Gastroenterology, Hepatology and Nutrition

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**35**
Joint Appointment Faculty	**2**
Research Fellows and Post Docs	**13**
Research Graduate Students	**3**
Total Annual Grant Award Dollars	**$9,395,075**
Total Annual Industry Award Dollars	**$1,781,771**

CLINICAL ACTIVITIES AND TRAINING	
Staff Physicians	**2**
Clinical Fellows	**14**
Inpatient Encounters	**9,837**
Outpatient Encounters	**22,015**

Row 1: C Wetzel, J Bezerra, AC Arce-Clacher, N Santucci

Row 2: T Takebe, M Farrell, H Kalkwarf, A Asai, D Mallon, A Taylor, M Mouzaki

Row 3: L Denson, P Minar, C Cole, M Rosen, M Abu-El-Haija, C Gandhi, Y Haberman-Ziv

Visit Gastroenterology, Hepatology and Nutrition

Our Vision

We will be the leaders in the care of children with digestive diseases

Our Mission

- Care: We will deliver exceptional, safe, and affordable care.
- Research: We will catalyze high-impact research in digestive diseases.
- Education: We will train the future leaders of the field.

Our Values

- We are respectful
- We are honest
- We speak the truth
- We value diversity
- We work as a team

Innovation in Clinical Care

The division is on the 8th and 9th floors of the clinical sciences building, where clinical, research, and training projects integrate to provide the most innovative, evidence- and expert-based care for children with all forms of digestive disease. The outpatient gastroenterology clinic delivers direct patient care, and in inpatient units for gastroenterology, and for hepatology and liver transplantation). Our team also provides

timely consultation to all clinical services at Cincinnati Children's Hospital, where we work as a multi-disciplinary team to improve the care of the children we serve. The scope of care starts with the most common digestive problems and extends to the most rare and complex disorders that require ever-improving technologies to aid in diagnosis and to design new therapies. Some of our specialized services include liver and intestinal transplantation, intestinal rehabilitation, total pancreatectomy and islet cell autotransplantation, inflammatory and complex esophageal and intestinal disorders, and others (described below).

Our medical and nurse specialists also provide care in satellite clinics with the goals to bring gastroenterology expertise to our communities and improve patient experience. We hold daily clinics at the Liberty campus focused on gastroenterology, an increasing number of subspecialty clinics (example: NASH clinic and Neurogastroenterology/Motility clinic), and gastrointestinal endoscopies. Other satellite gastroenterology clinics are held in the our facilities in Mason, Green Township, Anderson, Northern Kentucky, and Portsmouth. Our experts also hold TeleHealth Gastroenterology clinics with programs in Kalamazoo (MI) focused on children with liver and intestinal failure, and in Erlanger (TN) focused on children with intestinal failure.

Innovation and Research

The division is a scientific hub for digestive disease research for Cincinnati Children's Medical Center and the University of Cincinnati, College of Medicine. The foundation of our research programs is on the premises that defects in development, genetics, and immunology play key roles in determining the phenotypes of digestive diseases in children. We aim to discover the biological underpinnings of digestive diseases that begin in childhood. To this end, physician-scientists and researchers receive funding from the National Institutes of Health (NIH), and industry, to use novel model systems in the laboratory and to perform clinical trials. Our commitment is to increase the tempo of translation of new discoveries to the clinics so that the investments from our hospital and our society translate into actionable items in the clinic, and improve the outcome of children with digestive diseases. Individual centers of excellence within Cincinnati Children's reviews our broad research portfolio.

Innovation in Education

A T32 grant has funded our training program for over 15 years. Most of our graduates are on academic positions, and hold several positions as division chiefs in the U.S. Our commitment is to integrate the clinical and research programs into an arena of opportunities for advanced training in the field of gastroenterology and related subspecialties. Our training programs include:

• Fellowship program in Gastroenterology, Hepatology and Nutrition

• Advanced fellowship training in Transplant Hepatology, Neurogastroenterology/Motility, and Nutrition

• Short-term clinical observation/clerkships for U.S. and international trainees

• Research training for international scientists

Below, we present summaries and accomplishments by individual centers of excellence.

Digestive Health Center: A catalyst for research on digestive disease

The Digestive Health Center (DHC), directed by Dr. Jorge Bezerra, MD, and managed by Dr. Cynthia Wetzel, PhD, recently received a five-year, $5.9 million competitive renewal grant from the National Institutes of Health. The DHC is one of only 17 Silvio O. Conte Digestive Diseases Research Core Centers in the U.S., and the only one dedicated to pediatric diseases. Drs. Lee Denson, MD; Heidi Kalkwarf, PhD, RD; and Aaron Zorn, PhD, from the Division of Developmental Biology serve as associate directors. The center seeks to improve diagnosis, treatments and outcomes of children with digestive diseases. It does so by enabling investigators to have timely access to state-of-the-art technologies at three scientific Cores: Integrative Morphology, Gene Analysis, and Pluripotent Stem Cell and Organoid Cores. With 85 investigators, the DHC contributes to the research goals of faculty from 20 divisions in the Department of Pediatrics and seven other departments of the University of Cincinnati, College of Medicine, with a total grant portfolio of $33.8 million in extramural research. The DHC Pilot and Feasibility Program has invested $1.79 million among 42 early stage investigators since 2007. These investigators have since attracted $49.4 million in extramural grant funding. In addition to an outstanding record of publications with 185 digestive disease related articles during the past 12 months, the following center investigators received national and international recognition for their clinical, research, and educational accomplishments:

• Akihiro Asai, MD, PhD, received the George Ferry Young Investigator Development Award from North American Society of Pediatric Gastroenterology, Hepatology and Nutrition

• Takanori Takebe, MD, received the Innovator Award for Early Career Investigators in Translational Stem Cell Research from the New York Stem Cell Foundation

• Sing Sing Way, MD, named a 2016 Faculty Scholar by the Howard Hughes Medical Institute, the Simons Foundation, and the Bill & Melinda Gates Foundation

Advanced Nutrition

Our mission is to optimize nutritional status of children exposed to chronic medical conditions and environmental hardships through surveillance of patients at risk, and identification and implementation of best treatment practices. We seek to improve the prevention and treatment of childhood diarrhea and undernutrition by implementing best practices while creating new knowledge through bench-to-bedside research collaborations between Cincinnati Children's Hospital Medical Center and global partners. Drs. Conrad Cole, MD, MPH, MSc, and Stacey Huppert, PhD, continue established individual partnerships with investigators in Brazil, Ghana, Nigeria and Pakistan focused on micronutrient deficiencies (zinc and iron), undernutrition, diarrheal diseases, and environmental enteropathy. Drs. Simon Hogan, PhD (Division of Allergy and Immunology); Lee Denson, MD; and Huppert continue collaboration with investigators at the University of Virginia and The Aga Khan University in Pakistan on novel mouse models of environmental enteropathy.

Drs.Heidi Kalkwarf, PhD, RD, and Stavra Xanthakos, MD, MS, are investigating deficiencies of iron, vitamin B-12 and calcium in adolescents who have undergone bariatric surgery. They are also investigating deficits in bone density among adolescents with non-alcoholic fatty liver disease (NAFLD). Drs. Kalkwarf and James Heubi, MD, are investigating trajectories of bone mineral accrual in young children and the influences of dietary intake, growth, and body composition. These data will establish normal ranges for bone density based on age and enable detection of bone deficits in children with chronic medical conditions.

Cincinnati Center for Eosinophilic Disorders

The Cincinnati Center for Eosinophilic Disorders (CCED) is an established multidisciplinary referral center for evaluation and treatment of eosinophilic gastrointestinal disorders in children and adults. Physicians representing the Divisions of Gastroenterology, Hepatology, and Nutrition; Allergy and Immunology; and Pathology provide comprehensive clinical services supported by experienced nurses, dieticians, a psychologist and social worker. Over 70% of the patients agree to participate in clinical and basic science research studies. The clinical research portfolio includes important studies of both dietary and pharmacologic management of eosinophilic disorders. Drs. Philip Putnam, MD, and Vincent Mukkada, MD, collaborate with other leading investigators in the CCED in studies of genetic and immunologic factors responsible for eosinophilic inflammation in the gut, and in evaluating the effectiveness of anti-interleukin 5 (IL-5), biological agents and topical glucocorticoids in the management of eosinophilic disease. The CCED team was the first to investigate eosinophil progenitor (EoP) levels in patients with Eosinophilic Esophagitis (EoE), leading to the identification of a potential new noninvasive biomarker, which is an essential step toward simpler disease monitoring over time, with the potential of reduced discomfort, costs and side effects.

Recent research includes the transcriptomic study of Proton Pump Inhibitor-responsive Esophageal Eosinophilia (PPI-REE), providing convincing evidence that PPI-REE is an EoE sub-entity with significant molecular overlap with EoE in which PPI therapy reverses nearly the entire allergic inflammatory transcriptome. In a collaborative effort led by Dr. Margaret Collins, MD, from Division of Pathology, the investigators recently published a novel histologic scoring system using multiple microscopic changes seen in EoE patients who outperforms the current histologic gold standard. In addition, the CCED (with Dr. Marc Rothenberg, MD, PhD, Division of Allergy and Immunology, as principal investigator) continued work as the central site for a Patient Centered Outcomes Research Institute (PCORI) contract for a multicenter trial examining the efficacy of minimally restrictive empiric diets in the management of pediatric eosinophilic esophagitis. A genome wide association study (GWAS) further clarified the genes responsible for making the esophagus a target for eosinophilic inflammation; in particular, this effort has led to the identification of calpain-14 as a causative pathway in directing eosinophils to the esophagus and raised the possibility of enzymatic blockade of this pathway as a possible therapeutic strategy. Recent efforts have highlighted the role of IL-13 in eosinophilic esophagitis pathogenesis, and the positive effects of antibodies against IL-13 in human patients with EoE. This has led to a number of therapeutic trials in which the CCED is an active participant. A novel study continues to expand our understanding of eosinophilic gastritis, using techniques employed previously for studying the esophagus, including the elucidation of the transcriptome.

With support of a five-year, $6.25-million grant from the National Institutes of Health (NIH) to Dr. Rothenberg, the CCED leads a consortium of organizations with a common goal to conduct clinical research into eosinophilic disorders and to train investigators in how to conduct clinical research. This Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is a collaboration of clinician investigators, translational scientists, physicians, patients, families and patient advocacy groups and is part of the Rare Disease Clinical Research Network (RDCRN). Work from this collaborative group has focused on studies of the natural history of eosinophilic disease, particularly the comparatively rare types including eosinophilic gastritis and eosinophilic colitis, as well as determining the disease response to less-restrictive diet therapy in adult patients with EoE. A series of pilot studies supported through this consortium, include projects examining the use of the angiotensin receptor blocker losartan in the treatment of EoE and another assessing the role of esophageal distensibility monitoring in the management of EoE.

IBD-The Schubert-Martin Inflammatory Bowel Disease Center

The Division of Gastroenterology, Hepatology and Nutrition and the Schubert-Martin Inflammatory Bowel Disease / IBD Center sees more than 800 patients with irritable bowel disorder (IBD). The center diagnoses close to 100 new patients annually, and sees close to 90 second-opinion patients from more than 20 states, and abroad. These numbers reflect a significant increase in both total patient volume and second opinions, over the last five years.

The center is an integral and leading participant in collaborative consortia like the ImproveCareNow Quality Improvement Network and the Crohn's and Colitis Foundation's PRO-KIDS Clinical Research Network. This role reflects in superior outcomes for our patients with more than 85% of IBD patients within the center being in remission, 65% in sustained remission, and 84% having a good quality of life. The center's website shares these outcome measures transparently . Our Annual IBD Family Education Day, co-hosted by the local chapter of the Crohn's and Colitis Foundation, continues to be one of the largest educational events of its kind in the country. A rejuvenated and energized parent advisory board partners with center providers to identify priority areas for improvement, education, increased awareness and community involvement with an active Facebook page.

Center physicians continue to develop and lead basic, translational and clinical research to identify key etiopathogenic mechanisms for inflammatory bowel diseases, minimally invasive biomarkers for predication of disease flares and remission, development of mobile phone apps for patient engagement and self-management, transition of patients to adult providers, and pilot testing of eVisits. They reported in the journal *Gastroenterology* a novel gene expression panel which differentiates patients with Crohn's disease from those with ulcerative colitis and predicts treatment responses. This work suggests that Th2 immune responses may actually promote mucosal healing in ulcerative colitis, a novel mechanism which researchers are now investigating using state-of-the-art innate lymphoid cell:colonoid co-culture systems. They also reported in the journal *Lancet* results of the RISK Crohn's Disease inception cohort study, the largest study of its kind in the world. This study identified clinical, genomic, and serologic predictors of clinical outcomes in children with Crohn's Disease, and defined for the first time the relative benefit of early anti-TNF therapy in this setting. Collaborators from the Divisions of James M. Anderson Center for Health System Excellence, Behavioral Medicine and Clinical Psychology, Pediatric and General Thoracic Surgery, Allergy and Immunology, Adolescent and Transition Medicine, the Center for Adherence and Self-Managment, and the Department of Radiology continue to make significant contributions to finding a cure as well as improving outcomes and self-management skills for children suffering from IBD.

Interdisciplinary Feeding Team

Under the leadership of Drs. Scott Pentiuk, MD, MEd, and Vince Mukkada, MD, the Interdisciplinary Feeding Team (IFT) provides comprehensive evaluation for children with swallowing/feeding disorders. This multidisciplinary team includes experts from the Divisions of Gastroenterology, Hepatology and Nutrition; Pediatric Otolaryngology / Head and Neck Surgery; Speech-Language Pathology; Occupational Therapy, Physical Therapy and Therapeutic Recreation; and Social Services. The IFT evaluated over 1,300 patient visits in FY17. In addition to comprehensive consultation and care, the IFT offers unique multidisciplinary outpatient treatment sessions and Child Adult Relationship Enhancement training for families. Ongoing research projects by IFT investigators include the use and development of the pureed by G-tube diet, methods to evaluate children with swallowing dysfunction, and quality improvement projects to decrease patient wait times. The team will be adding a third gastrointestinal member, Dr. Stephanie Oliveira, MD, this fall who will bring additional nutrition expertise to the team.

Intestinal Rehabilitation and Intestinal Transplantation Programs

These two programs continue to expand their clinical profiles and facilitate the translational and clinical research conducted by both programs. The team's circumspect, thoughtful approach to intestinal rehabilitation has obviated the need for intestinal transplantation for many of the patients referred for transplantation. Its mission is to provide the best possible care for children with intestinal failure through innovation. Outcomes for both intestinal rehabilitation and intestinal transplantation are excellent. The central line-associated blood stream infection rate of <1.8/1000 catheter days is among the best in North America. The center leads an expanded multicenter pediatric clinical trial funded by Shire Pharmaceuticals for teduglutide (Gattex®) with Dr. Samuel Kocoshis, MD, as the lead investigator. Dr. Conrad Cole, MD, MPH, MSc, and Dr. Michael Helmrath, MD, MS (Division of Pediatric and Thoracic Surgery), are leading a multicenter trial evaluating the efficacy of encapsulated insulin as a potential therapeutic agent for infants with short bowel syndrome. Additional studies include the use of fish-oil derived lipid (Omegaven®) to prevent chronic liver disease associated with the use of parenteral nutrition, the efficacy of ethanol lock therapy for bloodstream infection prevention in patients with central venous catheters, and analysis of the value of selective decontamination of the small bowel in intestinal transplant recipients. In collaboration with Dr. David Haslam, MD (Division of Infectious Disease), Drs. Kocoshis and Cole are evaluating the interaction of diet and antimicrobials on intestinal microbiome and how this impacts adaptation. The small bowel transplant surgical team led by Dr. Jaimie Nathan, MD, is studying microbiome changes in stool and allograft intestinal tissue following intestinal transplantation to correlate them with diminution of the Treg population in tissue and blood during intestinal allograft rejection. Additionally, the intestinal transplantation team, noting much better survival with combined liver/intestinal transplantation than with isolated small bowel rejection, has (as a quality improvement measure) stratified risk for exfoliative rejection by: 1) intestine vs liver-intestine transplantation, or 2) the existence of preformed or de novo donor specific antibodies. The impact of these strategies is being analyzed with regard to overall survival, length of ICU stay, and length of overall hospital stay.

Liver Diseases

The Pediatric Liver Care Center provides comprehensive care for children with liver diseases. Staffed by eight pediatric hepatologists, four hepatobiliary surgeons, and two specialty nurses, the Center serves a national and international referral population via a comprehensive evaluation of all medical and surgical aspects of liver diseases. The evaluation includes a full spectrum of metabolic analysis, inflammatory processes, and gene sequencing technologies to diagnose mutations that cause clinical phenotypes. The multidisciplinary nature of the comprehensive care makes the Center a “one-stop-shop” in which the timely consultation with hepatologists, surgeons, pathologists, radiologists, and nutritionists with expertise in pediatric liver disease optimizes patient care. It also catalyzes patient-based research to narrow knowledge gaps and solve clinical challenges with the ultimate goal to improve outcomes.

Physicians, surgeons and scientists in the Center are performing exciting research with the goal to discover the causes and pathogenesis of pediatric liver disease, and to design new therapies to block progression of liver injury. Focusing on advances in the past year, the work by Drs. Jorge Bezerra, MD; Alexander Miethke, MD; and Pranavkumar Shivakumar, PhD, have focused on understanding the mechanisms of biliary injury, and biomarkers and new treatments of biliary atresia and sclerosing cholangitis. Key advances included: 1) Dr. Bezerra’s discovery that receptors of tumor necrosis factor increases in biliary atresia, and blocking of the type 2 receptor renders mice resistant to the disease phenotype (published in *JCI Insight*); and 2) Dr. Takanori Takebe’s report that vascular endothelial factor is important for a crosstalk between endothelial cells and hepatoblast during formation of human liver organoids (published in *Nature*). Ongoing disease-based research focuses on minimally invasive biomarkers of cholangiopathies, the function of novel liver-specific immune cells, and the crosstalk between the intestinal microbiome and liver immune cells.

Several lines of important clinical investigation are opening new diagnostic and treatment options for children with liver disease. Drs. William Balistreri, MD, and Jorge Bezerra are conducting new clinical trials to determine the efficacy of tenofovir in children with chronic hepatitis B infection, and the efficacy of direct acting antivirals to completely eradicate hepatitis C virus during childhood. Dr. Miethke is studying the clinical impact of molecular inhibition of bile acid re-circulation in patients with cholestasis syndromes. New this year are the studies led by Dr. Miethke on pathogenesis and biomarkers of autoimmune liver diseases, with an ongoing study to evaluate new MRI modalities to stage the liver and biliary injury and fibrosis.

Exciting laboratory work includes the studies by Drs. Stacey Huppert, PhD, and Chunyue Yin, PhD, focused on the development of the biliary system, and Drs. Yin and Miethke using the zebrafish model to study how human mutations in canalicular transporters can cause liver disease. Notable is the work by Dr. Takebe and his research team using pluripotent stem cells to engineer stem cell-derived liver organoids to study mechanisms of NASH and drug screening, and of Dr. Akihiro Asai, MD, PhD, modeling cholestatic liver diseases to discover mechanisms of cellular injury and identify new therapies.

Neurogastroenterology and Motility Disorders Center

Under the leadership of Dr. Ajay Kaul, MD, the Neurogastroenterology and Motility Disorders Program has continued to experience growth, with 763 outpatient encounters and approximately 40 new referrals per month as a destination excellence for patients from 35 states, and abroad. In collaboration with the Colorectal Center, Drs. Kaul and Khalil El-Chammas, MD, MS, started an interdisciplinary clinic in July 2014 to evaluate and treat children with complex colorectal and motility disorders such as Hirschprung's disease and severe idiopathic chronic constipation using standardization of practice and clinical research to improve short- and long-term outcome. In FY 2017, the team saw 158 patients. This highly innovative center has had a 35% increase in manometry procedures, and now has expanded the neurogastroenterology and motility services to the Liberty campus with the addition of a third neurogastroenterologist to start in August of this year. New technologies include: EndoFLIP, transrectal ultrasound and Smartpill to offer state-of-the-art diagnostic technologies to this group of patients with complex, challenging problems. Exploring new research opportunities, center investigators have initiated trials to investigate the efficacy of linaclotide in children with functional constipation and irritable bowel syndrome with constipation.

Pancreas Care Center

The Pancreas Care Center's (PCC) vision is to be the leader in delivering world-class healthcare to children with pancreatic disease, through a comprehensive multidisciplinary management that prioritizes patient outcomes. The clinical team implements chronic care algorithms that enhance the care coordination and apply state of the art research methodology to innovate and transform patient care.

The center, led by medical director, Dr. Maisam Abu-El-Haija, MD; surgical director, Dr. Jaimie Nathan, MD; associate director and endoscopy director, Dr. Tom Lin, MD; and endocrinology directory, Dr. Deborah Elder, MD, in collaboration with the Pain Managment Services team and the Division of Behavioral Medicine and Clinical Psychology, follows more than 280 patients with various pancreatic disorders including pancreatitis, exocrine pancreatic insufficiency, congenital anomalies of the pancreas, and pancreatic tumors. With its inception in 2013, the center has completed a survey of Cincinnati Children's providers to better understand the variation in management of acute pancreatitis, assembled a multidisciplinary care team to evaluate and treat complex pancreatic disorders, established a REDCap database for patient registry, and instituted an evidence-based order set for the management of acute pancreatitis which has led to decreased length of hospital stay and intensive care admissions. The center has provided timely evaluation, and highly innovative diagnostic and care protocols, to 290 patients in FY17; performed 17 Total pancreatectomy with islet autotransplantation (TPIAT) surgeries; one subtotal pancreatectomy with IAT for treatment of unremitting pain due to chronic pancreatitis; and 79 endoscopic retrograde cholangiopancreatography's (ERCP).

Center physician- and surgeon-scientists published several papers on severe acute pancreatitis, with validation of a prognostic severity tool, and launched the Pancreas Panel in collaboration with the Molecular Genetics Laboratory that evaluates 10 known genes causing inheritable pancreatitis using next generation sequencing (NGS). Since the launch in November 2016, >50 genetic tests have used the panel. In collaboration with Dr. Andrew Trout, MD, from the Department of Radiology, center investigators completed a study on the use of MRCP in normal healthy controls. Other studies include: molecular genetic studies of disease phenotypes and biomarkers of disease severity along with those pursued as a Center in the following three multi-center studies: 1) The CSCPDPC INSPPIRE International Study Group to Study Pediatric Acute Recurrent and Chronic Pancreatitis: In Search for a Cure (NIH-U01, Center PI: Abu-El-Haija), 2) Advancing Treatment for Pancreatitis: A Prospective Observational Study of TPIAT (NIH-R01, Center PI: Nathan), and 3) The use of MRCP to stage chronic pancreatitis in the pediatric population (National Pancreas Foundation (NPF), Co-PIs: Abu-El-Haija and Trout).

In addition, PCC members are actively involved in the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), as Dr. Abu-El-Haija is the vice chair of the Pancreas Committee, and in the NPF as a course organizer for their annual meeting. Dr. Lin is an active member in the NASPGHAN Pancreas Committee and the NASPGHAN ERCP special interest group. The PCC at Cincinnati Children's is one of only a few pediatric centers that are an NPF-approved center of excellence for pancreatic care in the nation, and is a destination sought out by patients from around the country based on its excellence of care and reputation.

Liver Transplant Center

The mission of the pediatric liver transplant program is to advance the care of liver transplant recipients by providing unparalleled clinical care, addressing gaps in knowledge through patient-based and basic laboratory research, improving health care delivery systems through continuous quality improvement, and serving as advocates for organ donation and allocation in our community and country. As one of the largest pediatric liver transplant program in the country, center surgeons have performed more the 650 liver transplants since the program

began in 1986. Patient and graft survival rates are at or above the national average at one month, one year and three years post-transplant. In addition to providing care for the most common pediatric liver disorders leading to transplantations, center physicians and surgeons are able to leverage institutional strengths to provide care and the best outcome available to a number of patients with rare diseases and extremely complex needs. This includes children with advanced liver tumors, with more pediatric liver transplants for hepatic tumors than any other center in the United States since its inception in 2007.

In addition to providing outstanding patient care, the Liver Transplant Center is a leader in multicenter clinical and translational research studies and national quality improvement efforts. These include: Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients (iWITH), the Studies in Pediatric Liver Transplantation (SPLIT) quality improvement community and clinical registry, Clinical Trials in Organ Transplantation in Children (CTOT-C) research initiative, the Medication Adherence in Liver Transplant (MALT) study group, and multiple local projects and initiatives.

Steatohepatitis Center

Understanding and treating nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatiti (NASH): The Cincinnati Children's Steatohepatitis Center (CCSC) is a multidisciplinary program that provides care to a growing population of children and adolescents with nonalcoholic fatty liver disease, the most common causes of liver disease in the United States and an increasing cause of liver transplantation in adults. NAFLD affects 1 in 10 children and 1 in 3 adults in the United States. About 1/4 to 1/3 of patients with NAFLD can develop a more severe progressive form of disease called nonalcoholic steatohepatitis (NASH) that can progress to severe fibrosis. Thus, early identification and intervention is critical to prevent progression to end-stage liver disease.

Because NAFLD and NASH are closely associated with obesity, cardiovascular disease, prediabetes and diabetes, the CCSC collaborates with the Center for Better Health and Nutrition, the Sleep Center, the Hypertension Clinic, the Lipid Clinic, the Diabetes Center, and the Surgical Weight Loss Program for Teens to help identify and manage comorbid conditions and help patients achieve a healthier weight. The program completed 578 patient visits in FY17. With increasing recognition of NAFLD as a major contributor to chronic liver disease, and promising new treatments on the horizon, the CCSC director, Dr. Stavra Xanthakos, MD, MS, and Dr. Kristin Bramlage, MD, welcomed two new faculty, Drs. Marialena Mouzaki, MD, MSc, and Cata Arce-Clachar, MD, and are expanding the number of clinics at our base and Liberty campuses.

The CCSC maintains a robust bio-specimen repository to facilitate translational work, and is a leading pediatric site in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded NASH Clinical Research Network (NASH-CRN), a multi-center consortium investigating the natural history and determinants of NASH in adults and children and conducting trials of novel therapies. Seminal research highlights in 2017 included investigating novel non-invasive magnetic resonance and ultrasound imaging modalities in children with NAFLD with collaborating investigators in radiology. Within the NASH-CRN, CCSC investigators are actively studying outcomes of children with NAFLD and NASH. The CCSC has an active National Institutes of Health (NIH)-funded clinical trial comparing the effectiveness of comprehensive lifestyle intervention to bariatric surgery in treating NASH in severely obese adolescents. Outcomes of NAFLD among participants in the Teen-Longitudinal Assessment of Bariatric Surgery cohort are also studied. The published work by CCSC investigators is in the journals: *Gastroenterology*, *Obesity*, *New England Journal of Medicine*, *Nature*, *JAMA Pediatrics*, *Journal of Pediatrics*, *Nature Reviews Gastro Hepatology*, and others.

Division Publications

1. Kugathasan S; Denson LA; Walters TD; Kim MO; Marigorta UM; Schirmer M; Mondal K; Liu C; Griffiths A; Noe JD. **Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study.** *The Lancet*. 2017; 389:1710-1718.

2. Camp JG; Sekine K; Gerber T; Loeffler-Wirth H; Binder H; Gac M; Kanton S; Kageyama J; Damm G; Seehofer D. **Multilineage communication regulates human liver bud development from pluripotency.** *Nature*. 2017; 546:533-538.

3. Turpin W; Espin-Garcia O; Xu W; Silverberg MS; Kevans D; Smith MI; Guttman DS; Griffiths A; Panaccione R; Otley A. **Association of host genome with intestinal microbial composition in a large healthy cohort..** *Nature Genetics*. 2016; 48:1413-1417.

4. Rosen MJ; Karns R; Vallance JE; Bezold R; Waddell A; Collins MH; Haberman Y; Minar P; Baldassano RN; Hyams JS. **Mucosal Expression of Type 2 and Type 17 Immune Response Genes Distinguishes Ulcerative Colitis From Colon-Only Crohn's Disease in Treatment-Naive Pediatric Patients.** *Gastroenterology*. 2017; 152:1345- 1357.e7.

5. Dellon ES; Katzka DA; Collins MH; Hamdani M; Gupta SK; Hirano I; MP-101-06 Investigators. **Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis.** *Gastroenterology*. 2017; 152:776-786.e5.

6. Brant SR; Okou DT; Simpson CL; Cutler DJ; Haritunians T; Bradfield JP; Chopra P; Prince J; Begum F; Kumar A. **Genome-Wide Association Study Identifies African-Specific Susceptibility Loci in African Americans With Inflammatory Bowel Disease.** *Gastroenterology*. 2017; 152:206-217.e2.

7. Schwimmer JB; Lavine JE; Wilson LA; Neuschwander-Tetri BA; Xanthakos SA; Kohli R; Barlow SE; Vos MB; Karpen SJ; Molleston JP. **In Children With Nonalcoholic Fatty Liver Disease, Cysteamine Bitartrate Delayed Release Improves Liver Enzymes but Does Not Reduce Disease Activity Scores.** *Gastroenterology*. 2016; 151:1141- 1154.e9.

8. Denson LA; Klein C. **Granulocyte-Macrophage Colony Stimulating Factor Bioactivity and Mucosal Homeostasis in Crohn's Disease: A Role for Genetic Variation.** *Gastroenterology*. 2016; 151:593-596.

9. Vos MB; Kaar JL; Welsh JA; Van Horn LV; Feig DI; Anderson CAM; Patel MJ; Cruz Munos J; Krebs NF; Xanthakos SA. **Added Sugars and Cardiovascular Disease Risk in Children: A Scientific Statement From the American Heart Association..** *Circulation*. 2017; 135:e1017-e1034.

10. Inge TH; Jenkins TM; Xanthakos SA; Dixon JB; Daniels SR; Zeller MH; Helmrath MA. **Long-term outcomes of bariatric surgery in adolescents with severe obesity (FABS-5+): a prospective follow-up analysis.** *Lancet Diabetes and Endocrinology*. 2017; 5:165-173.

11. Morris DW; Stucke EM; Martin LJ; Abonia JP; Mukkada VA; Putnam PE; Rothenberg ME; Fulkerson PC. **Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis.** *Journal of Allergy and Clinical Immunology*. 2016; 138:915-918.e5.

12. Wang KS; Tiao G; Bass LM; Hertel PM; Mogul D; Kerkar N; Clifton M; Azen C; Bull L; Rosenthal P. **Analysis of Surgical Interruption of the Enterohepatic Circulation as a Treatment for Pediatric Cholestasis.** *Hepatology*. 2017; 65:1645-1654.

13. Lages CS; Simmons J; Maddox A; Jones K; Karns R; Sheridan R; Shanmukhappa SK; Mohanty S; Kofron M; Russo P. **The Dendritic Cell-T Helper 17-Macrophage Axis Controls Cholangiocyte Injury and Disease Progression in Murine and Human Biliary Atresia.** *Hepatology*. 2017; 65:174-188.

14. Verkade HJ; Bezerra JA; Davenport M; Schreiber RA; Mieli-Vergani G; Hulscher JB; Sokol RJ; Kelly DA; Ure B; Whitington PF. **Biliary atresia and other cholestatic childhood diseases: Advances and future challenges.** *Journal of Hepatology*. 2016; 65:631-642.

15. Leung DH; Heltshe SL; Borowitz D; Gelfond D; Kloster M; Heubi JE; Stalvey M; Ramsey BW; Stecenko A; Schechter M. **Effects of Diagnosis by Newborn Screening for Cystic Fibrosis on Weight and Length in the First Year of Life.** *JAMA Pediatrics*. 2017; 171:546-554.

16. Newton KP; Hou J; Crimmins NA; Lavine JE; Barlow SE; Xanthakos SA; Africa J; Behling C; Donithan M; Clark JM. **Prevalence of Prediabetes and Type 2 Diabetes in Children With Nonalcoholic Fatty Liver Disease.** *JAMA Pediatrics*. 2016; 170:e161971.

17. Mishra R; Chesi A; Cousminer DL; Hawa MI; Bradfield JP; Hodge KM; Guy VC; Hakonarson H; Mauricio D; Schloot NC. **Relative contribution of type 1 and type 2 diabetes loci to the genetic etiology of adult-onset, non-insulin-requiring autoimmune diabetes.** *BMC Medicine*. 2017; 15:88.

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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Mike Leonis, MD	A Multi-Center Group to Study Acute Liver Failure in Children (PALF)	National Institutes of Health (University of Pittsburgh)	U01 DK072146	09/01/2010 - 08/31/2016	$24,130
Joseph Palermo, MD, PhD	Longitudinal Study of Cystic Fibrosis Liver Disease	Cystic Fibrosis Fdn Therapeutics, Inc (The Children's Hospital of Denver)	NARKEW07AO	01/01/2011 - 12/31/2017	$116,303
Lee A Denson, MD	Predicting Response to Standardized Pediatric Colitis Therapy: The PROTECT Study	National Institutes of Health (Connecticut Children's Medical Center)	U01 DK095745	05/01/2012 - 04/30/2017	$420,000
John C Bucuvalas, MD	Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients	National Institutes of Health (The Regents of the Univ of California)	U01 AI100807	07/27/2012 - 06/30/2017	$162,489
Lee A Denson, MD	Causes and Consequences of Neutrophil Dysfunction in Early	National Institutes of Health (Emory	R01 DK098231	09/17/2013 -	$259,854

	Onset Crohn’s Disease	University)		07/31/2018	
Lee A Denson, MD	Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn’s Disease	Crohn's & Colitis Foundation of America (Emory University)	CCFA 292052	07/01/2013 - 06/30/2017	$225,184
Heidi J Kalkwarf, PhD	Exposure and development of poor bone health among African American women	National Institutes of Health (University of Cincinnati)	R01 ES024074	06/09/2014 - 03/31/2018	$50,335
James E Heubi, MD	Sterol and Isoprenoid Diseases Rare Diseases Consortium	National Institutes of Health (University of Nebraska Medical Center)	U54 HD061939	09/04/2014 - 08/31/2019	$2,841
Stavra A Xanthakos, MD	Outcome of NASH in Adolescents after Bariatric Surgery vs. Lifestyle Intervention	National Institutes of Health	R01 DK100429	08/25/2014 - 06/30/2019	$547,628
Stavra A Xanthakos, MD	Clinical Research Network in NASH	National Institutes of Health (Cleveland Clin Lerner Col of Med of CWRU)	U01 DK061732	08/01/2014 - 06/30/2019	$185,516
Michael Rosen, MD, MS	Th2 Cytokines and Signaling in Pediatric Inflammatory Bowel Disease	National Institutes of Health	K23 DK094832	12/01/2013 - 03/31/2018	$189,945
Jorge A Bezerra, MD	Clinical Center for Cholestatic Liver Disease in Children	National Institutes of Health	U01 DK062497	08/10/2014 - 05/31/2019	$596,269
Jorge A Bezerra, MD	Biological Basis of Phenotypes and Clinical Outcomes in Biliary Atresia	National Institutes of Health	R01 DK083781	09/24/2014 - 08/31/2019	$494,545
Sean R Moore	Epigenetic Modeling of Environmental Enteropathy in Mice	Bill & Melinda Gates Foundation	ID OPP1109785	07/11/2014 - 06/30/2018	$254,100
Lee A Denson, MD	Pediatric Gastroenterology and Nutrition Training Grant	National Institutes of Health	T32 DK007727	07/01/2015 - 06/30/2020	$457,081
Lee A Denson, MD	Ulcerative Colitis Genetics Initiative	Crohn's & Colitis Foundation of America (Washington University)	326556	04/15/2014 - 04/14/2017	$245,006
Phillip P. Minar, MD	Therapeutic Monitoring and Targeting of Neutrophil Activation in Pediatric IBD	National Institutes of Health	K23 DK105229	04/06/2015 - 03/31/2019	$189,944
Jorge A Bezerra, MD	Colorado Center for Childhood	National Institutes of	U01 DK062453	06/01/2013	$3,238

	Liver Disease Research and Education	Health (University of Colorado)		- 05/31/2016	
Lee A Denson, MD	Gene Discoveries in Subjects with Crohn’s Disease of African Descent	National Institutes of Health (Emory University)	R01 DK087694	03/01/2014 - 02/28/2022	$10,000
John C Bucuvalas, MD	Biomarkers for Post-Transplant Lymphoproliferative Disorders in Children	National Institutes of Health (Stanford University)	60837668-107582 (U01)	02/01/2014 - 01/31/2018	$113,936
Chandrashekhar Gandhi, PhD	Mechanisms of Nonalcoholic Steatohepatitis	Department of Defense Army	W81XWH-15-1-0370	09/30/2015 - 09/29/2018	$438,053
Maisam Abu-El-Haija, MD	INSPPIRE To Study Pancreatitis in Children	National Institutes of Health (University of Iowa)	U01 DK108334	09/28/2015 - 08/31/2020	$24,180
Amanda Waddell, PhD	Role of Epithelial IL-33 Signaling in Chronic Colitis	Crohn's & Colitis Foundation of America	370202	01/01/2016 - 12/31/2018	$58,250
Stacey Huppert, PhD	Negative Regulation of Jagged1 by Glycosylation: Towards a Mechanism-based Therapy for Alagille Syndrome	National Institutes of Health (Baylor College of Medicine)	R01 DK109982	07/15/2016 - 06/30/2018	$57,305
Michael Rosen, MD, MS	Impact of ST2 Signaling and IBD Risk Variants on the Intestinal Epithelium	National Institutes of Health	R03 DK110487	07/01/2016 - 06/30/2018	$78,000
Stacey Huppert, PhD	Building a Functional Biliary System from Hepatocytes	National Institutes of Health	R01 DK107553	09/01/2016 - 07/31/2021	$549,895
Amy E. Taylor, MD	American Association for the Study Liver Diseases Foundation Advanced Heaptology Fellowship	Amer Assoc for the Study of Liver Dis	Taylor_AASLD	07/01/2016 - 06/30/2017	$60,000
Xiaonan Han, PhD	Regulation of Adult Intestinal Stem Cell Response to Enteric Infection and Inflammation in Pediatric Ileal Crohn’s Diseases	Crohn's & Colitis Foundation of America	426234	07/01/2016 - 06/30/2019	$115,830
Maisam Abu-El-Haija, MD	Magnetic Resonance Cholangiopancreatography (MRCP) A Reliable, Non-Invasive Method for Staging Chronic Pancreatitis from Minimal Change Disease to the Advanced Stages in Pediatrics	National Pancreas Foundation	Abu-El_Hajia_NPF	06/01/2016 - 05/31/2018	$50,000
Takanori Takebe, MD	Clinical Translation Of Organ Bud Transplant Therapy	The New York Stem Cell Foundation	NYSCF-R-I38	01/01/2017 -	$300,000

				12/31/2021	
Ajay Kaul, MD	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 7 to 17 Years, With Irritable Bowel Syndrome With Constipation (IBS-C)	Forest Research Institute	FRI_Kaul	12/15/2015 - 12/14/2018	$191,884
Jorge A Bezerra, MD	Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease	National Institutes of Health	P30 DK078392	06/01/2016 - 05/31/2017	$1,079,350
Alexander Miethke, MD	The Role of Regulatory T Cells in Biliary Atresia	National Institutes of Health	R01 DK095001	07/01/2016 - 06/30/2018	$333,825
Heidi J Kalkwarf, PhD	Bone Mineral Accretion in Young Children	National Institutes of Health	R01 HD076321	08/01/2016 - 07/31/2018	$1,035,013
Ajay Kaul, MD	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation (FC)	Forest Research Institute	Forest Research Inst	12/15/2015 - 12/14/2018	$99,672
Akihiro Asai, MD, PhD	Engineering Human Liver Organoids for Modeling of Inherited Cholestasis	NASPGHAN Foundation	NASPGHAN_Asai	11/15/2016 - 11/14/2018	$75,000
Chandrashekhar Ghandi, PhD Hamilton Parker Sorensen	Mechanisms of Liver Failure	Department of Veteran Affairs	IPA_Sorenson	06/06/2016 - 06/05/2019	$42,053
Dana M Dykes, MD	Anti-TNF Monotherapy versus Combination Therapy with Low Dose Methotrexate in Pediatric Crohn's Disease (COMBINE)	University of North Carolina	PCS-1406-18643	10/13/2016 - 10/31/2019	$9,710
Chandrashekhar Ghandi, PhD Sudhir Kumar, PhD	Mechanisms of Liver Failure	Department of Veteran Affairs	IPA_Kumar	10/05/2016 - 10/04/2019	$62,754
Jorge A Bezerra, MD	Childhood Liver Disease Research Network Data Coordinating Center	National Institutes of Health (Arbor Research Collaborative for Health)	U01 DK062456	09/27/2016 - 05/31/2020	$18,920

Phillip P. Minar, MD	Targeting the Inflammatory Signature to Personalize Biologics in Pediatric Crohn's (Refine)	Crohn's & Colitis Foundation of America	CCFA # 524285	01/01/2017 - 12/31/2017	$110,000
Chandrashekhar Ghandi, PhD Richa Rani, PhD	Mechanisms of Liver Failure	Department of Veteran Affairs	IPA-Rani	01/03/2017 - 01/02/2020	$57,037
Total Annual Grant Award Dollars					**$9,395,075**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Lee A Denson, MD	Janssen Research & Development, LLC	$239,447
Pranav-Kumar Shivakumar, PhD	Alexion Pharmaceuticals, Inc.	$100,000
Samuel Kocoshis, MD	NPS Pharmaceutical, Inc.	$274,347
Samuel Kocoshis, MD	Shire International GmbH	$79,262
Stavra A Xanthakos, MD	Ironwood Pharmaceuticals, Inc.	$54,292
Stavra A Xanthakos, MD	Resonance Health Ltd	$49,694
Takanori Takebe, MD	Japan Science and Technology Agency	$137,145
Takanori Takebe, MD	Ono Pharmaceutical Co., Ltd.	$435,039
Vincent A Mukkada, MD	Shire Human Genetic Therapies	$272,646
William F Balistreri, MD	Gilead Sciences, Inc.	$139,899
Total Annual Industry Award Dollars		**$1,781,771**