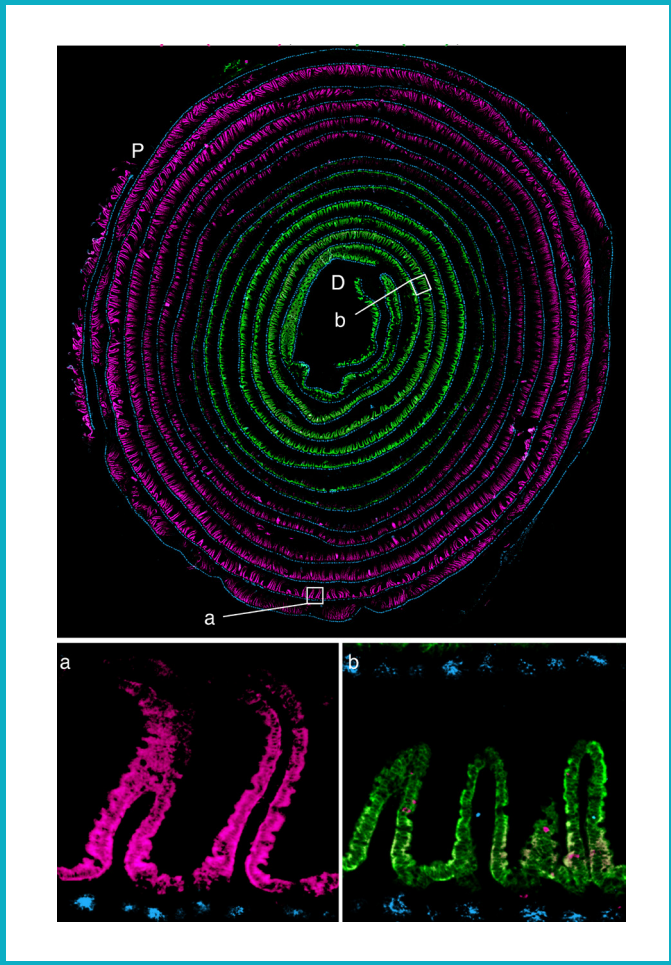

# NIDDK
## Recent Advances & Emerging Opportunities
## 2025

# Digestive Diseases and Nutrition

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: 25-DK-7962




Any basic anatomy class will teach that there are three regions of the small intestine: the duodenum, the jejunum, and the ileum. These regions were first defined in ancient times, mostly by their overall appearance. As described in this chapter, researchers have challenged this conventional wisdom by using modern molecular-based techniques to map out the entire length of both the human and mouse small intestine. They found that they are divided into not three, but five separate regions, with each region performing a unique step in digestion. The top panel in the image above shows a mouse small intestine, coiled tightly to display its entire length from its beginning where it joins the stomach ("proximal," labeled as "P"), to its end where it empties into the colon ("D," or "distal"). The colors in the image show three out of the five regions: The pink color marks two regions that are involved in absorbing fatty acids, and the green color labels a region that is important for absorbing cholesterol. The bottom two panels are higher magnifications of the sections marked as "a" and "b" in the top panel, showing the fingerlike projections (villi) in the intestinal lining that are critical for absorbing nutrients. Because gastrointestinal diseases commonly affect some intestinal regions more than others, this new way of looking at the small intestine is likely to be valuable for understanding, diagnosing, and treating disorders of the digestive system.

*From: Zwick RK, Kasparek P, Palikuqi B,...Klein OD. Epithelial zonation along the mouse and human small intestine defines five discrete metabolic domains. Nat Cell Biol 26:250-262, 2024, Springer Nature.*

# 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 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments in the United States each year.[1] Similarly, analyses with 2021 national inpatient samples identified 3.6 million hospitalizations with a primary diagnosis of digestive diseases and 15.6 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 16.2 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling $123.8 billion in 2021.[3] (Note that, similar to 2020 statistics during the pandemic, the 2021 statistics are likely underestimates due to continuing pandemic-related health care challenges.)

***Annual estimates of the burden of digestive diseases list these diseases as the primary diagnosis in 66 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments.***

Inflammatory bowel disease (IBD), an umbrella term for chronic and painful intestinal diseases that include Crohn's disease and ulcerative colitis, is marked by damaging intestinal inflammation that can cause rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. IBD often strikes early in life, with a peak age of onset in adolescence or young adulthood. The continued discovery of predisposing genetic variations, potential autoimmune and microbial influences, and new methods to repair damaged intestinal tissue will help predict the best course of treatment and catalyze the design of novel, more personalized therapeutic strategies.

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

---

[1] *Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey (NAMCS). https://www.cdc.gov/nchs/namcs/about/index.html. Accessed October 16, 2024.*

[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 7, 2024.*

[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 7, 2024.*

Diseases of the stomach and intestines also include peptic ulcer disease, which is typically caused by infection with the bacterium *Helicobacter pylori* or use of nonsteroidal anti-inflammatory drugs. Other stomach and intestinal disorders include functional GI disorders, such as irritable bowel syndrome (IBS), which can cause abdominal pain and altered bowel habits. Gastroesophageal reflux disease, in which caustic stomach acids rise up into the esophagus, can lead to a heightened risk of esophageal cancer. Gastroparesis is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. Fecal incontinence, or impaired bowel control, is a very prevalent condition, and because it is difficult to talk about, many people suffer without seeking treatment. Scientists continue to strive for a deeper understanding of the causes of GI disorders, which will lead to improvements in diagnosis and management. In individuals with celiac disease, the immune system reacts to ingestion of gluten—a protein component of wheat, barley, and rye—resulting in chronic diarrhea, bloating, anemia, and, in children, slower growth and short stature. The only current treatment for celiac disease is maintenance of a strict gluten-free diet, which is difficult for many people. Research advances in the understanding of genes and environmental triggers that are involved in the development of celiac disease may contribute to improved diagnosis and treatment.

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

The microbes that inhabit the GI tract—also known as the gut microbiome—are important in maintaining the balance between digestive health and disease. These bacteria, viruses, and other microorganisms can affect long-term health and nutritional status, depending on their interactions with each other, with intestinal cells, and with nutrients ingested by their human host. Disruptions in this microbial ecosystem are associated with diseases such as IBD or infections by the harmful bacterium *Clostridium difficile*. Scientists are gaining insights into the ways these GI microbes influence the development and function of the digestive tract and other systems throughout the body, such as those with immune and metabolic functions, as well as how the composition of the GI microbial community changes with factors such as age, geography, diet, and antibiotic usage. In acute and chronic pancreatitis, digestive enzymes attack the pancreas from within, causing inflammation, loss of function, and severe pain. Advanced pancreatitis can be debilitating and may lead to cancer or diabetes, and because pancreatitis is difficult to detect in its early stages, many cases are advanced by the time they are diagnosed. Research has elucidated genetic and other factors contributing to pancreatitis that may lead to ways to treat or prevent this disease.

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

*In recent years, nonalcoholic fatty liver disease, also referred to as metabolic dysfunction-associated steatotic liver disease, has been increasingly diagnosed in children and adults in the United States, concurrent with rising rates of overweight and obesity.*

NIDDK also funds research on nutrition-related disorders, including those that involve specific, inherited alterations in nutrient metabolism. NIDDK-supported research has enhanced knowledge of how these nutritional disorders develop and how they can best be treated. Investigators also conduct basic, clinical, and translational research on the requirements, bioavailability, and metabolism of nutrients and other dietary components to understand dietary needs in health and disease. NIDDK staff work collaboratively with representatives from across NIH, including in NIH's Office of Nutrition Research, to advance nutrition research efforts.

## EXPLORING INTESTINAL FUNCTION

**Study Upends Conventional Wisdom by Revealing Five Intestinal Regions:** A recent study has provided a new perspective on the small intestine in humans and mice, showing its length is divided into five functional regions, rather than the conventional three, with each region having a specific role in digestion.

Since ancient times, the human small intestine has traditionally been divided into three regions: the duodenum, the jejunum, and the ileum. Each segment is believed to have specific roles in digestion, working together to break down food and absorb nutrients in a stepwise manner. Exactly how this division of labor works is unclear, however, because the boundaries separating the three regions are not well defined, and it is difficult to map out all the different steps of digestion.

*A recent study has provided a new perspective on the small intestine in humans and mice, showing that its length is divided into five functional regions, rather than the traditional three, each having a specific role in digestion.*

One way to gain a better understanding of how the work of the small intestine is divided along its length would be to compare gene activity from many different regions of the intestine, since cells use different combinations of genes to perform different tasks—like using a specific set of tools from a toolbox. Researchers recently did this comprehensive analysis by collecting samples spanning the entire length of the intestine—from both female and male mice and humans—and comparing gene activity among enterocytes (intestinal cells that absorb nutrients), with the help of a type of computational artificial intelligence called "machine learning" that can be used to identify patterns in complex data. They mapped the different gene activity to specific locations, creating a kind of atlas that shows all the functional regions of the intestine. They found that the small intestine in both mice and humans is actually divided into five functional regions (which they labeled A to E), rather than the conventional three, each with its own population of enterocytes that specialize in processing specific types of nutrients. For example, the cells in region C showed higher activity in genes important for processing carbohydrates, while region E appeared to be important for processing cholesterol. Experiments in mice showed that the activity of genes associated with each region was affected by diet; genes associated with region C were boosted in response to a diet high in carbohydrates, for instance. The researchers also identified three populations of intestinal stem cells that are programmed to give rise to all the enterocytes in each region, which is important because knowing the origin of these cells could provide the basis for future therapies that aim to help heal the intestine.

Overall, these findings present a new, more complex view of the small intestine. Because gastrointestinal diseases commonly affect some intestinal regions more than others, this knowledge is likely to be valuable for understanding, diagnosing, and treating disorders of the digestive system.

*Zwick RK, Kasparek P, Palikuqi B,...Klein OD. Epithelial zonation along the mouse and human small intestine defines five discrete metabolic domains. Nat Cell Biol 26: 250-262, 2024.*

## UNDERSTANDING GUT INFLAMMATION

**Gut Bacteria and T Cells of the Immune System Contribute to Development of Serious Intestinal Inflammation, Colitis, After Certain Cancer Treatments:** Researchers recently developed a mouse model to analyze how colitis (a painful and often serious inflammation of the large intestine) develops following certain cancer treatments. Cancer cells frequently produce chemical signals that dampen the anti-tumor response of the immune system. Targeting these signals with a group of drugs that work via a process called immune checkpoint blockade (ICB) allows immune cells to remain active against the cancer. However, these drugs can also lead to unrestrained immune cell activation in the gut. Overactivity of the gut's immune

system can lead to inflammation and colitis, which can be so severe that ICB therapy must be halted. Understanding why this off-target effect occurs can help uncover options for preventing colitis with ICB therapy and ultimately make this cancer treatment more tolerable and effective.

*Scientists have discovered why certain cancer drugs can cause intestinal inflammation, paving the way for developing better therapies.*

For this study, researchers first developed an animal model that mimicked human ICB-associated colitis. Laboratory mouse colonies are typically maintained under "specific pathogen–free" conditions to prevent disease-causing microbes from interfering with experimental results. However, the lack of environmental pathogens also results in a community of microbes in the gut of these animals ("the microbiome") that does not resemble what is seen in the wild. This can affect how the mice respond to both disease-causing stimuli and therapeutic drugs. Therefore, the researchers utilized mice with microbiomes obtained from wild-caught mice, as this microbiome helps the animals more closely mimic human immune responses. These mice developed colitis when given ICB therapy, which enabled the scientists to study the role of the gut-resident immune cells in this pathology. The scientists found that one group of immune cells, T cells, was particularly affected in the guts of mice given ICB. There are several types of T cells, some of which cause inflammation while others work to regulate or turn off immune responses. Researchers found that mice with ICB-induced colitis had lower numbers of the regulatory T cells and higher activation of the inflammatory T cells. This increased the amount of a protein called interferon gamma, which causes intestinal inflammation. Importantly, they found that a small modification to the ICB drug could prevent these changes in the gut by avoiding inflammatory T-cell activation while still maintaining the drug's tumor-fighting abilities.

These insights into why ICB causes colitis could help scientists continue to develop new cancer therapies with fewer off-target consequences, making cancer treatments more tolerable and effective. The results also provide a deeper understanding of colitis, including the role of the microbiome, which could lead to the development of more therapies for all people living with this debilitating condition.

*Lo BC, Kryczek I, Yu J,...Nuñez G. Microbiota-dependent activation of CD4⁺ T cells induces CTLA-4 blockade-associated colitis via Fcγ receptors. Science 383: 62-70, 2024.*

**A Genetic Risk Factor for Crohn's Disease Could Disrupt Intestinal Healing:** Researchers have discovered how a genetic risk factor for Crohn's disease can slow down healing of damaged intestinal tissue in mice, providing new insight into the healing process and offering ways to pursue novel treatments.

Crohn's disease, a form of inflammatory bowel disease, is a chronic (long-lasting) disease that causes painful inflammation in the gut. This inflammation leads to tissue damage, resulting in patchy lesions that can develop anywhere in the digestive tract. Scientists have been trying to understand why these lesions occur—and mend so slowly—with the hope that new treatments can be developed. Research has shown that blood clotting within lesions typically launches a sequence of events that ultimately causes the cells of the intestinal lining (epithelial cells) to move into and fill the site of injury. However, genetic variations—particularly those found more commonly in people with inflammatory bowel disease—could cause defects in this process. The specific effects of these variations have been difficult to identify, though, because scientists are still trying to piece together all the steps that link blood clotting to epithelial cell movement and ultimately the repair of intestinal tissue.

*Researchers have discovered how a genetic risk factor for Crohn's disease can slow down the healing of damaged intestinal tissue, offering new paths toward the development of treatments.*

Using a mouse model and blood samples from people with Crohn's disease, researchers recently uncovered an important component of the gastrointestinal healing puzzle. They focused on a genetic variation associated with a higher risk of Crohn's disease that affects a protein known to play an important role in the wound-healing process. This protein, called hepatocyte growth factor activator (HGFAC), is switched on by blood clotting. HGFAC then activates another protein called macrophage-stimulating protein (MSP), which, the scientists found, triggers changes in epithelial cells that enable them to move into the damaged tissue. Additional

experiments showed these mobile epithelial cells release a chemical called retinoic acid, which stimulates the rebuilding of the intricate molecular network that surrounds cells and helps maintain the tissue's shape. The scientists found that the genetic variation results in a modified version of HGFAC that cannot effectively activate MSP, thereby crippling the movement of epithelial cells, inhibiting the release of retinoic acid, and slowing down the tissue's ability to heal itself.

The researchers also showed that the HGFAC variation affected MSP activation in blood samples from people who carry the variation, but more research is needed to confirm that this genetic variation has the same effect in people with Crohn's disease as it does in mice. Nevertheless, these results do suggest there may be ways to bypass the defect, such as providing active MSP. These findings also help researchers understand the complicated steps involved in repairing damaged tissue, which could lead to additional new therapies, not only for Crohn's disease but also for other diseases that feature defects in healing.

*Nakata T, Li C, Mayassi T,...Xavier RJ. Genetic vulnerability to Crohn's disease reveals a spatially resolved epithelial restitution program. Sci Transl Med 15: eadg5252, 2023.*

## UNCOVERING KEY PLAYERS IN CELIAC DISEASE

**New Celiac Disease Model Reveals Insights About Immune Response to Gluten:** Using intestinal cells from study volunteers, researchers have developed a more accurate and personalized laboratory model of celiac disease, leading to the discovery of a chemical signal's important role in the gut's immune response to gluten.

Celiac disease is caused by gut immune cells reacting abnormally to gluten in dietary grains such as wheat, rye, and barley. The resulting inflammation ravages the small intestine, destroying epithelial cells lining the intestine and causing abdominal pain, diarrhea, and other potentially severe symptoms. Finding ways to treat celiac disease—other than adhering to a very strict, burdensome gluten-free diet—has been challenging, largely because of a lack of accurate laboratory models to help scientists understand the disease and test potential therapeutics. Typically, intestinal cells grown in the lab do not replicate the environment of the human gut, which includes multiple layers consisting of not only epithelial cells but also immune cells that play a critical role in celiac disease.

Recently, a team of researchers, including scientists from NIDDK's Intestinal Stem Cell Consortium, developed the first laboratory model that faithfully replicates the complex interactions between human intestinal epithelial and immune cells. The cells were collected from intestinal biopsies provided by 135 female and male volunteers (81 with diagnosed celiac disease and 54 without the disease but who had undergone biopsies for a different condition). The majority of participants were female, as celiac disease is more common in females than in males. The researchers discovered how to cultivate the cells in clusters, called "organoids," in a way that enabled survival of both epithelial cells and underlying immune cells. When gliadin (a component of gluten) was added to the organoids from people with celiac disease, the immune cells reacted rapidly and similarly to how they would in the body, attacking the epithelial cells. The researchers found that a chemical called IL-7, released by the organoids' immune cells in response to gliadin, is vital to their destruction of the epithelial cells. Importantly, the researchers confirmed the validity of this discovery by showing that IL-7—which was not previously associated with celiac disease—is ramped up in the intestinal samples of people with active disease, which means it could potentially be a target for therapy.

*Researchers have developed a more accurate laboratory model of celiac disease using human cells, leading to new insights into mechanisms underlying the disease.*

As demonstrated in this study, this promising model can help identify the important players in celiac disease. It will also likely be a useful tool to test potential therapeutics before moving them forward into more complicated and expensive clinical trials. And, because the cells are from a person with celiac disease, it may eventually be possible to predict whether a certain therapy has a better chance of working in a specific individual—a step toward developing personalized medicine approaches for celiac disease.

*Santos AJM, van Unen V, Lin Z,...Kuo CJ. A human autoimmune organoid model reveals IL-7 function in coeliac disease. Nature 632: 401-410, 2024.*

## TREATING DIARRHEAL DISEASE IN CHILDREN

**Addressing Provider Misperceptions Could Limit Deaths in Children From Diarrheal Diseases:** Researchers recently worked to understand why health care providers do not prescribe a common treatment for childhood diarrheal diseases despite knowledge of its benefits. Diarrhea is a leading cause of death in young children worldwide. A low-cost, widely available treatment called oral rehydration salts (ORS)—a mix of sugar and electrolytes dissolved in water—is available and well accepted, but health care providers do not prescribe it in almost half of cases where it could be efficacious, despite these providers identifying it as the standard of care.

To study barriers that prevent the prescription of ORS, researchers implemented a randomized controlled trial in India, where nearly a quarter of the world's diarrhea-associated deaths in children occur despite more than 75 percent of caregivers seeking medical advice for the condition. The study aimed to determine if financial incentives (*i.e.*, clinics receiving higher payments for antibiotics versus ORS prescribing), supply issues, or patient prescribing preferences influenced whether a health care provider recommended ORS. With the approval of an institutional review board, trained male actors sought care from 2,282 private, mostly male health care providers across 253 medium-sized towns throughout two, culturally diverse northern and southern states of India. These actors pretended to be the father of a 2-year-old child with diarrhea, describing details to suggest the underlying cause was viral instead of bacterial, therefore warranting treatment with ORS over antibiotics. Different scripts were employed at different visits to test the potential barriers to ORS prescription.

The results indicate that provider misperceptions of patient preferences are the strongest barrier to ORS prescription. When the people portraying caregivers signaled a preference for ORS, they were twice as likely to be given it. This perceived patient preference was 6 to 10 times more important than either financial incentives or supply issues in explaining the providers' underutilization of ORS, and it was especially important when the would-be caregivers visited clinics that employed providers with no formal medical training. Importantly, these results could extend to other areas of the world where diarrheal diseases are common or to countries where health care providers receive limited formal training.

This study helps to identify why ORS prescription for treating childhood diarrhea is low despite its known benefits. These findings will hopefully inform the design of interventions to encourage ORS use, either through informing health care providers or promoting more communication of preferences by caregivers that will ultimately benefit thousands of young people at risk of diarrhea around the globe.

*Wagner Z, Mohanan M, Zutshi R, Mukherji A, Sood N. What drives poor quality of care for child diarrhea? Experimental evidence from India. Science, 383: eadj9986, 2024.*

## UNDERSTANDING HOW DIET AFFECTS HEALTH

**Feeding the Microbiome Helps Children Grow After Malnutrition:** A recent study found a diet that included complementary foods tailored toward promoting the expansion of healthy bacteria in infants' guts can help increase growth after malnutrition. Malnutrition remains a global public health concern, as it accounts for nearly half of deaths in children under the age of 5. Infants that experience either acute or prolonged malnutrition have an increased risk of infection, dampened immune response, and physical and cognitive growth deficits that can persist through the lifespan.

*Researchers have found a diet containing a complementary food formulated to nurture the gut microbiome can increase growth in infants with malnutrition in the early years of life.*

The bacteria that populate the gut—referred to as the "microbiome"—play an important role in growth and development. Children that experience malnutrition have decreased growth and diversity of the microbiome as they switch from milk to solid foods, which has been shown to slow child development. Therefore, researchers aimed to determine if early dietary intervention to promote a healthy microbiome could help overcome malnutrition-associated growth deficits. A total of 118 12- to 18-month-old Bangladeshi male and female infants with malnutrition participated in a 3-month study that compared feeding of microbiome-promoting complementary food containing local ingredients with a conventional supplemental food, in addition to the infants' background diet of solid food or breastmilk. Despite

the microbiome-promoting food having less calories than the conventional one, infants receiving the former had a significantly higher improvement in their rate of weight gain compared to those given the latter. Analysis of the infants' stools revealed specific types of bacteria were associated with growth of the children, and the abundance of these changed in the children consuming the microbiome-promoting food. Additionally, the stool analysis showed that the microbiome-promoting food changed how the bacteria convert carbohydrates (one of the basic building blocks of food) into energy, creating different byproducts that could affect both the gut bacteria and the infant.

This study provides some clues as to why a microbiome-promoting supplemental food proves superior to the conventional one for increasing growth in these infants with malnutrition. Additionally, it suggests that different bacteria may process carbohydrates from food in different ways to promote child growth. This may help inform efforts to create even better, culturally relevant diets for those who are living with malnutrition.

*Hibberd MC, Webber DM, Rodionov DA,…Gordon JI. Bioactive glycans in a microbiome-directed food for children with malnutrition. Nature 625: 157-165, 2024.*

**Switching to Vegan or Ketogenic Diet Rapidly Impacts Immune System and Metabolism:** Researchers observed rapid and distinct immune system changes in a small study of people who switched to a vegan or a ketogenic (also called keto) diet, opening the way to potential further study to determine effects on health. The vegan diet eliminates animal products and tends to be high in fiber and low in fat, while the keto diet is a low-carbohydrate diet that is generally high in fat. Understanding of how specific foods impact the human immune system and microbiome (communities of microbes living in the gut) has been limited. Therapeutic nutritional interventions—which involve changing the diet to improve health—are also not well understood, and few studies have directly compared the effects of different dietary patterns on the immune system.

This study comparing immune system and other responses to vegan and keto diets was conducted by researchers from NIDDK and NIH's National Institute of Allergy and Infectious Diseases at the Metabolic Clinical Research Unit in the NIH Clinical Center. The 20 adult participants were diverse with respect to ethnicity, race, gender, body mass index, and age. Both diets contained a healthy amount of non-starchy vegetables and minimized highly processed foods. Each person ate as much as desired of one diet (vegan or keto) for 2 weeks, followed by as much as desired of the other diet for 2 weeks. People on the vegan diet voluntarily consumed fewer calories than those on the keto diet. Throughout the study, blood, urine, and stool were collected for analysis. The effects of the diets were examined using a "multi-omics" approach that analyzed multiple data sets to assess the body's biochemical, cellular, metabolic, and immune responses, as well as changes to the microbiome. Participants remained on site for the entire month-long study, allowing for careful control of the dietary interventions. The scientists found that the vegan diet prompted responses linked to innate immunity—the body's non-specific first line of defense against pathogens. The keto diet prompted responses associated with adaptive immunity—pathogen-specific immunity built through exposures in daily life and vaccination. Metabolic shifts in the participants and their microbiomes were also observed. For example, the keto diet was associated with changes in participants' amino acid metabolism—an increase in human metabolic pathways for the production and degradation of amino acids and a reduction in microbial pathways for these processes—which might reflect the higher amounts of protein consumed by people on this diet.

*Only a few weeks on either a vegan or ketogenic diet prompted distinct changes in immune function and metabolism in adult study participants.*

The distinct metabolic and immune system changes caused by the two diets were observed despite the diversity of the participants, which shows that dietary changes can cause consistent effects to multiple pathways in the body. This study demonstrates that the immune system responds surprisingly rapidly to nutritional interventions. More research is needed to determine if these changes are beneficial or detrimental and what effects they may have on nutritional interventions for different diseases. Such research could lead to the development of more personalized diets to prevent or treat disease.

*Link VM, Subramanian P, Cheung F,…Belkaid Y. Differential peripheral immune signatures elicited by vegan versus ketogenic diets in humans. Nat Med 30: 560-572, 2024.*

*This writeup was adapted from an NIH News Release authored by the NIDDK Media Team and NIAID News & Science Writing Branch.*

## PREVENTING PANCREATIC DISEASE

**A Pancreatic Stent Lowers Risk of Pancreatitis Following Endoscopic Procedure:** A large clinical trial recently found that the combination of an anti-inflammatory drug and the insertion of a pancreatic stent is more effective than the anti-inflammatory drug alone at preventing pancreatitis after an endoscopic procedure called endoscopic retrograde cholangiopancreatography (ERCP).

A series of ducts connects the liver, gallbladder, and pancreas to the intestine to allow the flow of bile acids and digestive enzymes into the gut. ERCP is a valuable and effective procedure that uses an endoscope (a long, thin, flexible tube fitted with a tiny camera), in combination with X-ray imaging, to see and treat disorders of these biliary and pancreatic ducts. Pancreatitis—a painful inflammation of the pancreas—is one of the most common and potentially serious complications associated with ERCP, with risk varying from person to person. The medical community recommends several measures to prevent pancreatitis following ERCP, including hydration and anti-inflammatory drugs such as indomethacin, which has shown some promise to be an effective deterrent. It is also recommended that individuals considered to be at high risk for ERCP-associated pancreatitis be given a temporary stent (a small, tubular support) in the pancreatic duct, in addition to indomethacin, although the stenting procedure also carries risk of complications. It was not clear, however, whether indomethacin alone is as effective as the combination treatment of indomethacin plus a pancreatic stent. Importantly, treatment with indomethacin alone, if equally effective as the combination treatment, would avoid the additional risks and high costs associated with inserting a stent.

*A large clinical trial recently found that administering an anti-inflammatory drug along with a pancreatic stent is more effective at preventing pancreatitis after an endoscopic procedure than the anti-inflammatory drug alone.*

To compare the effectiveness of these two approaches, 1,950 women and men deemed to be at high risk for ERCP-associated pancreatitis—at 20 sites across the United States—were given either the combination treatment (indomethacin plus a pancreatic stent) or indomethacin alone when they underwent ERCP. The researchers found that the group receiving indomethacin alone had a 32 percent higher risk of developing post-ERCP pancreatitis (14.9 percent of those who received indomethacin alone developed pancreatitis compared to 11.3 percent of those who received the combination treatment). This means the combination treatment was more effective than indomethacin alone, and people at high risk for pancreatitis following ERCP would likely benefit from a pancreatic stent. More research is needed to develop additional (and perhaps even more effective) ways to limit the risk of pancreatitis following ERCP and to better understand and predict who is more likely to develop pancreatitis. Nevertheless, despite the preliminary evidence suggesting that indomethacin may eliminate the need for stent placement, the results of this important, large, multiregional clinical trial support pancreatic stent placement in addition to indomethacin in high-risk patients, in accordance with clinical practice guidelines.

*Elmunzer BJ, Foster LD, Serrano J,...Durkalski-Mauldin V; on behalf of the SVI Study Group. Indomethacin with or without prophylactic stent placement to prevent pancreatitis after ERCP: a randomized non-inferiority trial. Lancet 403: 450-458, 2024.*

## DISCOVERING FACTORS INVOLVED IN LIVER INFLAMMATION

**Key Protein Drives Liver Inflammation and Fibrosis:** Researchers identified the role of a particular protein in orchestrating the processes of liver inflammation and fibrosis that occur as part of the liver disease nonalcoholic steatohepatitis, or NASH (also referred to as metabolic dysfunction-associated steatohepatitis, or MASH), in studies in mice and cells. Nonalcoholic fatty liver disease (also referred to as metabolic dysfunction-associated steatotic liver disease) and its more severe form of NASH are common diseases experienced by adults and children in the United States and around the world. A leading cause of liver transplantation and liver cancer, NASH is marked by excess fat accumulation in the liver, inflammation, and fibrosis, or scar tissue formation. In addition to diet and exercise, the first drug to treat NASH with liver scarring was recently approved by the U.S. Food and Drug Administration (FDA). Further research on disease pathways could lead to the identification of new potential therapeutic targets and strategies to prevent scarring and other serious effects of the disease.

The liver inflammation and scarring of NASH are driven by a complex interplay of factors among and

within liver and immune cells. Mechanisms driving this process, or how to halt or possibly reverse it, are not fully understood. One research team looking at liver disease processes set their sights on a protein secreted by liver cells called CYR61. This protein is produced in greater quantities in livers from people with NASH, and is known to communicate with nearby immune and fibrosis-causing cells. However, the protein's effects on liver fibrosis are unclear. The studies were conducted in a mouse model of NASH, in which the mice are fed a diet high in fat, cholesterol, and sugar, resulting in excess liver fat and injected with a chemical that simulates fibrosis. Both female and male mice, some of which were genetically altered to lack the CYR61 protein in the main functional cells of the liver, were used for some of the studies, while only male mice were used for others. The researchers observed that, among mice lacking CYR61, those fed the NASH-inducing diet had reduced liver inflammation and fibrosis. By marking and examining specific cell types in studies of the mice and of cells grown in dishes, the researchers showed that CYR61 activated certain immune cells to promote inflammation and fibrosis. Conversely, blocking CYR61's activity with an antibody reduced fibrosis.

This research illuminates the cellular pathways utilized by CYR61 to promote liver inflammation and fibrosis. CYR61 and the cellular pathways it affects could serve as targets for developing future treatments that improve outcomes and limit the progression of NASH.

*Mooring M, Yeung GA, Luukkonen P,...Yimlamai D. Hepatocyte CYR61 polarizes profibrotic macrophages to orchestrate NASH fibrosis. Sci Transl Med 15: eade3157, 2023.*

**Understanding the Effects of Genetic Differences on Liver Immune Cells Involved in Inflammation:** Researchers studied a type of liver immune cell involved in inflammation and parsed the impacts of genetic differences between mice on the expression of genes within these cells under different conditions, providing clues as to how these cells may affect liver disease progression. The liver contains different types of macrophages, a type of immune cell that engulfs pathogens and activates other immune cells. Kupffer cells, named for the scientist who discovered them, are the most common type of liver macrophage, and play a key role in disease processes such as inflammation associated with the liver disease nonalcoholic steatohepatitis, or NASH (also referred to as metabolic dysfunction-associated steatohepatitis or MASH). Still unknown is exactly how Kupffer cells translate signals of infection and injury originating outside and within the cell into an inflammatory response.

Delving deeply into the complex cellular machinery at work, researchers used three genetically different mouse strains—one that is resistant to NASH and two that are susceptible to NASH to varying degrees when fed a diet high in fat, cholesterol, and sugar—and compared the activity of genes in the mice. They observed that Kupffer cells in these strains responded differently to this diet, in terms of regulating their activation of certain genes. They then asked what factors influence gene activity in the Kupffer cells in response to different conditions by comparing the NASH-resistant mice with the mice that were the most susceptible to NASH. They found that the answer was: It depends. Under conditions where cells were maintaining normal function, the researchers found that much of the gene activity variation between the Kupffer cells of the mouse strains resulted from the influence of factors coming from outside of the Kupffer cells, such as signals from other cells, with some effects from factors within the Kupffer cells acting indirectly to influence gene expression. But when the researchers tested a different inflammatory condition in response to a bacterial protein, they found that strain-specific responses within the Kupffer cells derived more from the genetic variations within the Kupffer cells having direct effects on the genes that were differentially active. This study shows how genetic differences associated with disease risk can influence cell functioning—either by altering gene expression through direct or indirect effects within the cells of interest or by influencing expression of factors in different cell types that can then act on the cells of interest. This insight can lead to a better understanding of disease processes and may have implications for developing new therapies.

These findings are relevant not only to defining cellular mechanisms involved in liver inflammation and disease, but also may be applied to studies of other cell types and disease processes.

*Bennett H, Troutman TD, Zhou E,...Glass CK. Discrimination of cell-intrinsic and environment-dependent effects of natural genetic variation on Kupffer cell epigenomes and transcriptomes. Nat Immunol 24: 1825-1838, 2023.*

## PREDICTING LIVER DISEASE OUTCOMES

**Using Noninvasive Liver Stiffness Measurement to Predict Liver Disease Outcomes:** In a study of adults with nonalcoholic fatty liver disease or NAFLD (also

referred to as metabolic dysfunction-associated steatotic liver disease or MASLD), NIDDK's NASH Clinical Research Network found that liver stiffness, measured noninvasively, may serve as an indicator for risk of outcomes such as liver cancer, liver failure requiring transplantation, or death. NAFLD, currently the most common form of liver disease in the United States, is a condition where fat accumulates in the liver. Its most severe form—known as nonalcoholic steatohepatitis, or NASH (also referred to as metabolic dysfunction-associated steatohepatitis or MASH)—involves excess fat accumulation in the liver, as well as inflammation and fibrosis (scar tissue formation), and is the leading reason for adult liver transplantation in the country. Early detection of liver disease is challenging because it requires a biopsy, and monitoring disease progression requires a series of biopsies. Researchers have been working for years on developing noninvasive but highly informative ways to diagnose and monitor the liver health of people with NAFLD.

***A study in adults participating in NIDDK's NASH Clinical Research Network found that liver stiffness measures may serve as a non-invasive indicator for risk of clinical outcomes from liver disease progression.***

In this study, a research team assessed whether measuring liver stiffness using a noninvasive technology called vibration-controlled transient elastography, or VCTE, could accurately predict increasing or decreasing risk of chronic liver disease. They studied more than 1,400 women and men, approximately 80 percent identifying as White and 11 percent as Hispanic, participating in the NASH Clinical Research Network at nine clinical centers across the United States. Participants received baseline and annual exams with liver stiffness measures for an average of over 4 years, during which information was collected on the number and types of liver-related adverse events they experienced. These events included liver cancer, liver failure requiring transplantation, liver-related death, and other clinical outcomes of NAFLD. The researchers observed that people whose liver stiffness measures increased during the study above a certain threshold—suggesting liver disease progression—had a four-fold increase in liver-related events compared to people whose liver stiffness remained under the threshold. Conversely, people whose liver stiffness measures started above the threshold but fell below it during the same period had a 75 percent decrease in their risk of liver-related events relative to people whose liver stiffness stayed above the threshold.

Based on these study results, the investigators view measures of liver stiffness over time as a useful noninvasive indicator of the direction of clinical outcomes from NASH. These measures can be used to improve clinical care by helping to identify people with NAFLD at risk for worse outcomes and to facilitate testing responses to new therapies in clinical trials.

*Gawrieh S, Vilar-Gomez E, Wilson LA,...Chalasani N; for the NASH Clinical Research Network. Increases and decreases in liver stiffness measurement are independently associated with the risk of liver-related events in NAFLD. J Hepatol 81: 600-608, 2024.*

FEATURE

# Study Explores Factors Underlying Healing of Crohn's Disease in Children

A new NIDDK-supported clinical trial is looking to better understand why some children with Crohn's disease experience complete healing after receiving a common therapy, while others do not.

Crohn's disease is a form of inflammatory bowel disease (IBD) that causes lesions in the lining of the small intestine and/or colon in both children and adults. Symptoms may include abdominal cramping, diarrhea, blood in the stool, weight loss, and delayed growth in children. While the cause is unclear, it is thought to stem from overactivity of the intestinal immune system in policing potential pathogens, so doctors typically use anti-inflammatory treatments to address the disease and ideally heal the gut. Some of the most common treatments inhibit the inflammatory molecule called TNF, but responses vary across individuals, and these treatments come with high costs and the risk of side effects. Some children with Crohn's disease treated with TNF-blocking drugs show complete intestinal healing, while others continue to experience symptoms or even progression of their disease, sometimes requiring surgery. Understanding the characteristics that determine whether the treatment will result in complete healing has the potential to profoundly influence patient care and outcomes.

To address this need for more knowledge, NIDDK launched a new study in 2023 called the Clinical, Imaging, and Endoscopic Outcomes of Children Newly Diagnosed with Crohn's Disease Study, or CAMEO. The study aims to identify features present at the time when children are diagnosed with Crohn's disease that can predict whether their disease will be healed in response to treatment. It is being conducted at 26 clinical centers researching IBD across the United States and Canada, in partnership with the hundreds of children ages 6 to 17 enrolled in the study and their families. The study is investigating the association between patients' pre-treatment clinical, radiologic (detectable with imaging such as MRI or X-ray), genomic, and microbial features and how well their bodies are able to completely heal in response to treatment. The children receive anti-TNF therapy for 1 year, guided by a computer program to optimize dosing for each patient. Participants provide periodic blood, stool, and tissue biopsy samples to measure pre-treatment factors and test for signs of inflammation. Study participants also undergo regular colonoscopies and a special type of MRI called magnetic resonance enterography, or MRE. These procedures allow the researchers to assess how much intestinal healing is occurring in response to the treatment. Currently, the study is continuing to enroll study participants, but once completed, the study's impact will be amplified through availability of data and samples to investigators in the broader research community for additional studies.

The hope of the CAMEO study is that its findings will help to determine the likelihood that pediatric Crohn's disease patients will experience responses and remissions with current treatments, as well as to inform future treatment development. These study efforts serve the larger goal of developing better ways to care for children with Crohn's disease.

FEATURE

# New Clinical Trial Aims to Compare Endoscopy Approaches for Preventing Esophageal Cancer

Esophageal cancer is one of the deadliest cancers in the United States. The disease starts when cancer cells form in the esophagus (the muscular tube that carries food and liquids from the mouth to the stomach), with symptoms usually not appearing until the cancer has spread to other organs. This makes the disease very difficult to treat, so major goals for NIDDK-supported scientists are to come up with ways to detect changes in esophageal cells before the cancer has a chance to develop and to compare approaches to intervene at these early stages to prevent cancer.

Prior studies have shown that one of the earliest changes that could lead to esophageal cancer is Barrett's esophagus, a relatively common condition wherein the cells in the esophagus take on characteristics of intestinal cells. Barrett's esophagus does not cause perceptible symptoms, though many with this condition also experience gastroesophageal reflux disease. While most people with Barrett's esophagus do not develop esophageal cancer, they are at higher risk for the disease.

When Barrett's esophagus transitions to cancer, it does so in a stepwise fashion. The first step is that the cells undergo dysplasia, or irreversible changes that typically start as "low-grade," which means the cells have some characteristics of cancer cells but are not defined as cancer. Low-grade dysplasia is fairly common in people with Barrett's esophagus, and only some people progress to the next step—"high-grade" dysplasia—in which esophageal cells look very abnormal and have a higher chance of becoming cancerous. As a preventive measure, doctors will routinely monitor the cells in Barrett's esophagus by surveillance endoscopy. This procedure uses a long, thin, flexible tube fitted with a tiny camera and other tools to see inside and collect small biopsy samples from the esophagus. If abnormal cells are found, doctors can use a treatment called endoscopic eradication therapy (EET) to remove the precancerous cells. Studies have shown that using EET is effective for preventing esophageal cancer in people with high-grade dysplasia, but it is unclear whether it should be used for low-grade dysplasia, since most cases of low-grade dysplasia do not progress to cancer, and EET is costly and carries risk of complications.

SURVENT
SURVEILLANCE VS ENDOSCOPIC ERADICATION THERAPY TRIAL

To determine whether EET would be more beneficial than the surveillance type of endoscopy alone for people with low-grade dysplasia, NIDDK is sponsoring a large, multi-center clinical trial called Surveillance Versus Endoscopic Eradication Therapy Trial (SURVENT). Adult participants with low-grade dysplasia will undergo either surveillance for 1 to 4 years or EET (followed by surveillance endoscopy). By monitoring (and treating) any progression toward cancer, the researchers can determine if there are benefits to using EET at this early stage.

The SURVENT trial also provides researchers with an opportunity to find new ways to predict if a person with Barrett's esophagus has a high chance of eventually developing esophageal cancer. Studies have shown that certain molecular and cellular markers linked to cancer can appear in some people with Barrett's esophagus years before dysplasia is detectable, which means these markers could act as very early warning signs that cancer is likely to develop in the future. Thus, another aim of the SURVENT trial will be to determine how accurately these markers predict if a person is at high risk for developing cancer, so appropriate treatment decisions can be made.

Overall, the SURVENT trial aims to help guide treatment decisions for Barrett's esophagus, with the ultimate goal of preventing esophageal cancer. It will also inform the management of Barrett's esophagus, improving the lives of millions of people in the United States living with this condition.

# Alicia: Crafting a Life With Gastroparesis

*Alicia is participating in the Gastroparesis Clinical Research Consortium, which aims to catalyze research and test new diagnostics and therapies for gastroparesis*

Dealing with a newly diagnosed disease is daunting—even more so during a global pandemic. In early 2020, at age 24, Alicia went to see a gastroenterologist for what she thought was worsening of the chronic heartburn she had experienced since adolescence. Her frequent symptoms of feeling overly full and nauseated were affecting her quality of life and ability to work. "It was getting to the point where I just wouldn't want to eat breakfast in the morning … because I was afraid that I was going to feel ill, and I wouldn't be able to get through my workday," she recalls. Her doctor prescribed different acid reflux medications and ran many tests, including one for gastric emptying that confirmed she had a chronic gastrointestinal (GI) motility disorder called gastroparesis—a potentially debilitating condition wherein the stomach empties too slowly. (For more information on gastroparesis, see the info box at the end of this feature.)

## ON THE OTHER SIDE OF CLINICAL RESEARCH

Alicia found herself navigating a new and unfamiliar diagnosis as the COVID-19 pandemic lockdowns began in March 2020. "I got diagnosed right when everything shut down, so I kind of was handed a diet, and it was like, 'We'll see you when the world opens back up,'" she says.

As a lab researcher with a biology degree working at a pharmaceutical company, Alicia was knowledgeable about clinical research. But even for someone with her background, being on the other side as a patient proved challenging in the months after her diagnosis as she continued to experience symptoms while taking the prescribed medications and consulting with a nutritionist.

In December 2020, Alicia saw Dr. Henry Parkman, a leading gastroparesis specialist at Temple University. He prescribed a targeted treatment plan for her type of gastroparesis, which is "idiopathic," or of unknown cause. Like many individuals with these types of disorders, Alicia's treatment journey was not straightforward. After trying a few different medications, her nausea and vomiting persisted, so in 2022, she underwent surgery to widen the opening between her stomach and small intestine. Simultaneously, surgeons placed a gastric stimulator—an electrical device that sends mild pulses to the stomach—in Alicia's abdomen. The surgeries helped, but she continued experiencing nausea, acid reflux,

and weight loss—a common problem for people with gastroparesis. Reluctantly, she had another surgery to place a plastic jejunostomy tube, or J tube, into her small intestine so she could directly ingest nutrients. Afterwards, she was hospitalized while recovering from a postoperative ileus, a potential surgical complication where the bowels stop moving, and was prescribed medication for severe constipation—another common condition for some individuals with gastroparesis.

*"I was terrified when they said I had to get a tube and I hated it at first," says Alicia, who underwent treatments for her gastroparesis, including placement of a tube in her small intestine to supply more nutrition. "And then I started feeling so good that I'm grateful I did it."*

While receiving what she viewed as excellent care at Temple, staff told Alicia about a registry study as part of NIDDK's Gastroparesis Clinical Research Consortium, involving several clinical sites around the country. The study goals are to understand the prevalence, progression, and outcomes of gastroparesis. "I had worked on the other side of clinical research for so long.... I was pretty adamant that I wanted to help contribute more data and to enroll," says Alicia. She has participated in the study ever since, traveling to Temple a few times a year to give blood samples, fill out symptom questionnaires, and undergo testing. Her family, many of whom experience acid reflux issues, have supported her participation and are now well-informed about gastroparesis. Alicia has even enjoyed some study procedures, such as a special gastric emptying test where she viewed her stomach movement.

## NOURISHING A NEW APPROACH TO LIFE

Alicia has emerged from the challenging period of her pandemic-era diagnosis with a new approach to nourishing herself—physically and socially. She is thriving on her regimen of nightly J tube feedings with a specialized nutritional formula to supplement what she is able to eat during the day, used in tandem with the gastric electrical stimulator and medications. The J tube has the added benefit of allowing her medications to be readily available in the intestine for absorption.

Alicia's health has improved to the point where she has gained 20 pounds in 1 year and hopes to soon reach her target healthy weight. "I was terrified when they said I had to get a tube and I hated it at first," says Alicia. "And then I started feeling so good that I'm grateful I did it." She's applied her newfound energy to her lifelong interest in doing "any and all crafts" while cozying up with her cat, Mittens, and has donated hand-sewn "tubie pads"—reusable fabric pads that fit around various types of feeding tubes, including J tubes, and help minimize leakage and irritation—to nonprofits that provide them in kids' care packages.

*"It can feel like you're just one person," says Alicia of her life with gastroparesis and why she chose to participate in the Gastroparesis Clinical Research Consortium adult registry study, "but when a bunch of people come together and participate, it brings together all of these data points that then can be used to better help others with these conditions."*

Though Alicia is still mindful about eating an easy-to-digest diet, she has learned how to manage this in social settings. "That's been the biggest change for me—to kind of keep that socialization while also protecting myself and not feeling ill," she says. Alicia has also met others with gastroparesis through social media to raise awareness, and often shares resources on gastroparesis, such as the International Foundation for Gastrointestinal Disorders. "It's made me feel a lot better about it, having people to talk to who also have the condition and who understand what it's like to go through a day with it," she says.

# PERSONAL PERSPECTIVE

## THE VALUE OF RESEARCH

Participating in research as a patient has given Alicia a renewed appreciation for her chosen line of work. "I think clinical research is *so* important," she remarks. "[Living with gastroparesis] can feel like you're just one person," she says, "but when a bunch of people come together and participate, it brings together all of these data points that then can be used to better help others with these conditions." One of Alicia's motivations for enrolling in the study was to answer remaining research questions, particularly those needed to better understand what drives her idiopathic form of gastroparesis.

Although life with gastroparesis has been challenging, Alicia remains optimistic that research can lead to even better options for treatment and prevention. She adds about her study participation that "if it was to help with developing better treatment options for people, and they were able then to get their lives back, I feel like that would be really rewarding."

*Alicia says of her motivation for participating in the Gastroparesis Clinical Research Consortium adult registry study, "If it was to help with developing better treatment options for people, and they were able then to get their lives back, I feel like that would be really rewarding."*

Alicia's self-care and study participation have paid off. "Now I can go out with friends … go to the Renaissance fair with my sister for the day," she says. "I am now excited to go on our beach vacation because I know I'll have the energy to walk the boardwalk and actually enjoy it with my family," Alicia shares. Although her health is much improved, she remains vigilant. "It's something that I can't not think about, especially since food is such a big part of our lives, and I don't really have a traditional meal during the day," says Alicia. "But I feel like it's finally manageable, and I finally feel like myself again."

## More Information on Gastroparesis and the Gastroparesis Clinical Research Consortium

Gastroparesis is a chronic disorder where movement of food by the stomach into the intestine slows down or stops without any signs of physical blockage. The unremitting digestive symptoms and pain that often result can limit overall health and quality of life. Research supported by NIDDK contributes toward more fully understanding this disorder and finding better ways to manage it.

Gastroparesis may result from diabetes; surgical injury to the vagus nerve that connects the brain to the digestive system; hypothyroidism; autoimmune or nervous system diseases; viral infections; or some cancer treatments. But in many cases, the cause is unknown or "idiopathic." The disorder is uncommon, but in the United States it is most prevalent in women and in those at higher risk for diabetes. Symptoms of nausea, feeling full soon after eating, and abdominal pain can lead to serious issues with dehydration from repetitive vomiting, fluctuating blood sugar (glucose), malnutrition in terms of calories and vitamins, and weight loss. The delayed stomach emptying of gastroparesis is diagnosed by tracking an ingested meal or wireless capsule. No dedicated therapies for gastroparesis have been approved by the U.S. Food and Drug Administration. However,

# PERSONAL PERSPECTIVE

treatment can include new dietary habits or starting on oral, nasal intravenous, or direct intestinal tube feeding; medications to control blood sugar or to improve stomach muscle function, control nausea and vomiting, and reduce abdominal pain; or surgeries to reduce stomach pressure or install a device delivering mild electrical impulses to the stomach.

In 2006, NIDDK established the Gastroparesis Clinical Research Consortium to catalyze research and test new diagnostics and therapies. Now in its fourth iteration, the consortium encompasses six adult clinical centers, six pediatric centers, and a scientific data research center. In addition to clinical trials, the consortium oversees gastroparesis registries for adults and, more recently, for children, to enable ongoing studies on epidemiology, natural history, and clinical outcomes. The consortium maintains the largest repository of gastroparesis data and samples in the world.

Consortium studies have proven invaluable for informing gastroparesis care by improving understanding of the clinical spectrum, symptom severity, and physical and mental impacts in people with this gastrointestinal disorder. Studies have identified several factors associated with disease course, including gender, age, race and ethnicity, viral illness, depression, and weight. They have found neuronal, muscular, and immune drivers of gastroparesis, as well as genetic factors, all of which could lead to new ways to diagnose or treat the disorder. Clinical trials have tested therapeutic approaches for idiopathic and diabetic gastroparesis, tracked outcomes with treatments such as gastric electrical stimulation, and developed new tools, including a diagnostic instrument for children. Through the NIDDK Central Repository, NIDDK provides broad researcher access to consortium samples and data for ancillary studies. The Institute also funds several investigator-initiated gastroparesis studies, such as clinical trials of new therapies and studies utilizing advanced imaging and cellular technologies.

NIDDK is continuing support for the consortium to enable its ongoing studies, as well as advance new efforts, including an annotated sample repository to identify disease biomarkers. NIDDK is also partnering with industry and advocacy groups, such as the International Foundation for Gastrointestinal Disorders, to increase patient engagement in the consortium. Through the consortium and other efforts, research will continue to inform advances in clinical care that improve the lives of people with gastroparesis.

*For information on the Gastroparesis Clinical Research Consortium:* https://jhuccs1.us/gpcrc