

NIDDK

Recent Advances & Emerging Opportunities

Digestive Diseases and Nutrition

January 2023

This is a chapter from the NIDDK's Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK's mission and is available at:

www.niddk.nih.gov/about-niddk/strategic-plans-reports/niddk-recent-advances-emerging-opportunities



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

TABLE OF CONTENTS

DIGESTIVE DISEASES AND NUTRITION.....42

Important Roles of Bile Acids
in Health and Disease.....44

Causes and Effects of Nonalcoholic
Fatty Liver Disease45

Investigating How Gut Cells Sense
and Communicate with Their Environments47

Factors Involved in Inflammatory Bowel Disease....49

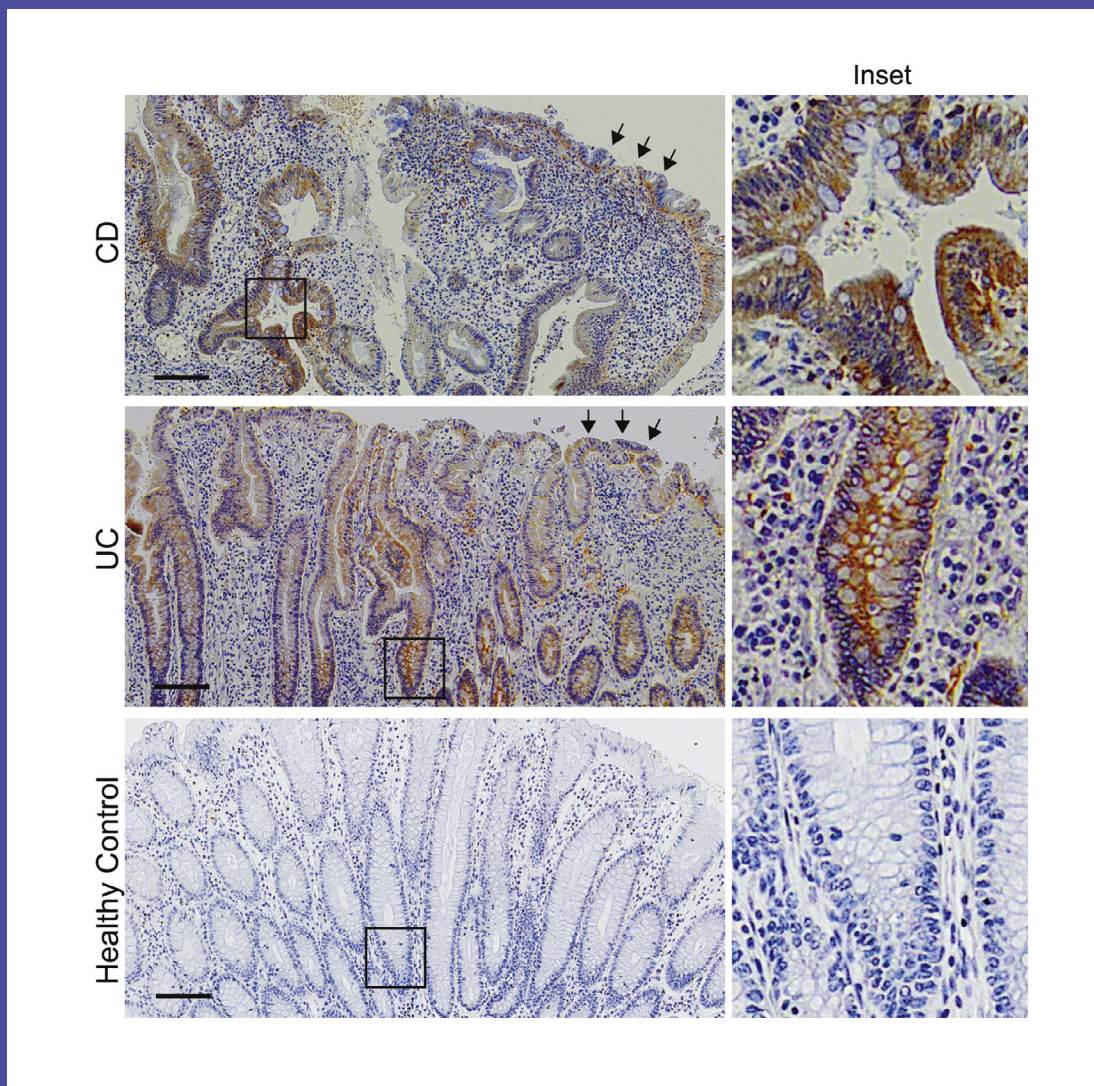
Understanding and Treating Intestinal Infections ... 50

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



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.

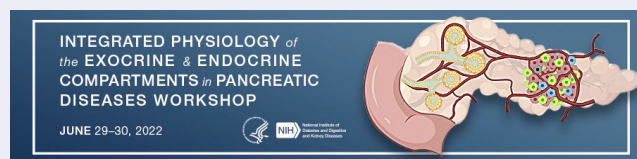
Understanding the Pancreas, Inside and Out: Efforts in Pancreatic Disease

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>.

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!”