

Pediatric Gastroenterology Research Agenda

NASPGHAN Mission Statement

The mission of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition is to advance understanding of normal development, physiology and pathophysiology of diseases of the gastrointestinal tract and liver in children, improve quality of care by fostering the dissemination of this knowledge through scientific meetings, professional and public education, and policy development, and serve as an effective voice for members and the profession.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)



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Executive Summary

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the NASPGHAN Foundation are dedicated to:

- **A**dvancing medical knowledge and technology
- **C**aring for patients with digestive disorders
- **E**ducating physicians and the public
- **S**upporting affected children and their families

While broad in nature, these activities are integrally linked and rely on research for their advancement. In this context, NASPGHAN and the NASPGHAN Foundation have been sources of research support and leading partners with government, industry, and relevant agencies to help fund research initiatives.

There have been numerous scientific advancements in the field of medicine, namely from molecular, clinical, and health economic perspectives. We now have a greater understanding of the molecular and genetic mechanisms of health and disease. In addition, there has been a growing emphasis on translating scientific discoveries to patient care, quality improvement, and improved use of healthcare resources.

In order to convey these needs, NASPGHAN has organized a Pediatric Gastroenterology Research Agenda that contains six key clinical categories for consideration:

Page Number	Category
4	Inflammatory Bowel Disease
5	Functional and Motility Disorders
6	Liver Disorders
7	Pancreatic Disorders
8	Allergy, Intestinal Failure, and Infection
9	Nutritional Disorders

Experts in each area were recruited in order to identify critical issues that should be emphasized for future research. The Pediatric Gastroenterology Research Agenda is by no means an exhaustive list of all of the problems associated with gastrointestinal disease in children. Rather, it is intended to serve as an overview of key areas for further research in the field of pediatric gastroenterology.

Nutritional Disorders

Inflammatory Bowel Disease

Functional and Motility Disorders

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Allergy, Intestinal Failure, and Infection

Pancreatic Disorders

Liver Disorders

Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a term that includes Crohn's disease and ulcerative colitis. The two major types of IBD are mainly distinguished by the area of the intestine that is involved. Both are caused by uncontrolled inflammation within the gastrointestinal tract that results from the individual's environment and genetic make-up.

This inflammation can lead to abdominal pain, uncontrolled diarrhea, gastrointestinal bleeding, fatigue, and stunted growth. In addition to suffering directly from the symptoms of their disease, children also frequently experience adverse psychological and social consequences from their IBD. Furthermore, potent medications that suppress the immune system of these children are often required, putting them at risk for severe complications such as infections and cancer. These are common disorders, affecting over one million people in North America, approximately a quarter of whom are children and adolescents. In addition, direct costs of IBD exceed six billion dollars per year.

The field of pediatric IBD research has grown exponentially in the last several years in diagnosing and treating IBD.

However, many key questions remain unanswered. For example, at the time of diagnosis, physicians are unable to accurately predict the disease course, or even which medications are best for a particular patient. Furthermore, as inflammation, psychological, and social dysfunction are intimately related, delineating pathways for disease activity and related dysfunction is essential.

Current research priorities in pediatric IBD are as follows:

- Determine the burden and natural history of IBD in children
- Improve our understanding of delayed growth and puberty in children with IBD
- Develop models that predict complications and guide optimal management
- Develop new markers of IBD activity and further delineate the role of endoscopy to assess therapy
- Examine the causes of IBD, including the gut bacterial environment and genetic make-up
- Identify novel, alternative therapies for pediatric IBD with fewer side effects
- Identify factors associated with psychological and social dysfunction

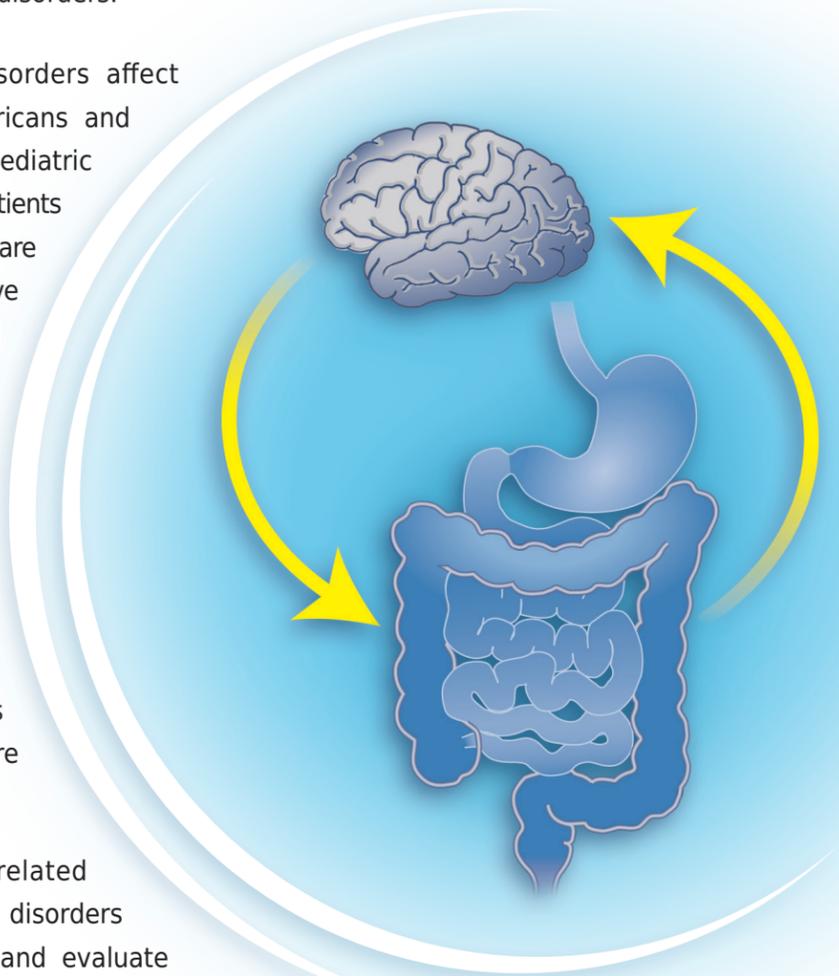
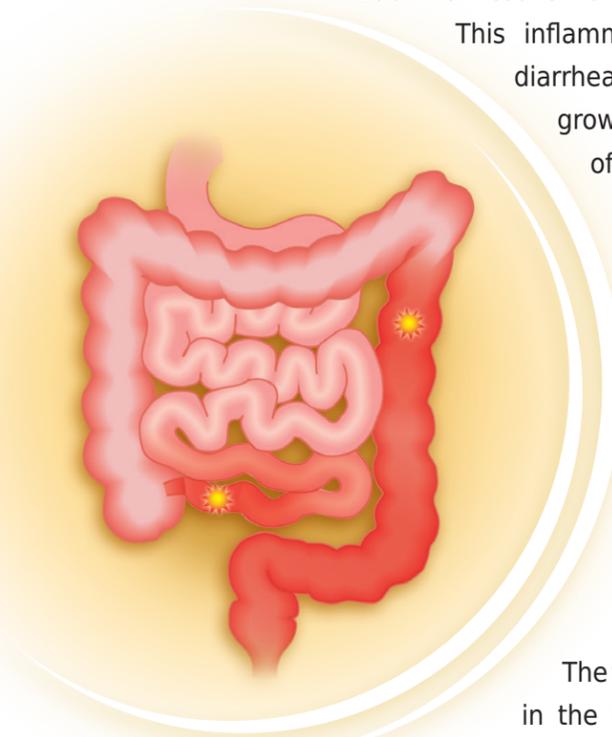
Functional and Motility Disorders

Functional gastrointestinal disorders are highly prevalent conditions that are defined by symptoms of disordered gut function. The symptoms include abdominal pain, nausea, vomiting, constipation, or diarrhea. Dysfunctional interactions between the patient's gut, environment, psyche, and nervous system can lead to these symptoms. In addition, problems with the movement of gastrointestinal contents (motility) can mimic or coincide with functional gastrointestinal disorders.

Functional gastrointestinal disorders affect an estimated 25 million Americans and account for over half of pediatric gastroenterology visits. These patients accrue billions of dollars in healthcare costs. Furthermore, they can have significant psychological and psychosocial problems - notably depression, anxiety, stress, missed school, inability to participate in extracurricular activities, and interpersonal discord.

Current research priorities in functional and motility disorders of the gastrointestinal tract are as follows:

- Define abdominal pain-related functional gastrointestinal disorders in children more clearly and evaluate the value of clinical symptoms and signs to direct medical testing
- Develop a better understanding of the mechanisms behind the development of pediatric functional gastrointestinal disorders; including the role of disordered motility, psychological dysfunction, stress, pubertal development, and the relationship between the brain and the gut
- Develop better methods to evaluate gut neuromuscular activity in children
- Optimize current medical and behavioral treatments and investigate novel treatments for pediatric functional gastrointestinal disorders and motility disorders



Liver Disorders

Pediatric liver diseases are a major health problem in children. These conditions can lead to a multitude of symptoms – including alterations in eye and skin discoloration, debilitating itching, life-threatening bleeding, and brain dysfunction.

A rising pediatric liver disorder is fatty liver disease, also known as non-alcoholic steatohepatitis (NASH). This condition is linked to the current epidemic of childhood obesity. Apart from the important intervention of diet and exercise, there are few effective medical therapies for NASH. In children, additional metabolic liver diseases include those that are associated with cystic fibrosis (CF) and various other genetic defects.

Infection of the liver with viruses such as Hepatitis B and C, can also result in chronic liver disease. Hepatitis B and C are the leading causes of liver cancer in the world. Additionally, Hepatitis C is the leading reason for liver transplantation among adults. The current therapies available for young children with chronic hepatitis B and C are only moderately effective in eradicating the infection.

One of the most common liver disorders in infants is a condition called Biliary Atresia, which is caused by obstruction of bile flow out of the liver. The majority of patients eventually require liver transplantation.

Current research priorities in pediatric liver disorders are as follows:

Metabolic Liver Diseases (NASH, CF-related, others)

- Determine the burden and natural history
- Examine the mechanisms that cause liver injury
- Develop accurate, minimally invasive markers to evaluate disease progression

Viral Hepatitis

- Increase participation and expedite clinical trials in children of novel therapies for viral hepatitis that are currently used in adults only

Biliary Atresia and Pediatric Liver Transplantation

- Determine cause, find ways to diagnose the disorders earlier, and develop novel therapies
- Propose solutions to the scarcity of available donors for liver transplantation in the United States
- Investigate better targeted immunosuppressive therapies to improve outcome of liver transplantation in children

Pancreatic Disorders

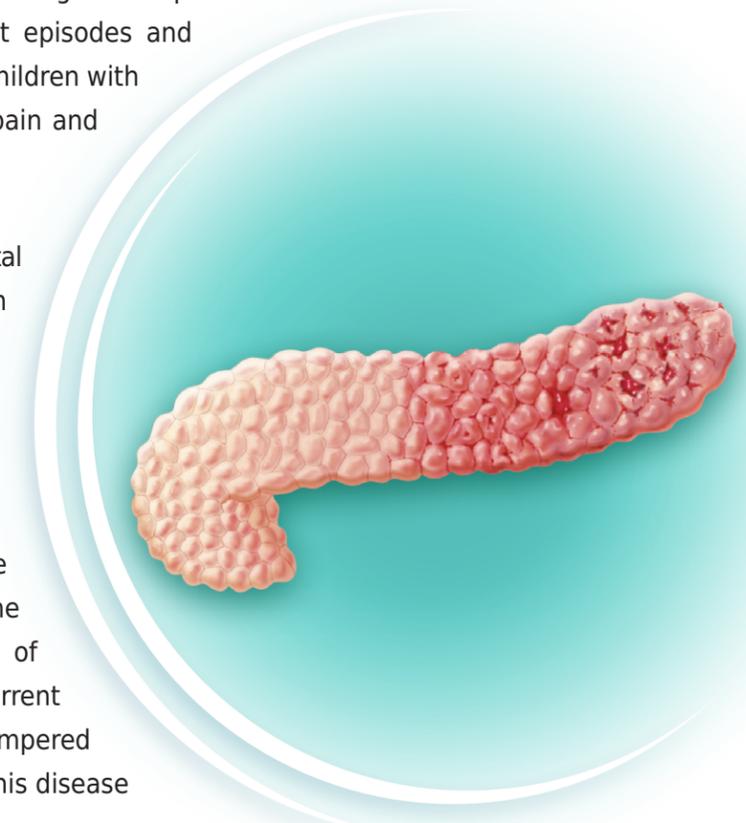
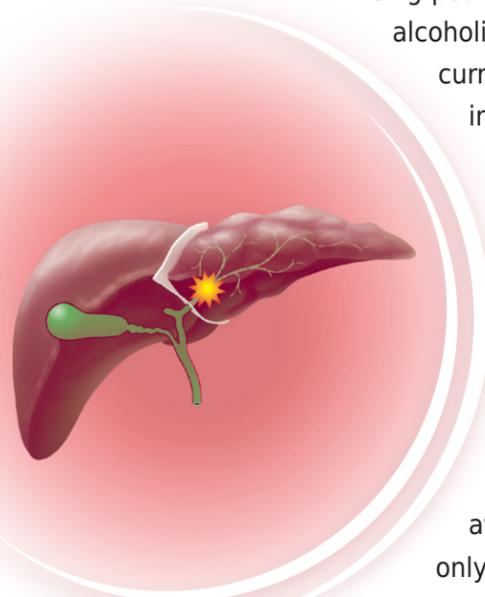
The most common pancreatic disorder in children is pancreatitis, which is a very painful inflammation of the pancreas. The main symptoms of pancreatitis include abdominal pain, vomiting, and difficulty feeding. Furthermore, there has been a major increase in the number of cases in children over the last decade.

Pancreatitis can be acute, recurrent, or chronic. Most children with acute pancreatitis have a single attack requiring hospitalization but they usually recover uneventfully. During hospitalization, they require fluid resuscitation, supplemental feedings, imaging studies, and frequent laboratory monitoring. Some patients with acute pancreatitis have recurrent episodes and may progress to chronic pancreatitis. Children with chronic pancreatitis have debilitating pain and improper functioning of the pancreas.

Pancreatitis poses a substantial societal disease burden. The lives of children with pancreatitis are dramatically altered by multiple hospital admissions, chronic pain, potential addiction to narcotic medications, nutritional problems, and psychological dysfunction. Therapies for pancreatitis are primarily supportive and have not advanced very far in the last half century. The development of novel, effective therapies for acute recurrent pancreatitis or chronic pancreatitis is hampered by the lack of basic knowledge about this disease in children.

Current research priorities in pediatric pancreatic disorders are as follows:

- Determine the burden and natural history of acute and chronic pancreatitis
- Establish and validate diagnostic criteria for acute and chronic pancreatitis
- Develop better endoscopic and non-invasive tests to assess for pancreatic insufficiency in children
- Develop better experimental models for acute and chronic pancreatitis
- Develop targeted therapies for acute, recurrent, and chronic pancreatitis



Allergy, Intestinal Failure, and Infection

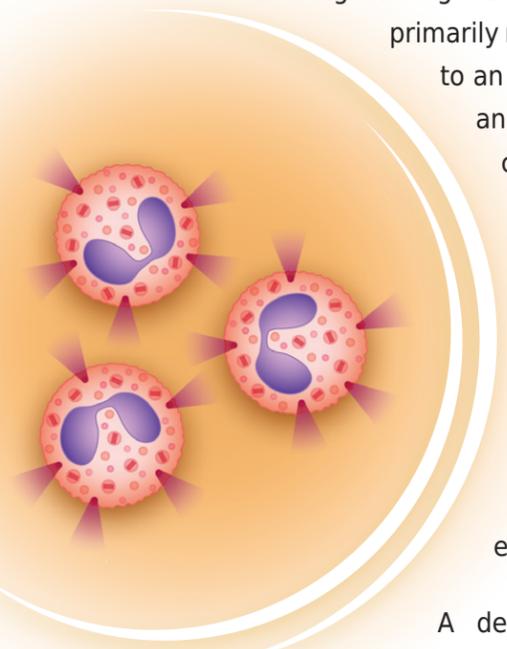
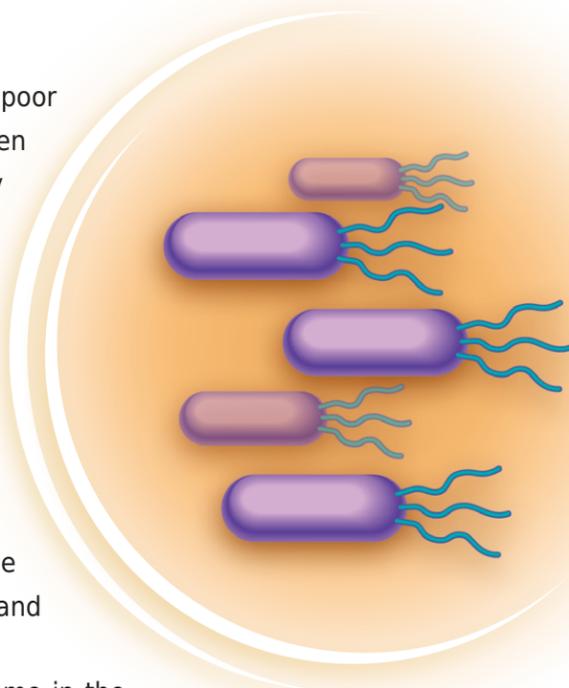
The intestine absorbs fluid and nutrients. This organ also protects the body from noxious ingested agents. In addition, the intestine harbors commensal bacteria, which primarily make up what is known as the microbiome. Inflammation due to an upset balance of the microbiome, gastrointestinal allergies, an inability to absorb enough nutrients, and infections can each cause intestinal dysfunction and may be interrelated.

A common and unrecognized intolerance to gluten-containing foods is a condition called Celiac disease. An emerging problem for children with gastrointestinal allergies is an allergy that primarily affects the esophagus, called Eosinophilic Esophagitis (EoE). EoE causes difficulty swallowing, chest pain, reflux, and can lead to irreversible narrowing of the esophagus.

A debilitating cause of poor intestinal absorption in children is short gut syndrome, which mainly occurs when extensive portions of diseased small intestine have to be removed. The most common reason for short gut syndrome is a life-threatening emergency of premature infants called necrotizing enterocolitis. Children with short gut syndrome are at risk for intestinal failure.

Current research priorities in understanding the intestinal microbiome, allergy, intestinal failure, and infection in children are as follows:

- Determine the role of the intestinal microbiome in the causes and course of pediatric gastrointestinal disorders
- Determine the burden and natural history of Celiac disease and EoE, how to monitor for complications, factors associated with poor outcomes, and optimal treatment
- Determine the mechanisms underlying intestinal failure
- Identify early markers for predicting those who will develop intestinal failure
- Develop better strategies to prevent intestinal failure and reduce its complications



Nutritional Disorders

Nutritional disorders in children encompass both conditions of undernutrition and obesity. These nutritional disorders can result from gastrointestinal disorders that, for example, limit nutrient absorption, or they can even provoke gastrointestinal illness. There is an alarming epidemic of childhood obesity in America. Thirty percent of children are either overweight or obese. The obesity problem has led to additional medical conditions including several pediatric gastrointestinal disorders.

Nutritional status can be positively or negatively affected by gastrointestinal disorders in children for a multitude of reasons – due to how food makes their bodies feel, medication side effects on appetite, and the adverse effects of their disease itself (such as vomiting and diarrhea).

There have been increasing amounts of dietary support, in the forms of specific diets, nutritional supplements, and food additives, promoted for optimal nutrition in pediatrics.

Current research priorities in pediatric nutritional disorders are as follows:

- Determine the spectrum, burden, and natural history of gastrointestinal illness in obese children and the impact of early interventions for this problem
- Determine the safety and efficacy in children, and particularly among adolescents, of various dietary regimens that are popular among adults
- Examine the effects of various dietary additives in the development of obesity and food intolerance
- Examine how appetite is regulated in pediatric gastrointestinal disorders that cause intestinal inflammation
- Determine the impact of chronic illness on growth and nutrition in children

