

Division Data Summary

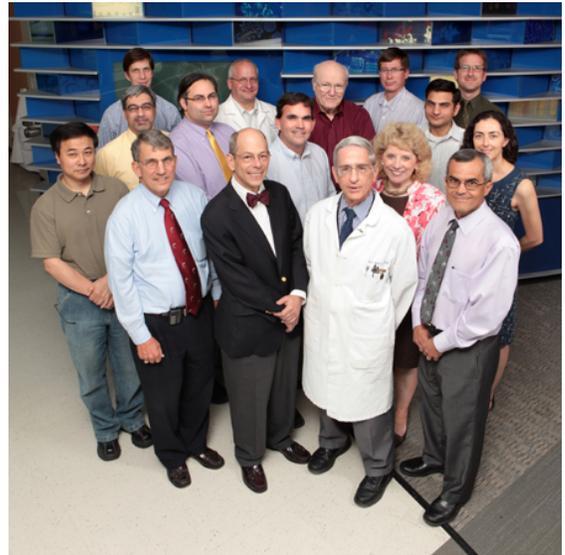
Research and Training Details

Number of Faculty	30
Number of Research Fellows	3
Number of Research Students	1
Number of Support Personnel	69
Direct Annual Grant Support	\$5,093,117
Direct Annual Industry Support	\$101,184
Peer Reviewed Publications	89

Clinical Activities and Training

Number of Clinical Staff	47
Number of Clinical Fellows	13
Inpatient Encounters	8714
Outpatient Encounters	15158

Division Photo



Row 1: X Han, J Heubi, M Cohen, W Balistreri, J Bezerra
Row 2: S Saeed, J Franciosi, L Denson, C Wetzel, S Xanthakos
Row 3: A Miethke, J Palermo, M Farrell, P Putnam, R Kohli, S Moore

Significant Publications

Moyer K, Kaimal V, Pacheco C, Mourya R, Xu H, Shivakumar P, Chakraborty R, Rao M, Magee J, Bove K, Aronow BJ, Jegga AG, **Bezerra JA**. **Molecular subtypes of biliary atresia with relevance to clinical outcome.** *Genome Med.* 2:33. 2010.

Matte U, **Miethke A**, Liu C, Mourya R, Kauffmann G, Moyer K, Zhang K, Wang N, Bull L, Thompson R, Spinner NB, **Bezerra JA**. **High-throughput sequence analysis of multiple genes in patients with inherited syndromes of intrahepatic bile ducts.** *J Ped Gastroenterol Nutr.* 51:488-93. 2010.

Biliary atresia and inherited cholestatic syndromes comprise the most common causes of chronic liver diseases in neonates and children. In two publications, Dr. Bezerra and co-investigators validated a molecular chip to screen for mutations that cause cholestasis in children. Using this chip, they were able to diagnose specific syndromes in a substantial number of children with chronic liver disease in whom no specific cause could be established. Further, analyzing livers of children with biliary atresia, they discovered a molecular signature that enables the staging of disease at the time of diagnosis. These findings will facilitate the diagnostic algorithms in clinical practice and improve clinical trials to take into account the biological makeup of children with liver disease.

Moore SR, NL Lima, Soares AM, Oriá RB, Pinkerton RC, Barrett LJ, Guerrant RL, Lima AA. **Prolonged episodes of acute diarrhea reduce growth and increase risk of persistent diarrhea in children.** *Gastroenterology.* 39: 1156-64. 2010.

We conducted a decade-long prospective cohort study of diarrhea among children (n=414) born into a poor periurban community in Brazil's tropical, developing Northeast region in order to elucidate the epidemiology and impact of prolonged episodes of acute diarrhea (ProD, duration >7 and <13 days) in a highly endemic setting. Our key findings include: 1) 50% of all days with diarrhea were attributable to ProD or persistent diarrheal (PD, >14 days) episodes, 2) ProD was associated with Shigella and Cryptosporidium infections, 3) a reciprocal relationship between ProD and undernutrition, and 4) a robust correlation of infantile ProD with future risk for PD. Taken together, these findings suggest that ProD accounts for significant morbidity and identifies children at risk of a vicious cycle of diarrhea and malnutrition.

Crandall W, Kappelman M, Colletti R, Leibowitz I, Grunow J, Ali S, Baron H, Berman J, Boyle B, Cohen S, del Rosario F, Denson L, Duffy L, Integlia M, Kim S, Milov D, Patel A, Schoen B, Walkiewicz D, Margolis P. **ImproveCareNow: The Development of a Pediatric IBD Improvement Network.** *Inflamm Bowel Dis.* 17:450-7. 2011.

Variation in care seems to be the norm rather than exception in care of chronic medical conditions. This is true for pediatric inflammatory bowel disease as well. It has been demonstrated that development of evidence based treatment guidelines and quality improvement science methods can help address unwarranted variation in care and outcomes. Here we report the establishment of The ImproveCareNow Network as a prototype for a model of improving subspecialty care that includes three components: 1) creating enduring multicenter collaborative networks of pediatric subspecialists, 2) sharing of performance data collected in patient registries, and 3) training in quality improvement. The network began with a focus on improving initial diagnostic testing and evaluation, the classification of the severity and extent of disease, the detection and treatment of inadequate nutrition and growth, and the appropriate dosing of immunomodulator medications. Changes are based on an evidence-based model of chronic illness care involving the use of patient registries for population management, previsit planning, decision support, promoting self-management, and auditing of care processes. Currently, patients are being enrolled at 31 sites. In the paper, we report analyzed data on over 2500 patients from over 7500 visits. Initial results suggest improvements in both care processes (e.g., appropriate medication dosing and completion of a classification bundle that includes the patient's diagnosis, disease activity, distribution and phenotype, growth status, and nutrition status) and outcomes (e.g., the percentage of patients in remission).

Kohli R, Kirby M, Setchell KDR, Jha P, Klustaitis K, Woollett LA, Pfluger PT, Balistreri WF, Tso P, Jandacek RJ, Woods SC, Heubi JE, Tschoep MH, D'Alessio DA, Shroyer NF, Seeley RJ. **Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity related co-morbidities.** *Am J Physiol.* 299: G652 - G660. Sep, 2010.

Surgical interventions for obesity (Bariatric Surgery) have become an established treatment for both adults and adolescents who are morbidly obese. The interposition of distal ileum into the proximal jejunum is a bariatric procedure that improves the metabolic syndrome. Changes in intestinal and hepatic physiology after ileal interposition (transposition) surgery (IIS) are not well understood. Our aim was to elucidate the adaptation of the interposed ileum, which we hypothesized, would lead to early bile acid reabsorption in the interposed ileum, thus short circuiting enterohepatic bile acid recycling to more proximal bowel segments. Rats with diet-induced obesity were randomized to IIS, with 10 cm of ileum repositioned distal to the duodenum, or sham surgery. A subgroup of sham rats was pair-fed to IIS rats. Physiological parameters were measured until 6 wk postsurgery. IIS rats ate less and lost more weight for the first 2 wk postsurgery. At study completion, body weights were not different, but IIS rats had reversed components of the metabolic syndrome. The interposed ileal segment adapted to a more jejunum-like villi length, mucosal surface area, and GATA4/ILBP mRNA. The interposed segment retained capacity for bile acid reabsorption and anorectic hormone secretion with the presence of ASBT and glucagon-like-peptide-1-positive cells in the villi. IIS rats

had reduced primary bile acid levels in the proximal intestinal tract and higher primary bile acid levels in the serum, suggesting an early and efficient reabsorption of primary bile acids. IIS rats also had increased taurine and glycine-conjugated serum bile acids and reduced fecal bile acid loss. There was decreased hepatic Cyp27A1 mRNA with no changes in hepatic FXR, SHP, or NTCP expression. IIS protects against the metabolic syndrome through short-circuiting enterohepatic bile acid recycling. There is early reabsorption of primary bile acids despite selective "jejunitization" of the interposed ileal segment. Changes in serum bile acids or bile acid enterohepatic recycling may mediate the metabolic benefits seen after bariatric surgery.

Steinbrecher KA, Harmel-Laws E, Garin-Laflam MP, Mann EA, Bezerra LD, Hogan SP, **Cohen MB. Murine Guanylate Cyclase C Regulates Colonic Injury and Inflammation.** *J Immunol.* 186(12):7205-14. 2011.

Guanylate cyclase C and its ligands, guanylin and uroguanylin, are expressed in intestinal epithelial cells (IECs) and regulate ion secretion, intestinal barrier function, and epithelial monolayer homeostasis via cGMP-dependent signaling pathways. Recent studies indicate that GC-C and its ligands direct the course of intestinal inflammation. We found that chemically-induced colitis and histological damage to the colonic mucosa were significantly less severe in GC-C knockout mice. Basal and inflammation-induced production of resistin-like molecule β (RELM β) was substantially diminished in GC-C knockout mice. RELM β is thought to stimulate cytokine production in macrophages in this disease model and, consistent with this, TNF α and IFN γ production was minimal in mice lacking GC-C. Colonic instillation of recombinant RELM β by enema into these animals restores sensitivity to DSS-mediated mucosal injury. These findings demonstrate a novel role for GC-C signaling in facilitating mucosal wounding and inflammation and further suggest that this may be mediated, in part, through control of RELM β production.

Division Highlights

Kathleen Campbell, MD; John Bucuvalas, MD; Jorge Bezerra, MD; Mike Leonis, MD, PhD

Pediatric Liver Transplant Program

The Pediatric Liver Transplant Program continues its' mission of advancing the care of liver transplant recipients by improving the health care delivery system, providing unparalleled clinical care, and addressing gaps in knowledge through patient-based and basic laboratory research. The program remains one of the largest pediatric liver transplant programs in the country, with excellent clinical outcomes at or above the national average. Clinical highlights in fiscal year 2011 included the incorporation of advanced practice nurses into the inpatient care delivery team, a successful site survey from the United Network for Organ Sharing (the primary regulatory agency for solid organ transplantation in the United States), and a growing niche area in transplantation for hepatic tumors, fostered in collaboration with the Oncology division. In Fall 2010 the Liver Transplant program was chosen, in combination with the Biliary Atresia Program, as one of the first "High Impact Conditions" defined by hospital leadership as a focus area for achievement of "Best In Class" status by 2015, highlighting the strong accomplishments and solid performance of the program over time. Members of the Liver Transplant Program continue to be leaders in national quality improvement efforts and multi-center clinical and translational studies. These include: the Pediatric Acute Liver Failure Study Group (PALF), Medication adherence in children who had a liver transplant (MALT), Functional outcomes in liver transplant recipients (FOG), Immunosuppression withdrawal for stable pediatric liver transplant recipients (iWITH), Studies in Pediatric Liver Transplantation (SPLIT) clinical registry, SPLIT Quality Improvement Initiative sponsored by the CCHMC Center for Education and Research on Therapeutics, Calcineurin Inhibitor Minimization and Foxp3+ T-regs post-transplant.

Stavra Xanthakos, MD; Rohit Kohli, MD

Cincinnati Children's Steatohepatitis Center

The Cincinnati Steatohepatitis Center (CCSC) is a multidisciplinary clinic initiated in November 2007 to care for the unique needs of pediatric patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NAFLD, the hepatic consequence of obesity and metabolic syndrome, affects about 10% of children and ranges from fatty liver alone (NAFLD) to fatty liver with varying degrees of liver inflammation and fibrosis (NASH). NASH is estimated to progress to cirrhosis and liver failure in an estimated 25% of adult individuals; we have shown that fibrosis can progress even in childhood.

The CCSC evaluates patients for alternate causes of elevated liver enzymes and screens for closely related comorbidities including insulin resistance, hypertension, dyslipidemia, type 2 diabetes mellitus, polycystic ovarian syndrome and obstructive sleep apnea. For therapy, enrollment into intensive weight management programs such as Healthworks! is encouraged, but the clinic also provides individualized dietary consultation and recommendations for families who cannot participate in more intensive programs and follows progress in meeting nutritional and activity goals.

The CCSC faculty include: Stavra Xanthakos MD, MS (medical director), Rohit Kohli MBBS, MS (co-director) and William Balistreri, MD. Access has been increased this year by incorporating a nurse practitioner into our program as well. Research programs in the CCSC have also significantly expanded since its inception and aim to improve our understanding and treatment options for this disease. Researchers in the CCSC are currently studying the outcome of NASH after bariatric surgery in adolescents (K23DK080888, PI: Xanthakos) and animal models of bariatric surgery and NASH (K08 DK084310, PI: Kohli). The CCSC is a major participating pediatric site in the NIH-funded NASH Clinical Research Network (U01 DK08505, Center PI: Xanthakos), a multi-center study investigating the natural history and determinants of NASH in adults and children and will be offering a clinical therapeutic trial anticipated to begin in early 2012.

The CCSC has published clinical and pre-clinical papers in the area of steatohepatitis research over the last year in the following journals: Hepatology; Journal of Pediatric Gastroenterology and Nutrition, and the American Journal of Physiology, and Journal of Hepatology. The CCSC continues to give talks to local community pediatric care providers and practices. The CCSC presented its outcomes data at the annual meeting of the North American Society for Pediatric Gastroenterology at its annual meeting last year.

Phil Putnam, MD; James Franciosi, MD

Cincinnati Center for Eosinophilic Disorders (CCED)

The CCED is a high volume, multidisciplinary tertiary referral care center specializing in Eosinophilic Gastrointestinal Disorders (EGID) in both the pediatric and adult populations. The core clinical group is made up of members from the Divisions of Gastroenterology, Nutrition and Hepatology, Allergy and Immunology, Social Work and Nutrition. The CCED extensively utilizes a number of ancillary services within the hospital during the process of treating these patients. Families are seen for a week long baseline visit and then subsequent, one day follow visits on a regular basis (at least once yearly).

In 2010, the CCED physician's and staff managed cared for 515 distinct patients that included: 190 new patient cases from 44 states (including Ohio) and one country outside of the U.S. (Peru), over 722 endoscopic procedures on patients with an EGID diagnosis (24% of the total GI endoscopies at CCHMC), and 607 GI clinic visits.

Research through the CCED involves basic, clinical and translational studies. Patients are offered enrollment in diverse research studies including epidemiology, quality of life research, descriptive research databanks,

specimen databanks (collections of endoscopy tissue, blood, and DNA), translational studies, and clinical trials. In 2010, members of the CCED team published over 15 papers on eosinophilic disorders in major medical journals including the journal *Nature Genetics*. Dr. Franciosi has further characterized the epidemiology of eosinophilic esophagitis as a chronic, under-recognized inflammatory condition in children. The CCED team has also determined that EGID conditions have a significant negative impact on quality of life. Dr. Rothenberg's laboratory has identified a gene possibly involved in susceptibility to eosinophilic esophagitis at the 5q22 locus.

As a continuation of our \$1.5 million NIH stimulus research grant awarded in 2009, the first national Registry for Eosinophilic Gastrointestinal Disorders (www.regid.org) has been launched in 2010 and will begin enrolling patients in 2011. The CCED is leading a multi-center registry collaboration with eight pediatric and adult hospitals with plans for further expansion.

Jorge Bezerra, MD; Mitchell Cohen, MD; Cynthia Wetzel, PhD

Digestive Health Center (DHC)

The DHC is one of 17 Silvio O. Conte Digestive Diseases Research Core Centers in the nation supported by the National Institutes of Diabetes & Digestive & Kidney Diseases. The DHC, located within the Division of Gastroenterology, Hepatology, and Nutrition at Cincinnati Children's Hospital Medical Center is the only Core Center dedicated to research on pediatric digestive diseases. The DHC cores provide services to increase the tempo of scientific discoveries in digestive disease research and to attract new investigators to the field. The overall goal of the DHC, is to promote research that will yield insights into the fundamental processes and pathogenic mechanisms of digestive disease in children and generate innovative treatment to restore digestive health. Specifically, the long term goals are to improve child health through better diagnosis, treatments and outcomes for our 4 key focus areas and diseases: 1) Chronic Liver Disease (biliary atresia, chronic cholestasis, and liver transplantation); 2) Inflammatory and Diarrheal Diseases (inflammatory bowel disease, eosinophilic gastrointestinal disorders, and infectious diarrhea) 3) Obesity and the Digestive System (including liver and metabolic complications of obesity), and 4) Development and Digestive Diseases (molecular basis of organogenesis, adult stem cell/homeostasis, and intestinal organoids from stem cells). The focus areas are linked by four highly innovative Biomedical Research Cores: Gene and Protein Expression, Bioinformatics, and Integrative Morphology; a Biostatistical Service is also available through a collaborative effort with the Center for Clinical and Translational Science and Training Program). In addition, the DHC provides 3-6 pilot and feasibility awards each year to investigators starting research projects with the potential for extramural funding. The DHC director is Dr. Jorge Bezerra, the associate Directors are Drs. Mitchell Cohen, Aaron Zorn, and Marshall (Chip) Montrose, and the Project Manager is Dr. Cynthia Wetzel. The DHC has 56 investigators and 29 associate members from 17 different divisions within the Department of Pediatrics and a total of 8 departments within the University of Cincinnati, College of Medicine.

Scott Pentiuik, MD

Interdisciplinary Feeding Team (IFT)

This multi-disciplinary team provides comprehensive evaluation of children with swallowing/feeding disorders. It includes members from gastroenterology, otolaryngology, human genetics, speech therapy, occupational therapy, social work, and nutrition. Dr. Scott Pentiuik MD is the pediatric gastroenterologist on the team. The IFT continues to grow at nearly 10% per year with over 1200 patient visits over the last year. The team has also expanded its outpatient treatment programs with the development of co-treatment sessions and Parent-Child Interaction Training for families. Current IFT research projects include the use and development of a

pureed by G-tube diet, quality of life assessment of feeding therapies, methods to evaluate children with swallowing dysfunction, and the creation of a prospective database in order to track the effectiveness of therapies and patient outcomes.

Jorge Bezerra, MD; Alex Miethke, MD

Chronic Liver Disease Program

The Bezerra laboratory investigates regulatory mechanisms of liver and biliary injury. One major research focus is pre-clinical and translational research on biliary atresia, the most common cause of chronic liver disease in children. He has used large-scale expression arrays and bioinformatics to develop transcriptional maps for human and murine biliary atresia. These maps generated hypotheses regarding pathogenic mechanisms of disease. Testing these hypotheses in the laboratory, he began dissecting the cellular and molecular basis of neonatal injury and obstruction of extrahepatic bile ducts using unique *in vitro* and experimental models of disease. Experiments identified key regulatory functions for hepatic dendritic cells and CD8+ and NK lymphocytes in recognition and induction of apoptosis of the bile duct epithelium. Ongoing experiments are identifying co-stimulatory signals controlling cell survival during early postnatal development and small molecules regulating biliary diseases. In translational studies, he is also applying state-of-the-art approaches to identify the molecular determinants of treatment response in multi-center studies of children with biliary atresia and syndromes of intrahepatic cholestasis.

Division Collaboration

Biomedical Informatics » Bruce Aronow, PhD; Anil Jegga, DVM, MRes

Collaboration through the Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease
- Jorge Bezerra, MD

Studies of the molecular basis of clinical phenotypes of biliary atresia - Jorge Bezerra, MD

Developmental Biology » S Steven Potter, MD; Aaron Zorn, PhD; James Wells, PhD

Collaboration through the Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease
- Jorge A. Bezerra, MD

Studies of development and function of the biliary system - Jorge Bezerra, MD

Pathology » David P Witte, MD; Keith F Stringer, MD; Rachel Sheridan, MD; Kevin Bove, MD

Collaboration through the Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease
- Jorge Bezerra, MD

Studies of mechanisms of hepatic tumorigenesis - Jorge Bezerra, MD

Molecular staging of liver injury in biliary atresia - Jorge Bezerra, MD

Molecular Immunology » Claire Chougnet, PhD; Kasper Hoebe, PhD

Studies of the role of the immune system in pathogenesis of biliary atresia - Jorge Bezerra, MD

Studies of mechanisms of hepatic tumorigenesis - Jorge Bezerra, MD

Animal models of liver diseases - Jorge Bezerra, MD

Immunobiology » Marsha Wills-Karp, PhD; Jochen Mattner, MD, PhD

Collaboration through the Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease
- Jorge Bezerra, MD

Studies of mechanisms of auto-immune liver disease - Jorge Bezerra, MD

Pediatric Surgery; Liver Care Center » Greg Tiao, MD; Jaimie Nathan, MD

Studies of the virologic basis of biliary atresia - Jorge Bezerra, MD

Studies of immunologic injury of bile ducts - Jorge Bezerra, MD

Allergy & Immunology » Simon Hogan, PhD

Effects of weanling undernutrition and glutamine dipeptide supplementation on intestinal barrier function in mice - Sean Moore, MD

Paired Immunoglobulin Receptor B Regulation of Innate Intestinal Immunity - Kris Steinbrecher, PhD

Pathogenic role of the macrophage in ulcerative colitis - Kris Steinbercher, PhD

Role of Signal Transducer and Activator of Transcription 5 in Gut Injury - Xiaonan Han, PhD

Global Health Center; Infectious Diseases » Mark Steinhoff, MD; Elizabeth Schlaudecker, MD

Interactions of diarrhea, pneumonia, and malnutrition in childhood - Sean Moore, MD

James M Anderson Center for Health System Excellence » Peter Margolis, MD, PhD; Michael Seid, PhD

Collaborative Chronic Network (C3N) / Enhanced Registry grant - develop a network of collaborators (physicians, patients, researchers) that transforms the outcomes and experience of patients with IBD, accelerate discovery and application of new knowledge by employing Quality Improvement tools, and information technology - Shehzad Saeed, MD

Psychology » Kevin Hommel, PhD

Adherence in Pediatric IBD - Examine the effects of telehealth behavioral treatment (TBT) on medication adherence in children with IBD, disease severity, quality of life and health care utilization versus education only (EO) intervention - Shehzad Saeed, MD

Adolescent Medicine » Ellen Lipstein, MD, MPH

Assessment of decision making in choosing biological therapy for treatment of Crohn's disease employing qualitative interviewing tools - Shehzad Saeed, MD

Adherence Center » Sandra Corina, PhD

Developing culturally sensitive behavioral therapies for patients of middle eastern origin admitted to CCHMC - Shehzad Saeed, MD

Pulmonary Medicine » John P Clancy, MD

Centralized Intestinal Current Measurement testing, and comparison of suction and forceps-based biopsy performance - Shehzad Saeed, MD

Otolaryngology; Human Genetics; Speech Therapy; Occupational Therapy; Social Services »

Interdisciplinary Feeding Team

Multi-disciplinary team provides comprehensive evaluation of children with swallowing/feeding disorders - Scott Pentiuk, MD

Hematology/Oncology » Joseph Palumbo, MD

Hemostatic Factors in Colitis and Colitis-Associated Colon Cancer - Kris Steinbrecher, PhD

Pathology » Kenneth Setchell, PhD; Lili Miles, MD; Peter Tang, PhD; Michael Miles, PharmD

Bile acids in animal models of bariatric surgery - Rohit Kohli, MD

Hepatic histology in NASH animal models - Rohit Kohli, MD

Coenzyme Q as a biomarker for NASH - Rohit Kohli, MD

Allergy » Senad Divanovic, PhD

The role of IL-17 in NASH - Rohit Kohli, MD

Infectious Diseases » Monica McNeal, MS; David Bernstein, MD

Effect of weaning malnutrition on the immunogenicity of oral rotavirus vaccines - Sean Moore, MD

Pathology » Kevin Bove, MD

Histomorphology of inherited cholestatic liver diseases - Alexander Miethke, MD

Molecular Immunology » Claire Chougnet, PhD

The role of regulatory T cells in biliary atresia - Alexander Miethke, MD

Neonatology; Pediatric Surgery » Andrew South, MD; Michael Helmrath, MD

Clinical and translational research characterizing children with and at risk for intestinal failure - Conrad Cole, MD; Samuel Kocoshis, MD; Adam Mezoff, MD; Noah Shroyer, PhD

Pediatric Surgery; Neonatology; Biostatistics & Epidemiology » Michael Helmrath, MD; Andrew South, MD; Eileen King, PhD

Efficacy of enteral glutamine in pediatric SBS - Conrad Cole, MD; Samuel Kocoshis, MD; Adam Mezoff, MD

Surgical Weight Loss Program for Teens; Center for Bariatric Research & Innovation » Thomas H Inge, MD, PhD; Todd Jenkins, PhD

Biological Determinants of Steatohepatitis - Stavra Xanthakos, MD

Teen LABS U01 - Stavra Xanthakos, MD

Surgical Weight Loss Program for Teens - Stavra Xanthakos, MD

Endocrinology » Nancy Crimmins, MD

NAFLD in Youth with Type 2 diabetes: An Important but Under-Recognized Co-Morbidity - Stavra Xanthakos, MD

General & Community Pediatrics; Cardiology; Endocrinology » Robert Siegel, MD; Holly Ippisch, MD; Nancy Crimmins, MD

Advanced Metabolic Clinic, a monthly multidisciplinary clinic for children with multiple obesity-related complications - Stavra Xanthakos, MD

Nephrology & Hypertension » Jens Goebel, MD

Calcineurin Inhibitor Minimization and Foxp3+ Tregs Post-Transplant - John Bucuvalas, MD

Center for Adherence and Self-Management » Dennis Drotar, PhD

Clinical Center for Medical Adherence in Liver Transplant Recipients: Etiopathogenesis and clinical outcome - John Bucuvalas, MD

Immunology » Lisa Filipovich, MD

Acute Liver Failure in Children: Role of immune dysregulation - John Bucuvalas, MD

Center for Health Care Quality; Pulmonary Medicine » Peter Margolis, MD, PhD; Michael Seid, PhD

"Transforming Chronic Illness Care" - The specific aim is to design, prototype, optimize, and evaluate a

patient-provider C3N to improve clinical practice, patient self-management, and disease outcomes of pediatric inflammatory bowel disease (IBD) - John Bucuvalas, MD

Allergy & Immunology; ; Behavioral Health » Marc Rothenberg, MD, PhD; J Pablo Abonia, MD, PhD; Kevin Hommel, PhD

Quality of Life and Symptom Severity Outcome Measures in Eosinophilic Esophagitis: Beyond Eosinophil Counting - James Franciosi, MD

Allergy & Immunology; ; Biomedical Informatics; Pathology » Marc Rothenberg, MD, PhD; J Pablo Abonia, MD, PhD; Keith Marsolo, PhD; Margaret Collins, MD

Eosinophilic Esophagitis Comparative Effectiveness - James Franciosi, MD

Allergy & Immunology; Neonatology & Pulmonary Biology; Developmental Biology » Simon Hogan, PhD; Jeffrey Whitsett, MD; James Wells, PhD

iPSC-derived intestinal tissue from CF patients - Noah Shroyer, PhD

Developmental Biology » James Wells, PhD

In vitro growth and differentiation of gastrointestinal tissue from human pluripotent stem cells - Noah Shroyer, PhD

Neonatology & Pulmonary Biology » Jeffrey Whitsett, MD

Transcriptional control of intestinal differentiation and neoplasia by SPDEF - Noah Shroyer, PhD

Neonatology & Pulmonary Biology; Developmental Biology » Jeffrey Whitsett, MD; James Wells, PhD

KLF5 control of gastrointestinal morphogenesis and stem cell homeostasis - Noah Shroyer, PhD

Pediatric Surgery; Developmental Biology » Michael Helmrath, MD; James Wells, PhD

Mesenchymal control of intestinal stem cells - Noah Shroyer, PhD

Pulmonary Medicine; Radiology » John Clancy, MD; Alexander Towbin, MD

Identifying early markers of liver disease in patients with cystic fibrosis - Joseph Palermo, MD, PhD

Faculty Members

Mitchell B Cohen, MD, Professor

Gastroenterology Endowed Chair

Vice-Chair of Pediatrics for Clinical Affairs

Director, Division of Gastroenterology, Hepatology and Nutrition

Associate Director, Digestive Health Center

Research Interests Diarrheal diseases

William F Balistreri, MD, Professor

Dorothy M.M. Kersten Endowed Chair

Director Emeritus, Pediatric Liver Care Center

Medical Director Emeritus, Liver Transplantation

Program Director, Advanced Hepatology Fellowship

Editor, Journal of Pediatrics

Research Interests Chronic liver disease

Jorge A Bezerra, MD, Professor

William and Rebecca Balistreri Chair in Pediatric Hepatology

Director of Research, Division of Gastroenterology, Hepatology and Nutrition

Director, Biliary Atresia Center

Director, Digestive Health Center

Research Interests Biliary atresia and chronic liver disease

John C Bucuvalas, MD, Professor

*Endowed Chair in Pediatric Transplant Hepatology
Associate Medical Director, Pediatric Liver Care Center
Director, Disease Specific Innovations and Outcomes Program*

Research Interests Liver failure and liver transplantation

Kathleen M Campbell, MD, Assistant Professor

Medical Director, Pediatric Liver Transplant

Research Interests Liver failure and liver transplantation

Conrad R Cole, MD, Associate Professor

Associate Medical Director, Intestinal Rehabilitation Program

Research Interests Intestinal failure

Lee A Denson, MD, Associate Professor

*M. Susan Moyer Chair in Pediatric IBD
Director, Schubert-Martin Pediatric IBD Center
Director, Fellowship Training Program in Pediatric Gastroenterology, Hepatology and Nutrition*

Research Interests Inflammatory Bowel Diseases

Michael K Farrell, MD, Professor

Chief of Staff

Research Interests Nutrition

James Franciosi, MD, Assistant Professor

Research Interests Eosinophilic Gastrointestinal Disorders

Jose Garza, MD, Assistant Professor

Research Interests Neurogastroenterological disorders

Xiaonan Han, PhD, Assistant Professor

Research Interests Inflammatory Bowel Diseases

James E Heubi, MD, Professor

*Associate Chair for Clinical Investigation of Pediatrics
Associate Dean for Clinical and Translational Research
Co-Director, Center of Clinical and Translational Science & Training*

Research Interests Chronic liver disease

Ajay Kaul, MD, Associate Professor

*Director, Impedance/Motility Disorders Program
Medical Director, Liberty Campus for GI*

Research Interests Intestinal motility disorders

Samuel A Kocoshis, MD, Professor

*Medical Director, Pediatric Nutritional and Intestinal Care Center
Medical Director, Small Bowel Transplantation Program*

Research Interests Intestinal Failure and Intestinal Transplantation

Rohit Kohli, MD, Assistant Professor

Co-Director, Steatohepatitis Center

Research Interests Non-alcoholic steatohepatitis

Mike A Leonis, MD, PhD, Assistant Professor

Associate Fellowship Director, Training Program in Pediatric Gastroenterology, Hepatology and Nutrition

Research Interests Liver failure and liver transplantation; liver tumors

Adam G Mezoff, MD, Professor

*Associate Medical Director, Pediatric Nutritional and Intestinal Care Center
Clinical Director for Gastroenterology*

Research Interests Intestinal failure and intestinal transplantation

Alexander Miethke, MD, Assistant Professor

Research Interests Biliary atresia and primary sclerosing cholangitis

Sean Moore, MD, Assistant Professor

Research Interests Diarrheal Diseases and International Health

Joseph Palermo, MD, PhD, Assistant Professor

Research Interests Disorders of the bile ducts

Scott Pentiuk, MD, Assistant Professor

Pediatric Residency Course Director for Gastroenterology

Research Interests Feeding disorders; medical education

Philip E Putnam, MD, Professor

Director, Endoscopy Services

Medical Director, Cincinnati Center for Eosinophilic Disorders

Research Interests Eosinophilic Gastrointestinal Disorders

Shehzad A Saeed, MD, Associate Professor

Associate Director, GI Fellowship Program

Clinical Director of the Schubert-Martin IBD Center

Research Interests Inflammatory Bowel Disease

Charles Samson, MD, Instructor

Research Interests Inflammatory Bowel Disease

Pranav Shivakumar, PhD, Assistant Professor

Research Interests Biliary Atresia

Noah Shroyer, PhD, Assistant Professor

Research Interests Intestinal development

Kris Steinbrecher, PhD, Assistant Professor

Research Interests Diarrheal diseases; Inflammatory Bowel Diseases

Cynthia C Wetzel, PhD, Assistant Professor

Program Manager, Digestive Health Center

Research Interests Research Administration

Stavra Xanthakos, MD, Assistant Professor

Medical Director, Surgical Weight Loss Program for Teens

Co-Director, Steatohepatitis Center

Research Interests Obesity; Non-alcoholic steatohepatitis

Nada Yazigi, MD, Associate Professor

Associate Medical Director, Multivisceral Transplantation Program

CSI Inpatient Co-Director, A4N

Research Interests Liver failure and liver transplantation

Trainees

- M Kyle Jenson, MD, PL-7, Children's Hospital and Health System and the Medical College of Wisconsin
- Stephanie Appleman, MD, PL-6, INOVA Fairfax Hospital for Children

- Benjamin Kuhn, DO, PL-6, Penn State Children's Hospital
- Anna Trauernicht, MD, PL-6, Indiana University
- Amy Tsai, MD, PL-6, New York Medical College
- Frank Dipaola, MD, PL-5, Vanderbilt Children's Hospital
- Dana Dykes, MD, PL-5, Children's Hospital at UAB
- Jaime Echartea-Gonzalez, MD, PL-5, Cincinnati Children's Hospital Medical Center
- Kristin Bramlage, MD, PL-5, NS-LIJ Health System
- Monique Choquette, MD, PL-4, Cincinnati Children's Hospital Medical Center
- Phillip Minar, MD, PL-4, Medical College of Wisconsin
- George Zacur, MD, PL-4, University of Miami/Jackson Memorial Hospital
- Kazuhiko Bessho, MD, PhD, Osaka University, Japan
- Ingrid Jurickova, MD, Second Medical Faculty, Charles University, Prague, Czech Republic
- Jun Li, MD, PhD, Beijing Medical University and Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China
- Elizabeth Mann, PhD, State University of New York at Buffalo
- Taeko Noah, PhD, University of Nevada, Reno
- Vijay Saxena, PhD, Kanpur University, India
- Celine Silva-Lages, PhD, University Paris Diderot, Paris 7, Paris, France
- Samir Softic, MD, Wright State University - Boonshoft School of Medicine, Dayton, Ohio
- Tara Willson, BS, University of Kentucky, Lexington

Significant Accomplishments

The Chronic Liver Disease Program

Staffed by nine pediatric hepatologists, the Chronic Liver Disease Program serves a national and international referral population via a comprehensive evaluation of all medical and surgical aspects of liver disease and offers prompt initiation of conventional and innovative treatments. The evaluation includes a full spectrum of metabolic analysis, inflammatory processes and high-throughput gene sequencing to screen for genetic diseases. The clinic allows for timely consultation with surgeons, pathologists, radiologists and nutritionists with expertise in pediatric liver disease, thus enabling a thorough evaluation of the impact of the illness on the child's well-being. For children with advanced stages of liver disease, an evaluation for liver transplantation and close follow-up in the pre-transplant clinic enable the implementation of the most comprehensive treatment protocol to minimize complications and improve post-transplant course.

Recognizing that research is critical to improved care, clinic staff members lead multicenter studies sponsored by the National Institutes of Health to advance knowledge on mechanisms of pediatric liver disease and to develop diagnostic and treatment modalities. Recent innovations include: 1) the development of a high-throughput gene chip to diagnose mutations in children with genetic liver diseases, 2) an ongoing trial to determine the efficacy of corticosteroids in children with biliary atresia, 3) a study to examine the role of immune dysregulation in the etiology of acute liver failure, 4) studies to discover biomarkers and therapies for fatty liver disease, and 5) the development of therapies for bile acid disorders. The clinical and research programs create an outstanding environment for the training of future leaders in the field via a fellowship training program in advanced hepatology.

Intestinal Rehabilitation Program

The Intestinal Rehabilitation Program has experienced considerable growth during the past year to position

itself for a national leadership role in conducting basic scientific, translational and clinical research. The multidisciplinary initiative to standardize care and facilitate research among the three disciplines (gastroenterology, neonatology and surgery) providing care to infants and children with intestinal failure was implemented. Currently the rate of survival without significant liver disease (as measured by cholestasis) of our patients with intestinal failure is among the highest nationally. Major clinical initiatives include weekly multidisciplinary bedside rounds; development of a specific emergency department protocol for standardized evaluation and treatment of fevers among children with central venous catheters; and pre-clinic planning meetings, which are expected to improve the patient's clinic experience. In addition, we have protocolized management of central venous catheters with suspected bacterial biofilms by initiating ethanol lock therapy and laboratory assessment of nutritional markers. These initiatives have significantly reduced the incidence of outpatient acquired central line bloodstream infections.

Translational and clinical trials research initiatives were also implemented. These include evaluating the relative value of biomarkers of infection (sTREM2 [triggering receptors of myeloid cells] and LBP [lipoprotein binding protein]) for identifying acute bloodstream infections (BSI) and for predicting need for liver/bowel transplant and death among our population on total parenteral nutrition (TPN). Other studies include developing *in vitro* culture methods to grow and expand both normal and diseased intestinal tissue from patients with intestinal failure; validating the use of bomb calorimetry as a measure of enteral energy balance among intestinal failure patients; and feeding advancement trial in patients with gastroschisis to identify the method that optimally decreases the duration of TPN. We continue participation in the 15-center Pediatric Intestinal Failure Consortium and are in the process of analyzing data describing factors impacting outcomes in pediatric intestinal failure.

Inflammatory Bowel Disease

The number of patients receiving multidisciplinary care for IBD has continued to grow, with children from more than 25 states seen over the past year. State-of-the-art services including diagnostic imaging modalities, which do not require radiation exposure, and targeted psychology interventions for nonadherence have been implemented. We have continued to contribute to international genome-wide association studies to identify susceptibility genes specifically for pediatric-onset disease. Investigators have received funding from the National Institutes of Health (NIH) to develop the first multicenter North American randomized controlled trial in newly diagnosed children with ulcerative colitis, the PROTECT study. Within this trial, we will develop a model to predict individual patient therapeutic responses and clinic outcomes that will incorporate clinical, genetic and immune biomarkers that we have developed. At Cincinnati Children's, this trial will include collaborators in the Divisions of Pulmonary Biology and Biomedical Informatics. Under the leadership of Kevin Hommel, PhD, in the Adherence Center, we will be one of three centers to participate in the first randomized controlled trial of telehealth interventions to improve medication adherence in children with IBD.

It is anticipated that the knowledge gained from these studies will be rapidly translated to practice through our collaborations with Peter Margolis, MD, PhD, in clinical effectiveness, via his leadership of the ImproveCareNow (ICN) pediatric IBD quality improvement network. The IBD Center has continued to play a leading role in ICN, which has achieved a 20 percent improvement in patient remission rates with implementation of consensus patient care guidelines and practices. This network was the basis for an NIH award to Margolis in the Center for Health Care Quality to develop an innovative web-based social networking model to improve outcomes for children with IBD, termed C3N. As part of this collaborative network, patient-focused activities are being developed to improve patient outcomes and engage patients and their families to become more involved in the care of their IBD. A pilot trial of daily symptom assessment using innovative bioinformatics tools was undertaken with the patient participating in daily and weekly

surveys of the symptoms and QOL measures.

Division Publications

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Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

BEZERRA, J

Clinical Center for Cholestatic Liver Disease in Children

National Institutes of Health

U01 DK 062497

09/10/09-05/31/14

\$489,645

Bezerra, J.	Administrative Core	\$394,826
Bezerra, J.	RNA Core	\$30,810
Heubi, J.	Bile Acid Core	\$29,808
Bove, K.	Histopathology Core	\$34,201

Biological Basis of Phenotypes & Clinical Outcomes in Biliary Atresia

National Institutes of Health

R01 DK 083781

09/01/09-08/31/13

\$237,600

Digestive Health Center: Bench to Beside Research in Pediatric Digestive Disease

National Institutes of Health

P30 DK 078392

08/01/07-05/31/12

\$843,422

Bezerra, J.	Administrative Core	\$373,722
Witte, D.	Integrative Morphology Core	\$114,769
Potter, S.	Gene Expression Core	\$54,717
Grabowski, G.	Sequencing Core	\$21,466
Aronow, B.	Bioinformatics Core	\$110,942
Wills-Karp, M.	Luminex Service	\$38,792

Bezerra, J.	Flow Cytometry Service	\$29,014
Diavanovic, S.	Pilot & Feasibility Grant	\$50,000
Spence, J.	Pilot & Feasibility Grant	\$50,000
Immunologic Dystunction in Biliary Artresia		
National Institutes of Health		
R01 DK 064008	02/25/08-01/31/13	\$208,271

BUCUVALAS, J

Medication Adherence in Children Who Had Liver Transplant

National Institutes of Health(Mount Sinai Medical Center)

R01 DK 080740 12/22/09-06/30/14 \$59,348

Immunosuppression Withdrawal for Stable Pediatric Liver

National Institutes of Health(The Univ of California, San Francisco)

U34 DK 083031 09/30/09-08/31/11 \$44,132

Calcineurine Inhibitor Minimization and FOXP3+ Tregs Post Transplant

National Institutes of Health(Children's Hospital of Philadelphia)

RC1 DK 087270 09/30/09-07/31/11 \$83,323

Functional Outcomes In Peds Liver Transplantation-Per patient

National Institutes of Health(Children's Memorial Hospital)

R01 HD 045694 04/01/05-06/30/11 \$577

COHEN, M

Phase I Study ETEC dmLT

National Institutes of Health(University of Maryland)

NO1 AI 40014 07/19/10-02/16/13 \$554,427

COHEN, M/DENSON, L

Pediatric Gastroenterology and Nutrition Training Grant

National Institutes of Health

T32 DK 007727 07/01/10-06/30/15 \$401,858

COHEN, M/STEINBRECHER, K

Expression and Function of the Guanylin Ligand Family

National Institutes of Health

R56 DK 047318 08/01/10-07/31/11 \$250,000

DENSON, L

Risk Stratification and Identification of Immunogenetic and Microbial Markers of Complicated Disease Course in Pediatric Crohn's Disease

Crohn's & Colitis Foundation of America(Emory University)

S305815 07/01/09-06/30/13 \$114,799

Complicated Disease Course in Pediatric Crohn's Disease

Crohn's & Colitis Foundation of America(Emory University)

S305815 07/01/09-06/30/13 \$46,308

Biomarkers for Inflammatory Bowel Disease Behavior and Treatment Response

National Institutes of Health

R01 DK078683 04/01/09-03/31/13 \$362,674

HEUBI, J

Intervention to Reduce Body Burden of PCBs in Residents

National Institutes of Health(University of Cincinnati)

R21 ES 019206 08/01/10-07/31/12 \$67,350

A Model to Predict Outcome of Liver Disease in Alagille Syndrome

The American Liver Foundation(The Hospital for Sick Children)

07/01/10-06/30/11 \$6,039

Sterol and Isoprenoid Diseases Rare Diseases Consor

National Institutes of Health(Orgeon Health Sciences University)		
U54 HD061939	09/29/09-07/31/14	\$179,566
KOHLI, R		
Role of Ileum in Reducing Obesity Related Comorbidities		
National Institutes of Health		
K08 DK 084310	09/01/09-08/31/13	\$139,300
Ethicon Enhanced Assay Development		
Ethicon Endo-Surgery, Inc(University of Cincinnati)		
	07/01/10-06/30/11	\$73,150
LEONIS, M		
The Ron Receptor Tyrosine Kinase In Hepatic Tumorigenesi		
National Institutes of Health		
K08 CA 111819	08/01/06-07/31/11	\$123,000
MIETHKE, A		
Regulatory T cells and the Pathogenesis of Biliary Atresia		
American Liver Foundation		
	07/01/09-06/30/12	\$75,000
PALERMO, J		
Bacterial Survival in the Mammalian Urothelium		
National Institutes of Health		
K08 DK 068359	09/01/10-06/30/12	\$108,438
SAMSON, C		
Granulocyte-Macrophage Colony Stimulating Factor and Homeostatic Responses to Gut Injury		
AGA Fdn for Digestive Health & Nutrition		
	07/01/09-06/30/11	\$40,000
SHROYER, N		
SPDEF in Intestinal Differentiation		
National Institutes of Health		
R03 DK 084167	07/15/09-06/30/11	\$49,500
The Role of ATOH1 as a Tumor Supressor in Colorectal Cancer		
National Institutes of Health		
R01 CA 142826	02/23/10-01/31/15	\$201,001
Cystic Fibrosis Foundation Research Development Program (Project 2)		
Cystic Fibrosis Foundation		
	07/01/07-06/30/11	\$80,000
XANTHAKOS, S		
Bio Determinants of Steatohepatitis after Adolescent Bariatric Surgery		
National Institutes of Health		
K23 DK 080888	07/01/08-06/30/13	\$164,300
CRN in Non-Alcoholic Steatohepatitis (NASH CRN)		
National Institutes of Health(Case Western University)		
U01 DK 061732	08/30/09-04/30/14	\$75,673
YAZIGI, N		
Development & Validation of a Health-Related Quality of Life Questionnaire for Children After Liver Transplantation		
Canadian Institutes of Health Research(IWK Health Center)		
	04/01/07-06/30/11	\$14,416
Current Year Direct		\$5,093,117

Industry Contracts

SAEED, S.

UCB Pharma

\$385

HEUBI, J.

Asklepios Pharmaceuticals, LLC

\$83,763

KAUL, A.

Pfizer, Inc.

\$16,863

SAMSON, C.

Connecticut Children's Medical Center

\$173

Current Year Direct Receipts

\$101,184

Total

\$5,194,301