater in African Americans, 2.1 times greater in American Indians or Alaska Natives, 1.9 times greater in Hispanic Americans, and 1.3 times greater in Asian Americans, compared to Whites.²

In 2019, over 809,000 Americans were living with end-stage renal (kidney) disease.²

NIDDK supports a significant body of research aimed at understanding the biology underlying CKD and developing treatment strategies. The chronic renal diseases research program supports basic, translational, 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 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, NIDDK also supports studies of inherited diseases—such as polycystic kidney disease, congenital kidney disorders, and

¹ Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2021*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2021.

² United States Renal Data System. *2021 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, 2021.

focal segmental glomerulosclerosis—and immune-related kidney diseases, such as IgA nephropathy and hemolytic uremic syndrome. One feature common to kidney diseases arising from varying causes is the deposition of fibrotic scar tissue in the kidney. Research supported by NIDDK has enhanced our understanding of the origin of this scar tissue, how it can impair kidney function, and how it might be prevented or treated.

Racial and ethnic minority populations in the United States, particularly African Americans, Hispanic and Latino Americans, and American Indians and Alaska Natives, bear a disproportionate burden of chronic kidney disease and end-stage renal disease.²

Urologic diseases and conditions affect people of all ages, result in significant health care expenditures, and can lead to substantial disability and impaired quality of life. 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 urinary tract infections and urinary stone disease, two of the most common and costly urologic conditions affecting people in the United States. Urinary incontinence is another prevalent problem. Based on national public health surveys conducted over several years, it is estimated that about 54 percent of women 20 years and older experience urinary incontinence each year.³ Urinary incontinence was self-reported by approximately 15 percent of men surveyed.³ Many suffer in silence due to embarrassment and lack of knowledge about treatment options available.

About 54 percent of women 20 years and older experience urinary incontinence each year.³

Many people are also living with one of a cluster of disorders collectively called urologic chronic pelvic pain syndrome (UCPPS). The two most common examples of UCPPS are interstitial cystitis/bladder pain syndrome (IC/BPS)—also known as IC/painful bladder syndrome (PBS)—and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). IC/BPS is a debilitating, chronic, and painful urologic disorder. Based on a large, national interview survey, it is estimated that among U.S. women

18 years or older, 3.3 million (2.7 percent) have pelvic pain and other symptoms, such as urinary urgency or frequency, that are associated with IC/BPS.⁴ 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 IC/BPS.⁵ 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.

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 interstitial cystitis/bladder pain syndrome.³

Research on UCPPS is one example of how NIDDK is seeking a broad-based understanding of symptoms affecting the lower urinary tract (LUTS). LUTS—including pain, bladder leakage, and problems urinating—are not always associated with discrete conditions or tissue dysfunctions: different conditions can share the same symptoms and symptom causes may actually lie outside the urinary tract. For example, urinary incontinence symptoms have been linked to anxiety disorders in some cases. For the wide range of LUTS, we still need to learn more about causes and contributing factors to improve management and treatment of symptoms. Thus, NIDDK is supporting multiple efforts to identify and understand different subgroups of people with LUTS through improved measurement of their symptom experiences that can inform future therapeutic strategies. Simultaneously, NIDDK is supporting research to better understand factors that contribute to bladder health over the lifespan, with the ultimate goal of preventing LUTS.

² Feinstein L, et al. *Urological Diseases in America, 2018 Addendum*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication Number 12-7865, 2018.

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

⁵ Link CL, et al. *Prevalence and psychosocial correlates of symptoms suggestive of painful bladder syndrome: results from the Boston area community health (BACH) survey*. *J Urol* 180: 599-606, 2008.

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

Blood diseases and disorders—some of which cause severe, debilitating pain and premature death—affect millions of Americans.

ADVANCING KNOWLEDGE OF KIDNEY PHYSIOLOGY

Detailed “Kidney Atlas” Characterizes Cells of the Healthy Adult Kidney: In an advance that is dramatically deepening our understanding of normal kidney physiology, researchers have produced a reference source that shows in detail the way healthy adult human kidneys are organized at the cellular level. The kidney is a remarkable example of biological architecture, with a complex array of structures called nephrons, each consisting of many cell types. Together, these structures perform the critical job of regulating fluid and salt levels in the body, among other tasks. Subtle disruptions of kidney cell function can therefore lead to serious health consequences.

The NIDDK-led Kidney Precision Medicine Project (KPMP) seeks to revolutionize kidney care by identifying critical cells, pathways, and targets for potential novel kidney disease therapies and prevention strategies. To achieve this lofty goal, KPMP investigators first developed an intricate “atlas” of the healthy human kidney for comparison purposes. They accomplished this through a comprehensive analysis of kidney tissue

biopsies ethically obtained from study volunteers. This atlas delineates the biology of individual cells in various parts of the nephron and its surrounding tissue, demonstrating how they are defined not only by their position in the kidney, but also by the precise molecular signatures of genes and proteins active within them. Through their analyses, the researchers also found areas within the nephron that might be vulnerable to damage resulting from low oxygen levels, and enhanced understanding of other aspects of kidney function.

The Kidney Precision Medicine Project has produced an “atlas” revealing remarkable cellular and molecular details of the healthy human kidney.

The KPMP research team has made their kidney atlas available on the web to share this valuable new resource broadly with the research community. Thanks to these discoveries, KPMP scientists and other researchers are now poised to compare biopsies from diseased kidneys against this reference atlas to yield critical new insights into the causes of kidney diseases and new ways to prevent, diagnose, and treat them.

Hansen J, Sealfon R, Menon R, ...Azeloglu EU; for the Kidney Precision Medicine Project. A reference tissue atlas for the human kidney. *Sci Adv* 8: eabn4965, 2022.

RESEARCH ON KIDNEY DISEASE

Studies Identify Immune Cell Types Associated with Progression of Different Forms of Kidney Disease: A recent study of chronic kidney disease (CKD) in mice shows that one type of immune cell may have an important role in accelerating kidney fibrosis, or scarring, which can lead to kidney failure, while another study linked a group of immune cell types to accelerated cyst growth after kidney injury in a mouse model of cystic kidney disease.

The immune system is thought to drive inflammation leading to kidney fibrosis and loss of function in common forms of CKD, but the mechanisms by which it does so have not been well understood. A group of researchers therefore examined kidney cells of male mice with CKD that were showing signs of inflammation and fibrosis and discovered the cells were secreting a factor that attracts a type of immune cell known as a basophil.

In further experiments, they found that they could slow the process of fibrosis by reducing the number of basophils in the animals or interfering with the basophils' ability to signal to other cells. Notably, an analysis of kidney cells from people with and without CKD showed that CKD was associated with substantially higher basophil levels and that higher basophil levels correlated with more fibrosis. These results suggest that basophils may play an important role in the progression of common forms of kidney disease, and that it may one day be possible to slow CKD progression by interfering with basophils.

Another group of researchers sought to investigate the role of various immune cells in the progression of cystic kidney diseases like autosomal dominant polycystic kidney disease (ADPKD). Previous research had suggested that kidney inflammation caused by injury or infection results in rapid acceleration of the disease by promoting both the formation and growth rate of cysts. The researchers therefore examined female mice with a model of cystic kidney disease and found several differences in the proportion of different types of immune cells between healthy kidneys, kidneys with slow-growing cysts, and kidneys where cysts grew rapidly due to injury. In particular, there were differences in a group of immune cells associated with adaptive immunity (*i.e.*, cells that acquire the ability to fight an infection from previous exposure to the same pathogen). To explore the roles of these cells in kidney cyst growth, they used a technique to eliminate adaptive immune cells from the mice. Interestingly, kidney injury did not lead to the usual acceleration of cystic disease in mice without the adaptive immune cells, while the absence of these cells did not affect disease progression in uninjured kidneys. If these cells are found to have similar effects on human kidney cysts, it may one day be possible to protect people with ADPKD or other cystic kidney diseases from rapid disease progression after injury or infection by modulating the activities of specific groups of immune cells.

Doke T, Abedini A, Aldridge DL,...Susztak K. *Single-cell analysis identifies the interaction of altered renal tubules with basophils orchestrating kidney fibrosis.* *Nat Immunol* 23: 947-959, 2022.

Song CJ, Li Z, Ahmed UKB,...Zimmerman KA. *A comprehensive immune cell atlas of cystic kidney disease reveals the involvement of adaptive immune cells in injury-mediated cyst progression in mice.* *J Am Soc Nephrol* 33: 747-768, 2022.

Metabolites Linked to a Range of Symptoms Experienced by People with Chronic Kidney Disease:

Researchers have identified metabolites (molecular byproducts of metabolism) that are associated with specific symptoms of uremia—a condition in which poor blood filtration from reduced kidney function leads to a buildup of toxins in the blood—a discovery that could one day lead to improved care for people with chronic kidney disease (CKD). People with CKD often experience a range of uremic symptoms that adversely affect quality of life. These symptoms can be gastrointestinal (*e.g.*, loss of appetite, nausea, vomiting) or neurological (*e.g.*, reduced alertness, forgetfulness, lack of energy) in nature. While blood toxins are known to contribute to uremic symptoms, the specific causative metabolites are unknown. In a recent study, scientists determined the blood levels of more than 1,100 metabolites in 695 participants with CKD (38 percent female, 86 percent White) and developed a “score” for each uremic symptom based on reported severity and duration in each individual. They then looked for associations between metabolite levels and symptom scores. Eleven metabolites were found to be associated with gastrointestinal symptoms and seven metabolites were associated with neurological symptoms. The authors acknowledge that the size of the cohort was relatively small, and the relative representation of CKD causes within the cohort may limit the applicability of the findings. Laboratory testing, validation, and randomized controlled trials would be needed to determine definitively whether specific metabolites cause certain uremic symptoms. Further studies of the metabolites identified in this study could lead to novel therapeutic approaches to alleviate the uremic symptoms experienced by many people with CKD.

Hu J-R, Myint L, Levey AS,...Shafi T. *A metabolomics approach identified toxins associated with uremic symptoms in advanced chronic kidney disease.* *Kidney Int* 101: 369-378, 2022.

Reversing Polycystic Kidney Disease in Mice: Using mouse models, researchers showed that, in early stages of polycystic kidney disease (PKD), kidney damage can be reversed by reactivating an inactive gene—findings that raise the possibility of using gene therapy to treat people with PKD. PKD is a genetic disorder that causes numerous fluid-filled cysts to grow in the kidneys. Over time, growth of these cysts results in enlarged kidneys in which normal tissue is displaced and kidney function is impaired, sometimes quite severely. The most common form of PKD is autosomal dominant polycystic kidney disease (ADPKD), which results from mutations

in either the *PKD1* or *PKD2* genes. Previous research has shown that therapies targeting molecular pathways affected by disruption of the *PKD1* or *PKD2* genes can slow progression of the disease, but not reverse the kidney damage.

In a new study, scientists used complex genetic strategies to first inactivate either of the corresponding genes in mice—*Pkd1* or *Pkd2*—specifically in the kidney, which led to enlarged kidneys, characteristic cyst formation, and other forms of damage. They later reactivated the genes relatively early in the course of the disease, which led to a dramatic reduction in kidney size in the mice. Further analyses showed that the gene reactivations reversed many hallmarks of PKD: the cysts resolved, cell and tissue structures returned to normal, and many signs of kidney damage (e.g., inflammation, tissue scarring) dramatically improved. When the scientists waited to reactivate the genes until the mice had reached an advanced stage of PKD, they observed partial, but not complete, reversal of disease characteristics, suggesting that eventually some damage from the disease can become permanent. Although kidney damage was once considered almost invariably permanent, this study demonstrates that, in some cases, reversal may be possible, at least in mice. If these findings hold true in humans, gene therapy approaches may one day be able not just to slow disease progression in people with ADKPD, but potentially to reverse it.

Dong K, Zhang C, Tian X,...Somlo S. Renal plasticity revealed through reversal of polycystic kidney disease in mice. *Nat Genet* 53: 1649-1663, 2021.

In mice, kidney damage caused by autosomal dominant polycystic kidney disease was largely reversed by activating the normal version of a faulty gene.

Chronic Kidney Disease in Children Affects Brain Development:

Researchers have observed differences in brain structure in children with chronic kidney disease (CKD) compared to children without CKD. CKD is characterized by a reduced ability of kidneys to filter blood the way that they should over an extended period of time. Diabetes and high blood pressure are the leading causes of CKD in adults. However, the most common causes of CKD in children are kidney birth defects or genetic diseases. Deficits in mental function are often associated with CKD in pediatric patients, with children displaying difficulties concentrating, learning, and remembering. While these cognitive deficits are

known to manifest, there have been very few brain-imaging studies to determine their cause.

In this study, researchers used a brain imaging technology called diffusion weighted magnetic resonance imaging to view the integrity of tissues deep in the brain known as white matter. The researchers compared brain scans of 17 boys with CKD (ages 6 to 16) to 20 healthy boys (ages 7 to 16). Their aim was to identify differences between the groups and to discern their potential links to cognitive deficits in those with CKD. The analysis revealed reduced white matter integrity in children with CKD that mapped to multiple distinct brain regions when compared to children without CKD. The scientists did not, however, find that the observed decrease in white brain matter integrity correlated with cognitive deficits. In fact, the researchers observed that, among the children with CKD, there was an unexpected potential association between higher white brain matter integrity and decreased executive functions (mental processes directing a child's thought, action, and emotion during problem solving).

This study suggests that there are differences in the brains of children with CKD compared to children without the disease. Further research on a larger number of children, including girls as well as boys, may provide insight into whether white matter differences contribute to the cognitive deficits observed in children living with CKD and whether the correlations observed in this study are truly representative of the population.

van der Plas E, Solomon MA, Hopkins L,...Harshman LA. Global and regional white matter fractional anisotropy in children with chronic kidney disease. *J Pediatr* 242: 166-173, 2022.

PREVENTING KIDNEY STONE RECURRENCE

Removing Asymptomatic Kidney Stones During Symptomatic Stone Removal Surgery May Result in Lower Risk of Recurrence:

A small study has found that people have a lower chance of future kidney stone problems if smaller, asymptomatic kidney stones are also removed during surgery to remove larger, symptomatic ones. Kidney stones are hard, pebble-like structures that form in the kidneys when a person has high levels of certain minerals in their urine. Depending on their location and size, some kidney stones may be able to pass through the urinary tract without treatment. Others, however, can cause complications including severe pain, bloody urine, and urinary tract infections. Asymptomatic kidney stones are more common than

and are often found alongside of symptomatic stones. There are conflicting views about the impact of leaving these asymptomatic stones behind during removal of symptomatic ones, and current guidelines leave it to doctors and patients to decide whether to remove them or simply monitor for recurrence of symptoms.

Researchers found that removing both symptomatic and asymptomatic kidney stones during the same surgery may reduce the likelihood of recurrence.

One approach to treatment for people with symptomatic kidney stones is endoscopic surgery, during which a small, thin camera is inserted into the urethra to find and remove any stones. In a recent study, 73 people undergoing endoscopic surgery for removal of symptomatic kidney stones were randomized either to have their asymptomatic stones removed during the procedure (treatment group) or not (control group). Both groups were then monitored up to 5 years post-surgery for recurrence in the form of an emergency room visit for stones on the same side as the removal, subsequent stone removal surgery on the same side, or visualized growth of an asymptomatic stone via a CT scan. The researchers found that recurrence occurred substantially more often in the control group than in the treatment group—63 percent compared to 16 percent—and that the time to recurrence was an average of 697 days longer in the treatment group than in the control group. Removal of asymptomatic stones did increase the duration of the surgery time, usually by less than 30 minutes.

The findings from this study suggest that removing both symptomatic and asymptomatic kidney stones during endoscopic surgery may reduce the likelihood of recurrence of stone-related complications. It is important to note that this was a small study in which approximately 90 percent of participants were White, so it is not yet clear whether the results will apply broadly across the population. However, if these findings are replicated in larger, more diverse studies, they could lead to new recommendations that may help reduce the risk of kidney stone recurrence.

Sorensen MD, Harper JD, Borofsky MS,...Lingeman JE. Removal of small, asymptomatic kidney stones and incidence of relapse. *N Engl J Med* 387: 506-513, 2022.

IDENTIFYING NEW THERAPEUTIC TARGETS FOR BENIGN PROSTATIC HYPERPLASIA

Potential New Therapeutic Targets To Treat Benign Prostatic Hyperplasia: Two recent studies explored new potential approaches for treating prostate enlargement. The prostate, a small gland surrounding the urethra just below the bladder, is part of the male reproductive system and commonly becomes enlarged with age. This condition, called benign prostatic hyperplasia (BPH), is caused by the non-cancerous growth of the prostate due to increased reproduction of cells. As the prostate enlarges, it may squeeze the urethra and affect the flow of the urinary stream leading to symptoms involving changes or problems with urination. Many available BPH therapeutics aim to relax the muscles of the bladder and prostate to allow for urine flow.

Scientists studied new approaches to lessen the symptoms of benign prostatic hyperplasia, which could pave the way for needed alternative therapies for this condition.

One study utilized mouse models to explore the impact of targeting a protein called soluble guanylate cyclase, or sGC, on BPH symptoms. This protein is involved in proper functioning (contraction and relaxation) of muscles in the bladder and prostate and affects other processes, such as cell proliferation. Although some approved medicines treat BPH by affecting other proteins in the same pathway, they occasionally lose their effectiveness. In this study, researchers compared urination and prostate characteristics of aged mice displaying BPH-like symptoms with those of younger adult mice. Treatment of aged mice with an sGC-activating compound called cinaciguat for 2 weeks was able to restore normal urinary function in the BPH mice. The researchers also found that cinaciguat was able to reduce the frequency of bladder contractions in a different mouse model of BPH that mimics resistance to some approved therapeutics.

Another study investigated the contribution of autoimmune inflammatory diseases to BPH and the use of autoimmune disease therapeutics to treat the condition. Researchers analyzed the medical records of 112,152 men over the age of 40 and found the prevalence of BPH was substantially higher among individuals with autoimmune diseases compared to

those without. However, in further analysis of each BPH diagnosis in relation to the timing of an autoimmune disease diagnosis, the researchers found that BPH was less common in males previously diagnosed with an autoimmune disease compared to those who were not. This result suggested that prior autoimmune disease-specific treatments may effectively treat or reduce the development of BPH. The researchers observed that tissue from donated human BPH prostates contained high levels of an inflammatory molecule, tumor necrosis factor (TNF), and found that TNF exposure triggered certain cells from human prostates to multiply. The researchers therefore investigated whether a class of anti-inflammatory autoimmune disease therapeutics known as TNF antagonists might be effective for treating BPH. Indeed, analyses of prostate tissue donated from people with BPH and of two different BPH mouse models revealed that a TNF antagonist reduced cell multiplication and markers of prostate inflammation compared to untreated controls.

Because TNF antagonist treatment can result in serious side effects, future studies to identify safer alternatives to reduce the inflammatory aspects of BPH will be important. If new treatments, including anti-inflammatory medications or cinaciguat or another sGC activator, are shown to be safe and effective, individuals with BPH may one day have valuable alternatives to existing therapies.

Zabbarova IV, Ikeda Y, Kozlowski MG,...Kanai AJ. Benign prostatic hyperplasia/obstruction ameliorated using a soluble guanylate cyclase activator. *J Pathol* 256: 442-454, 2022.

Vickman RE, Aaron-Brooks L, Zhang R,...Hayward SW. TNF is a potential therapeutic target to suppress prostatic inflammation and hyperplasia in autoimmune disease. *Nat Commun* 13: 2133, 2022.

RESEARCH ON URINARY TRACT DISORDERS

Cellular Response to Urinary Tract Infection Helps Halt Bacterial Growth: Researchers have identified a new bodily defense mechanism deployed in the fight against urinary tract infections (UTIs). UTIs are very common in adults as well as in about 8 percent of children, most frequently girls. The leading cause of UTIs is exposure to uropathogenic *E. coli* bacteria, also referred to as UPEC. While antibiotics resolve many infections, recurrence is common, and antibiotic resistance is rising; a better

understanding of the natural course of UTIs could help lead to new treatments. In addition to flushing bacteria and infected bladder cells out of the urinary tract through urination, the body employs innate defenses, such as production of antimicrobial molecules, to stymie UTIs.

In a new study, scientists examined one such molecule, the protein ribonuclease 7, to understand how genetic variations in the protein affect its antimicrobial properties and the person's risk of UTI. By comparing girls in the NIDDK-funded Randomized Intervention for Children with Vesicoureteral Reflux trial or the Careful Urinary Tract Infection Evaluation study to age-matched girls without recurrent UTIs, the researchers discovered that girls with a common variant of ribonuclease 7 were more likely to develop UTIs. Further investigation using bladder cells grown in the laboratory revealed that increasing levels of the standard form of ribonuclease 7 helped prevent infection by UPEC. However, the variant form of the protein was less effective at fending off the bacteria. Discovery of the way common differences in the ribonuclease 7 protein affect its ability to defend against bacteria may help explain why some children are more susceptible than others to UTIs. These results also suggest that boosting ribonuclease 7 levels in the bladder might one day be a means for treating or preventing UTIs.

Pierce KR, Eichler T, Mosquera Vasquez C,...Spencer JD. Ribonuclease 7 polymorphism rs1263872 reduces antimicrobial activity and associates with pediatric urinary tract infections. *J Clin Invest* 131: e149807, 2021.

INVESTIGATING WAYS TO PREVENT BLOOD DISORDERS

Ferretting Out a Possible Way To Inhibit Ferritin Processing and Prevent Iron Overload: Research in mice suggests it may one day be possible to treat hemochromatosis by inhibiting a protein that can contribute to the overabsorption of iron. The body responds to iron deficiency by absorbing iron through the small intestine. The intestinal cells protect themselves from potentially toxic iron levels by packaging the absorbed iron into a protein complex called ferritin. As needed, the cells process the ferritin and release iron into the bloodstream. The body responds to sufficient iron levels by inhibiting this process to help avoid a potentially toxic iron glut. Unfortunately, this inhibitory system sometimes goes awry, allowing the body to absorb and release too much iron, a dangerous condition known as hemochromatosis.

Research has now illuminated new details on the process of ferritin processing, revealing a potentially beneficial approach to treating hemochromatosis. Scientists identified a protein known as NCOA4 that plays a key role in processing ferritin to allow release of iron in the blood. In mice with a version of hemochromatosis, eliminating the protein from intestinal cells protected the animals from iron overload, while still allowing sufficient iron absorption to meet their needs. If the process is found to work the same way in people, and if a safe and effective way to control NCOA4 in the intestine can be identified, it may one day provide an effective means for treating hemochromatosis to people with the disease.

Das NK, Jain C, Sankar A,...Shah YM. Modulation of the HIF2 α -NCOA4 axis in enterocytes attenuates iron loading in a mouse model of hemochromatosis. Blood 139: 2547-2552, 2022.

Workshop Held To Address the Role of Structural Racism and Importance of Achieving Health Equity in People with Kidney Disease

NIDDK hosted a virtual, 2-day workshop to catalyze efforts toward overcoming structural racism and achieving health equity in kidney disease. Structural racism is the embedded social, political, and economic system in which policies, practices, and institutions systematically create inequalities in resources and opportunity, thereby creating and perpetuating the marginalization of communities. Structural racism permeates society, impacting sectors such as housing, education, employment, and health care. The existence of structural racism has led to adverse social determinants of health, such as housing inequality, food insecurity, health care inequities, and other damaging factors that impact quality of life.

Health disparities are the preventable differences in the burden of disease experienced by people of racial, ethnic, and other minorities. Many social determinants of health—such as restricted access to health-promoting resources or marked differences in cost or quality of treatment—contribute to health disparities.

Kidney disease is one example of a disease with substantial disparities in health care and health outcomes. Kidney disease spans a broad array of diseases and conditions that affect millions of Americans and poses a significant public health issue. People who belong to racial and ethnic minority groups experience reduced access to and quality of nephrology referrals, home dialysis modalities, and kidney transplants, and they are at higher risk for kidney disease and failure.

Health equity (*i.e.*, the ability for each individual to achieve his or her full health potential) cannot be achieved without addressing the mechanisms by which structural racism leads to disparities. NIDDK



recognizes its responsibility to seek out opportunities to address both the upstream (*e.g.*, systemic policies) and downstream (*e.g.*, direct care differences) causes of racial and ethnic disparities in kidney disease. The NIDDK workshop “Designing Interventions That Address Structural Racism to Reduce Kidney Health Disparities” held February 24-25, 2022, sought to address two key goals: to describe the mechanisms through which structural racism contributes to health and health care disparities, and to identify actionable research recommendations for interventional research.

In keeping with NIDDK’s commitment to engaging diverse stakeholders, participants in this workshop included kidney disease and health disparities experts; people with kidney disease, as well as their families and caretakers; and other key stakeholders—all of whom brought a wide array of experience and expertise.

Issue experts reviewed the many ways that structural racism underlies health care systems and practices and the ways it is reflected in health disparities, particularly for people with kidney disease. People with kidney disease and their caregivers spoke to their lived experiences, identifying gaps in care and opportunities for improvement.

Through robust discussions, participants considered numerous prospects for intervention, including: mitigating individual burden by seeking broad structural changes; promoting patient-centered outcomes through community engagement; applying

FEATURE

an anti-racist lens to research; adopting health care models and practices—such as increased insurance access, improved data collection, broadened types of care, and reinforcement of safety nets—that advance health equity; encouraging long-term financial investments in research and increased access to research funding; increasing scientific workforce diversity; and building organizational capacity to advocate for change. In doing so, participants laid the framework for NIDDK-funded initiatives focused on dismantling or addressing the effects of structural racism to reduce disparities in care and improve outcomes for people living with kidney disease.

A summary of the meeting is available to the public [here](#) on the NIDDK website.

Meeting Held To Discuss Research on the Relationship Between Enlarged Prostate and Lower Urinary Tract Symptoms

On March 30 and April 1, 2022, NIDDK hosted a virtual workshop entitled “BPH and Male LUTS: Intersection between Pathology and Disease.” The workshop sought to integrate recent understandings on the origins of, and symptoms associated with, prostate enlargement. The overall goals were to better understand the condition, assess the effectiveness of current treatments, and potentially determine new directions for improved therapies.

Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland that affects 50 percent of men over age 50 and 90 percent of men over age 80. Those with BPH often experience lower urinary tract symptoms (LUTS), which include difficulty with emptying the bladder, an urgency to urinate, and/or increased urination frequency.

Men who experience LUTS are typically first treated with medications that reduce the size of the prostate and relax the muscles of the bladder and prostate. Additionally, treatment can include resection (surgical removal) of the prostate. These treatments are not always successful in managing LUTS, however, and research has shown that the size of the prostate is often unrelated to the severity of LUTS. Thus, more research is needed to understand the relationship between BPH and male LUTS.

In this workshop, researchers and clinical providers considered whether BPH and LUTS are intrinsically related, or whether future research directions should consider the progression of diseases and symptoms of the bladder and prostate separately. Workshop participants reviewed the development and structure of the prostate as they relate to the risk of prostate enlargement and urinary symptoms, as



well as other factors that are thought to contribute to these conditions. The workshop also provided an opportunity to examine recent advances in the understanding of prostate enlargement and its relationship to bladder dysfunction, including the roles that aging, autoimmune disease, and environmental exposures during fetal development may play in these processes.

Participants also used this opportunity to consider research priorities, such as developing new research models and imaging approaches; identifying more meaningful treatment options; and determining the necessary methods, tools, and approaches to continue making progress in this scientific area. Potential next steps would address a range of opportunities, from basic science to clinical intervention, with emphases on precision medicine approaches and patient involvement in clinical and research efforts.

A summary of the meeting is available to the public [here](#) on the NIDDK website.

Providing HOPE for a Better Way To Manage Dialysis Pain

Hundreds of thousands of Americans are living with end-stage renal disease (ESRD), also known as kidney failure. Except for a small minority who receive a kidney transplant from a suitable donor, dialysis to carry out the critical process of filtering waste materials from the blood becomes essential for life. Most often this occurs in a hemodialysis center during three 4-hour sessions each week.

The well over 600 hours each year of sitting still in a dialysis facility is a substantial burden, but very often it is not the only one: more than half of dialysis patients experience significant pain, which increases the risk for depression and lowers quality of life. Prescription opioids such as hydrocodone, oxycodone, or tramadol are often used to treat pain, including pain associated with dialysis. While often effective at easing pain, these prescription drugs also carry the risk of addiction.

As the United States grapples with the opioid epidemic, there has been renewed attention to the consequences of addiction and other side effects of this class of medications. Research showed that their use increased the likelihood of death among people treated with dialysis, and that the increase in mortality was proportional to the dose of the opioid. In 2019, NIDDK began the Hemodialysis Opioid Prescription Effort (HOPE) consortium—sometimes also known as the Hemodialysis Pain Reduction Effort—to find better approaches to managing hemodialysis-associated pain. (See insets for perspectives about the HOPE consortium from a patient participating on the study team and a clinical trial participant.)

ABOUT THE HOPE CONSORTIUM

Part of NIH's broader Helping to End Addiction Long-term® (HEAL) Initiative, the HOPE study is

testing a novel pain coping skills training intervention for people being treated with dialysis, with the goals of improving pain management and reducing opioid prescription rates in this population. The 3-month, one-on-one intervention is comprised of weekly, 45-minute telehealth sessions that employ pain coping skills training and motivational interviewing to provide a non-medical option for people to manage dialysis-related pain, comparing that to usual care. After the initial 12 sessions, the intervention provides another 12 weeks of daily, automated interactive calls designed to boost the intervention's message and assess how the participant is doing.

Not all the people enrolled in the study are taking opioid medicines for pain, but for those who are, the therapy also provides participants with coping skills designed to decrease dependence on opioids while managing pain. After the intervention is complete, participants still taking opioids—whether or not they received the coach-led therapy—are eligible to participate in an additional observational study of buprenorphine, an alternative opioid that is generally considered safer than traditional opioids. Those who elect to receive buprenorphine are encouraged to stop taking their current opioid medication and take buprenorphine instead but are allowed to stay on their current medication if they prefer.

Both interventions together last a total of 8 to 10 months. Before and after receiving the pain coping skills training, and also after the buprenorphine intervention, the participants are asked to describe not just their pain, but also other key things that can be adversely affected by opioid use, such as how well they are sleeping, whether they can think clearly, and how their quality of life is being affected by their pain or their pain treatment. This information will help scientists determine if either or both interventions

PERSONAL PERSPECTIVE

can successfully help patients manage their pain and reduce dependence on opioids.

PROMOTING PATIENT ENGAGEMENT THROUGH HOPE

Importantly, HOPE is in the vanguard of NIDDK-supported clinical studies that are giving individuals with the conditions being studied a leadership role on the research team. This way, people with lived experience of these conditions contribute their voices at every stage of the research as Patient Advisors—ensuring that the work will meet the needs of the study population, developing culturally appropriate recruitment materials, helping spread the word about newly developed treatments, and more. NIDDK feels this approach will improve the science, help speed the adoption of better health care approaches, and advance health equity.

The HOPE Patient Advisors are full members of the study team, and their goal is to keep the research focused on better meeting the needs of people treated

with dialysis. This approach, referred to as patient engagement, has already paid major dividends for the study. For example, the Advisors helped develop a 5-minute recruitment video, explaining the study and why people treated with dialysis who are experiencing pain should consider participating. The video and other key input from these community members have helped keep study recruitment well ahead of schedule and meeting its goal that 50 percent of study participants are Black. Although kidney disease affects people from all racial and ethnic backgrounds, the disease disproportionately affects people with African ancestry, who have historically been underrepresented in clinical research.

HOPE FOR THE FUTURE

The HOPE study is actively recruiting participants toward its goal of enrolling approximately 640 people at 8 clinical centers across the United States. Because of the dedication of study participants, Patient Advisors, and scientists, HOPE is poised to provide future knowledge that can benefit people with ESRD.

Dave's Story: Helping Fellow Kidney Patients by Serving on the HOPE Study Team



Dave is a Patient Advisor and steering committee member for the NIDDK-supported HOPE study

Dave had a difficult decade during his 40s. Not long after he retired early from his high-pressure job, he found himself hospitalized with end-stage renal disease (ESRD), also known as kidney failure. The dialysis he received then saved his life, but the three 4-hour maintenance dialysis sessions per week he required thereafter presented difficult hurdles for him: apart from being very time consuming, even getting to the clinic was a challenge. He took public transit as far as it would go, but walking the remaining blocks was surprisingly strenuous, as he was weakened by anemia (*i.e.*, his blood could not carry enough oxygen throughout his body). Getting home was even harder, because the procedure itself was also draining, so

he was exhausted all the time. Then there was the discomfort. When Dave was asked by health care providers at the dialysis clinic if it hurt, "I'd say 'yes.' When they asked me where, I couldn't pinpoint a spot. I'd just say it hurts all over." He notes that the experience is not the same for everyone: some people treated with dialysis do experience localized pain, while others have relatively little discomfort. For Dave, dialysis kept him alive, but also meant living with generalized pain. This was particularly true during dialysis itself because the procedure required him to sit for hours in a single position.

Unfortunately, the exhaustion and pain led him to miss some dialysis appointments. After about 6 months of this, his care team called him and his wife to a meeting that would change his life. They asked why he was missing appointments and worked with him to help solve some of the logistic and financial issues that were making dialysis such a challenge for him. They also told him if he kept missing dialysis sessions he wouldn't live much longer. It was the nudge Dave needed to take ownership of his own health: he took it as a challenge to get to every appointment on time. After a couple of months of regular dialysis, he began to feel better. "Perhaps 'less crappy'" would be a better way of putting it, he says. Soon he began making other healthful choices—quitting smoking, eating better, exercising, and becoming stronger.

Not long thereafter, Dave accepted a role on a kidney patient advisory committee that was seeking volunteers. He says "a lightbulb went off," as he knew some things could be done better, and so

PERSONAL PERSPECTIVE

began a role in patient advocacy that continues today. Dave had also experienced firsthand the transformative moment when his care team listened to him, and he listened to them. As an advocate, he has had the chance to help ensure such moments happen whenever possible for others living with ESRD, and to make a difference for people in his community who need dialysis; he feels he's "had a pretty good run as a patient advocate." In 2015, after almost 6 years on dialysis, Dave received a kidney transplant. Since then, he has become healthier still. And—more than a decade after he retired and soon thereafter got his ESRD diagnosis—Dave was able to accept a paying job proofreading documents for a law firm.

Dave says that during his years receiving dialysis he was invited to join several clinical trials, participating in most. He says he would have been more receptive to one he declined to join if they had done a better job answering his questions about the study. So, when a scientist who had heard about his advocacy work invited him to join the steering committee for a new study to improve pain treatment in people who are receiving dialysis, he was keenly interested. (A steering committee plays an integral role by setting priorities for and overseeing research studies.) The scientist said that as a Patient Advisor and member of the Steering Committee, Dave would have a major role in ensuring the study meets the needs of its participants. Dave realized this might be another opportunity to make a difference for people with ESRD. He agreed to join, and Dave—along with others from the community of people living with ESRD—soon became an integral part of the Hemodialysis Pain Reduction Effort (HOPE) research team.

"The HOPE trial exceeded my expectations.... And my expectations were high," says Dave, speaking about how the HOPE study has prioritized including the patient perspective in all its activities.

Dave recalls that at the first Steering Committee meeting, the NIDDK project scientist, Dr. Paul Kimmel, insisted Dave and the other Patient Advisors sit at the table with the scientists—as equal members of the team. "He always looks out for us. Any opportunity to make the patient voice felt, he... makes sure we have that opportunity." Indeed, Dr. Kimmel also "challenged us [the Patient Advisors] to champion" the patient perspective. "The HOPE trial exceeded my expectations in that regard. And my expectations were high."

Another thing he remembers from that first meeting was seeing how valuable it was to hear the differences between the perspectives of the other Patient Advisors and his own. "Not all dialysis patients think the way that I do.... I have to keep that in mind when I think about how to approach people and how to make [study] processes go better."

"We're all proud to be living proof of what can be done when we're given the opportunity to contribute," says Dave, speaking about how patient engagement has benefited the HOPE study.

As promised, the Patient Advisors are helping ensure that the HOPE study is patient centered and patient friendly by serving not only on the Steering Committee, but also the Patient Advisory Committee and the Recruitment and Retention Committee, among others. Indeed, they have played a major part in helping to guide the participant recruitment process. In a key effort, Dave and two of the other Advisors are featured in a 5-minute recruitment video on the study website, www.HOPEHDTrial.org, explaining the trial. In it, the Patient Advisors provide their own perspectives on what it is like to experience pain from dialysis, and the value of the HOPE Study. "Between the three of us we had really different takes on it, but each take was really personal—you could tell that it was just us telling our stories," Dave says. Notably, HOPE recruitment has been faster than

PERSONAL PERSPECTIVE

expected and is meeting its goal of having 50 percent Black participants (as of the time of writing). Many of the participants cited the video as one of the reasons they joined the study. “That video has been well received,” Dave adds with understatement.

“We’re all proud to be living proof of what can be done when we’re given the opportunity to contribute.” Dave agrees with the NIDDK’s philosophy about patient engagement in research, saying, “if you want studies done well, we have to be at the table.” By never giving up his own hope, Dave has improved his health and life in countless ways. Through his ongoing advocacy and patient engagement work, Dave is also giving HOPE to others living with ESRD for better health and quality of life.

Leroy's Story: Helping Fellow Kidney Patients by Participating in the HOPE Study



Leroy participated in the NIDDK-supported HOPE study

Leroy has led a life of service to others. A veteran, he retired to take care of his aging mother after years of driving a school bus, among other occupations. Leroy continues finding ways to contribute, such as by serving in the tenant council in his apartment building and being an advocate for other former servicemen and women and area seniors. He's a consensus builder who prides himself on patience and common sense.

His mother had kidney failure, so he was familiar with the routine of dialysis. But his own diagnosis still came as something of a surprise. He had missed an appointment with his social worker at the Veterans Affairs (VA) clinic because he hadn't felt well. When he came to the rescheduled appointment, the social

worker thought that he still seemed ill. She called in a doctor—a kidney specialist who told Leroy that he had kidney failure and needed to go on dialysis right away. Leroy told them he needed to “get things straightened out” at home first, and the doctor replied “well, you be here first thing in the morning.” When he arrived the next day, the staff wasted no time starting hemodialysis.

For Leroy, like many people, dialysis was a painful experience. He recalls that when he first started going to dialysis “they would ask me about pain.... Every question has to have a scale, you know, from 1 to 10. But if you look at the question... there is no scale to it. Pain is pain.... So, when they asked ‘do you have pain? What is it from 1 to 10?’... I have to say a 10 because there is nothing else but 10.” What hurt in particular? “I was never afraid of needles, ... but the needles hurt.” (Needles are a necessary part of receiving hemodialysis, and not all methods to reduce the discomfort of insertion work for all patients.) Leroy says that it wasn't so bad for him at first, but the repeated procedures made the area where they insert those needles sensitive. He also noted that much of the pain—especially in the shoulder of the arm with that needle in it—comes from the many hours of having to sit very still to avoid serious bleeding that could result from dislodging the needle. Eventually it wasn't just hurting during the procedure—it was also bad enough to wake him in the middle of the night. He says that he would sometimes take over-the-counter medicines to help with pain management.

Leroy had learned from his mother's experiences when she was on dialysis, so he knew that it was

PERSONAL PERSPECTIVE

important to pay close attention to his health care providers, and to be knowledgeable about what was going on. “I have very, very good people taking care of me there” at the VA clinic, he says. “I trust them.”

That trust is one reason why Leroy was open to participating in a clinical trial that he found out about during one of his dialysis sessions at the VA clinic. One day, as he sat in the center, he was approached about participating in NIDDK’s Hemodialysis Pain Reduction Effort (HOPE) clinical trial. Leroy found out that he was eligible for the trial and was glad to participate, knowing it might help not only himself but many others with kidney failure who were undergoing dialysis and experiencing pain.

As part of the HOPE study, Leroy was randomly selected to receive a novel pain coping skills training intervention that provides a non-medical option to manage dialysis-related pain and involves one-on-one coaching sessions. He said that his participation began with a questionnaire about his experience with dialysis—his pain, and his quality of life. Later, a coach suggested strategies for dealing with pain and other challenges. Leroy says when he tried one of these strategies, “it worked, and I gave them feedback.” One of the strategies Leroy has found most helpful has been deep breaths. “This program got me doing it more. If something got on me—whether it was physically or mentally—I would stop for a minute and just take some deep breaths and blow it out.... And when I did that, my mind seemed to clear.... That helped me mentally and physically.”

He also found that the questions study staff asked him during his trial participation got him talking more openly, helping him reflect more clearly on his own needs and experiences. “Psychologically, I learned some things,” Leroy says, relating it to the Parable of the Mustard Seed, where what starts as a tiny speck grows to become so large an entire flock of birds can nest: the various HOPE pain management skills work together, becoming larger than their individual parts, and working together to combat pain. When asked if

his participation in HOPE has improved his quality of life, he replies “Yes.”

“If something got on me—whether it was physically or mentally—I would stop for a minute and just take some deep breaths and blow it out.... And when I did that, my mind seemed to clear,” says Leroy, describing one of the strategies he learned about to help manage dialysis-related pain through participating in the HOPE study.

Would he encourage other people to participate in clinical research studies like HOPE? “Oh, definitely. I would give [the study] an A plus.... Give it a try.” He also said he enjoys talking to HOPE staff.

Leroy says that his perspective on his dialysis treatments has changed. “I don’t look at it as going to dialysis, now. It’s my job.... I go 3 days a week, I work 4 hours,” referring to the 4 hours that he spends on the dialysis machine at each session. On those days he is on a strict schedule: he gets up at 5:00 a.m., is out of the house at 6:30 a.m., and is on the dialysis machine at 7:00 a.m. At 11:00 a.m. he heads back home.

Dialysis is medical care that Leroy must do to stay alive because of his kidney failure. However, his decision to participate in the HOPE study represents another way that Leroy has continued his lifetime of service to others—people treated with dialysis stand to benefit from future HOPE research findings thanks to him and other HOPE study volunteers.

When asked if he would encourage other people to participate in clinical research studies like HOPE, Leroy responds: “Oh, definitely. I would give [the study] an A plus.”

ACKNOWLEDGMENTS

January 2023

Research

NIDDK gratefully acknowledges the researchers whose studies are described in this report, other study members, and the many volunteers who make this research possible.

Writing and Production

Overall Production

Julie A. Wallace, Ph.D., Office of Scientific Program and Policy Analysis

Rebecca J. Cerio, Ph.D., Office of Scientific Program and Policy Analysis

Highlights of Research Advances and Opportunities

Staff of the NIDDK Office of Scientific Program and Policy Analysis

Heather Rieff, Ph.D., Director

Lisa Gansheroff, Ph.D., Deputy Director

Julie A. Wallace, Ph.D., Deputy Director

Erica Bizzell, Ph.D.

Rebecca J. Cerio, Ph.D.

Sandeep Dayal, Ph.D.

Mary Hanlon-Tilghman, Ph.D.

Erica R. Hennes, B.A.

Sophia Jeon, Ph.D.

B. Tibor Roberts, Ph.D.

Megan Singh, Ph.D.

Jaime J. Smith, Ph.D.

Robert Tilghman, Ph.D.

Input from staff within NIDDK's scientific program and research divisions: the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; the Division of Kidney, Urologic, and Hematologic Diseases; the Division of Extramural Activities; and the Division of Intramural Research

Contributions from the NIDDK Office of Communications and Public Liaison

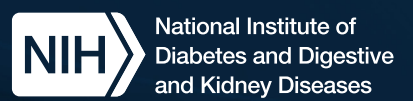
Heather Martin, M.P.H.

Alyssa Voss, M.P.H.

Contributions from the NIH Office of Communications and Public Liaison

Brian Doctrow, Ph.D.

For more information on NIDDK and its mission, and links to other sites, visit: www.niddk.nih.gov.



National Institute of
Diabetes and Digestive
and Kidney Diseases

NIH Publication Number: 23-DK-7962