

GASTROENTEROLOGY

DIGEST

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Disclosures: Drs. Bataller, Behari, Bettner, Dugum, and Klinge have reported no relevant relationships with entities producing health care goods or services.

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Message From the Chief

"...and you [Moses] shall strike the rock, and water will come out of it, and the people will drink."

Book of Exodus 17:6



Water from a rock — a miracle! Miracles are the difference between expectation and reality. Minnesota Vikings' football fans celebrated the "Minnesota Miracle," an improbable victory on the last play of the NFL playoffs game against the New Orleans Saints. At that point, when hope for a win was but a faint glimmer, some would have said impossible. But, yesterday's miracles are today's reality. And, with perseverance, indomitable will, hard work, and a little bit of luck, today's miraculous hopes could become tomorrow's reality. Medical research, a core mission of our Division of Gastroenterology, attempts to transform the impossible into the actual. Before Dr. Thomas Starzl's contributions to the development of liver transplantation, a cure for people with end-stage liver disease was considered nothing short of a miracle. Now, deceased and living-donor liver transplants — although still incredibly challenging — are thankfully far from miraculous.

In this issue, we highlight the efforts of our Hepatology faculty in addressing the vexing problems of alcoholic liver disease and fatty liver disease. **Ramon Bataller, MD**, our new section chief of medical hepatology recruited from the University of North Carolina, in collaboration with second year GI fellow, **Matthew Klinge, MD**, discusses new technology and multidisciplinary approaches, including addiction counselors and social work interventions, to combat alcoholic liver disease.

An emphasis on multidisciplinary care is also highlighted at the UPMC FLOW Center™ (Fatty Liver, Obesity and Wellness), led by faculty member **Jaideep Behari, MD, PhD**. Concentrating on nonalcoholic fatty liver disease (NAFLD), dietitians and social workers partner with hepatology, gastroenterology, cardiac, endocrine, and bariatric subspecialists to support weight loss and overall health for fatty liver disease patients. For both of these diseases, noninvasive assessment for liver fibrosis is now routine. And with continued effort, intractable problems — like cirrhosis, first described by Hippocrates in the fifth century BC — may one day be even more preventable and remediable.

In good health,

Robert E. Schoen, MD, MPH

Professor of Medicine and Epidemiology
Chief, Division of Gastroenterology, Hepatology and Nutrition



Affiliated with the University of Pittsburgh School of Medicine, UPMC Presbyterian Shadyside is ranked among America's Best Hospitals by *U.S. News & World Report*.

UPMC LIFE
CHANGING
MEDICINE

The UPMC Fatty Liver Disease Program: Adapting Hepatology Care for a 21st Century Epidemic

In the last decade, few medical specialties have experienced such a dramatic shift in disease epidemiology and management as hepatology. With effective antiviral therapies for chronic hepatitis C infection in hand, current hepatology attention is beginning to address the risks of nonalcoholic fatty liver disease (NAFLD). NAFLD now has the dubious distinction of being the most common chronic liver disease and is on track to become the most common indication for liver transplantation in the U.S.



Jaideep Behari, MD, PhD, is an associate professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition. As a practicing

hepatologist, he also directs the Division's multidisciplinary UPMC FLOW Center™, which operates at the Digestive Disorders Center at UPMC Presbyterian.

A UPMC patient survey yielded several important insights about the challenges faced by our patients and opportunities for more patient-centric care. Initially, our NAFLD patients were seeing multiple physician specialists for their cluster of disorders (i.e., an internist, endocrinologist, dietitian, and gastroenterologist). Without straightforward options for weight-loss management in traditional medical practices, patients were enrolling in commercial weight-loss programs, which often recommended dietary supplements with potential hepatotoxicity. Patients were also frequently obtaining conflicting messages about medication therapies from their providers. A good example of a medication conflict involves a prescription of sulfonylurea for T2DM by one physician, which challenged NAFLD weight-loss management.

To address the special needs of patients with NAFLD, the multidisciplinary UPMC FLOW Center™ was launched in 2017. In addition to treating all stages of NAFLD, the clinic is staffed by Maja Stefanovic-Racic, MD, from the Division of Endocrinology and Metabolism and dietitian Elise Wade, RD. Our clinical workflow allows patients to see multiple specialists during their visit and has enabled enhanced communication and coordination of care, decreased cost, and increased convenience for patients.

An important aspect of NAFLD management is risk stratification for liver-related outcomes determined by the severity of liver fibrosis. To minimize the need for routine liver biopsies to stage fibrosis, our patients are offered free, noninvasive liver fibrosis assessment through a Fibroscan®. To better define the accuracy and limitations of noninvasive fibrosis assessment technologies, we conducted a prospective clinical study in collaboration with Alessandro Furlan, MD, in the Department of Radiology, which compared several noninvasive imaging technologies. Study results are expected later in 2018.

An explosion of research into the pathogenesis and molecular pathways underlying nonalcoholic steatohepatitis (NASH) development and liver fibrosis has led to more than 200 international clinical trials. Our center offers opportunities for fatty liver patients to participate in several major Phase II and III clinical trials to assess early-, mid-, and advanced-stage NASH as well as compensated cirrhosis.

Several clinical features of NAFLD make its management particularly challenging in routine clinical practice:

1. There is no FDA-approved treatment for NAFLD.
2. NAFLD is closely associated with obesity and type 2 diabetes mellitus (T2DM) and shares many common pathophysiologic risk factors with this metabolic syndrome. Since the most common cause of mortality in patients with NAFLD is heart disease rather than liver-related outcomes, an important part of NAFLD management involves controlling systemic metabolic risk factors.
3. Lifestyle changes and weight loss are currently recommended as the initial intervention for NAFLD. However, we have shown that clinically significant weight loss, defined as 5% weight loss from baseline, is uncommon in routine clinical care.¹ Furthermore, few subspecialty practices have the appropriate resources or clinical workflow to incorporate lifestyle and weight management support into routine practice.

Pharmacotherapy is not suitable for all patients, and major professional society guidelines and expert opinions strongly support lifestyle modifications and weight loss to address all stages of NAFLD. Since many patients have limited or no insurance coverage for nutrition counseling and weight management services, we have integrated nutrition counseling in the clinic, providing appropriate care for all patients regardless of their insurance coverage. In January 2018, we began to offer our patients an additional weight management program with low-calorie diet meal replacement.

To address an epidemic as large as NAFLD, it is insufficient to have just a few specialized clinics at large medical centers. There is an urgent need to integrate care throughout the community and increase awareness of this disorder among PCPs, non-GI specialists, and the general population. Our UPMC team has partnered with local organizations and community-based GI practices to form the Pittsburgh Fatty Liver Coalition to increase awareness of NAFLD and to promote healthy living.

The diabetes and obesity epidemics have taught us that a focus on pharmacotherapy alone will be an unsuccessful treatment strategy for a disorder so closely linked to diet and lifestyle. We continue to envision a UPMC multidisciplinary fatty liver disease program that models integrated and innovative care for NAFLD patients, and these services will include cutting-edge diagnostic technologies and advanced medical therapies. Most importantly, we will provide a full complement of essential nutrition counseling and lifestyle management services to restore patients' overall metabolic health.

For appointments or more information about the UPMC FLOW Center™, please call **412-647-2000**.

Reference

¹ Dudekula A, Rachakonda V, Shaik B, Behari J. *PLoS One*. 2014; Nov 6(9): e111808. eCollection 2014.

UPMC Offers Living-Donor Liver Transplants Through Hospital Partnerships

UPMC recently implemented UPMC Complex Care Connect™, a partnership with outside hospitals that provides UPMC's expertise in living-donor liver transplant to hospitals with deceased-donor programs. The partnership offers living-donor transplant for difficult cases and where a living donor may benefit the patient by reducing the wait time.

Through this program, the patient undergoes pre- and postoperative care at the partner hospital, and comes to UPMC for the transplant and associated care. UPMC is consistently one of the country's leading centers for living-donor liver transplants, forged on the legacy of transplant pioneer, Dr. Thomas Starzl.

Living Donors Must:

- Be between the ages of 18-55
- Be in good physical and mental health
- Have a BMI less than or equal to 32
- Not engage in active, ongoing drug or substance abuse
- Have an unselfish desire to contribute to another person's life in a healthy way
- Be in good general health and have no history of: liver disease, including cirrhosis and hepatitis; significant diseases involving lungs, kidneys, or heart; pulmonary hypertension; HIV; or active malignant cancers.

To learn more about this program, visit upmc.com/careconnect or call **412-864-4320**.

What Is This?

CASE PRESENTATION

A 21-year-old female with an underlying childhood genetic disease was transferred with a three-day history of nausea, decreased appetite, and dull epigastric pain. Labs (CBC, CMP, lipase) were normal and the physical exam was notable for a non-tender, flesh-toned nodule on the ventral tongue only. Computed tomography scans from her admission are shown in Figures 1 and 2 with image findings unchanged compared to a study completed five years previously. What is the underlying genetic disease? What pathologic sequelae are demonstrated on imaging?

Compare your answer to Dr. Bettner's on Page 7.



Weston Bettner, MD, is a year 1 gastroenterology fellow with the Division of Gastroenterology, Hepatology and Nutrition.

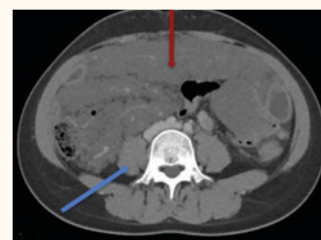


Figure 1.

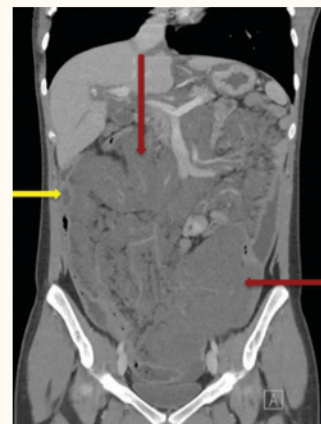


Figure 2.

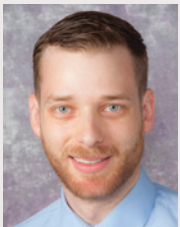
New Approaches for Alcoholic Liver Disease

The research and clinical teams working with Ramon Bataller, MD, PhD, focus on alcoholic liver disease (ALD), one of the main causes of advanced liver disease in the U.S. ALD includes a wide range of clinical syndromes that range from simple hepatic steatosis to progressive steatohepatitis, leading to fibrosis and ultimately cirrhosis with its associated complications. A particularly severe form of ALD, alcoholic hepatitis (AH), presents with jaundice and progressive liver failure in patients with heavy alcohol intake. The three-month mortality for AH can be as high as 60%.



Ramon Bataller, MD, PhD, is a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition. Dr. Bataller also serves as the section

chief of medical hepatology as well as the associate director of the Pittsburgh Liver Research Center.



Matthew Klinge, MD, is a year II gastroenterology fellow with the Division of Gastroenterology, Hepatology and Nutrition.

ALD is the main cause of liver-related hospitalization at UPMC and remains a significant clinical challenge. In contrast with recent viral hepatitis treatment advances, few improvements for the treatment of ALD are available. For instance, AH therapy remains largely unchanged since the introduction of prednisolone in 1978 and, subsequently, pentoxifylline in 2000, with a recent landmark study (Steroids or Pentoxifylline for Alcoholic Hepatitis) showing no benefit to treatment beyond 30 days.¹ Moreover, few studies have investigated the impact of alcohol abuse relapse after an episode of AH. In Barcelona and during his time with UNC-Chapel Hill, Dr. Bataller developed a multidisciplinary care team to manage patients with ALD. Most notably, an addiction counselor saw clinic patients in conjunction with a hepatologist to expedite and facilitate access to substance abuse treatment. These programs were successful because the root cause of disease — alcoholism — was addressed with equal weight by both addiction professionals and physicians. No ALD patient who is still drinking will get better.

To replicate this success at UPMC, Dr. Bataller started a multidisciplinary clinic to treat patients with ALD and AH, which includes addiction support balanced with medical care. The key to preventing alcohol-related morbidity and mortality relies on the timely detection of high-risk alcohol use and early recognition of substance abuse complications. Noninvasive Fibroscan® technology helps with early identification of progressive liver disease and is available in the primary care and

addiction treatment center settings to diagnose patients with advanced fibrosis. We expect that early detection will be followed by lifestyle modifications to halt the progression of decompensated liver disease.

Despite maximal medical treatment, many AH patients face exceedingly high short-term mortality. Dr. Bataller's clinical team has developed a protocol for early liver transplantation in selected patients with AH who fail to respond to medical therapy. Suitable transplant candidates presenting within their index episode of AH are identified using criteria that select for insight into their substance abuse behavior as well as low likelihood of relapse following transplant. Additionally, strong social support and commitment to ongoing substance abuse treatment are imperative. Ultimately, UPMC will be one of just a few transplant centers in the country to offer select patients with alcohol-related disease this life-saving transplant treatment option.

To complement ALD and AH clinical work, the Bataller research lab performs clinical, translational, and epidemiological studies in the field of ALD. From a clinical and epidemiological research standpoint, Dr. Bataller's group recently used the WHO 2014 Global Status Report (www.who.int) to show that 60% of cirrhosis in North America and Europe is attributable to alcohol (Figure 1). Interestingly, the percentage of heavy drinkers in these countries determines the burden of alcoholic cirrhosis (i.e., rather than the per capita consumption).² Other worldwide epidemiological studies are investigating

the prevalence of alcohol abuse and alcoholic cirrhosis as well, and are studying the impact of various alcohol policies, the impact of cold weather and sunlight hours, and the role of economic and social inequality. In fact, Dr. Bataller's former multidisciplinary team from Barcelona reported recently on a follow-up study from a large patient cohort that survived an episode of AH.³ In this Spanish study, two simple prognostic factors of increased alcohol relapse were identified, including an age younger than 48 years and failed prior alcohol rehabilitation attempts.

Primary lab goals in the basic science and translational research realms are focused on identification of primary determinants of alcohol abuse, noninvasive assessment of advanced fibrosis, and new treatments for AH patients. For example, the Bataller lab has classified several scoring systems using both clinical and histologic criteria to predict short-term survival in AH (ABIC and AHHS scores) and has identified the

systemic inflammatory response syndrome as a key driver of multi-organ failure and death.⁴⁻⁶ The Bataller team is also seeking to identify new therapeutic targets for AH. In addition to several molecular drivers (i.e., CXCL chemokines, Fn14, osteopontin, and p90RSK), they found that AH is characterized by poor hepatic regeneration and inefficient ductular reaction.^{7,8} Work is ongoing to identify the molecular drivers of hepatocellular failure in AH, potentially leading to a new family of targeted therapies.

After the discovery of effective all-oral therapies for hepatitis C, we are now entering a new era in hepatology in which most liver disease will be caused by ALD and nonalcoholic fatty liver disease or its combination. UPMC aims to lead this new era by offering a multidisciplinary treatment approach and by fostering continued research to serve these growing patient populations.

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IMPACT OF ALCOHOLIC LIVER DISEASE ON THE BURDEN OF CIRRHOSIS WORLDWIDE

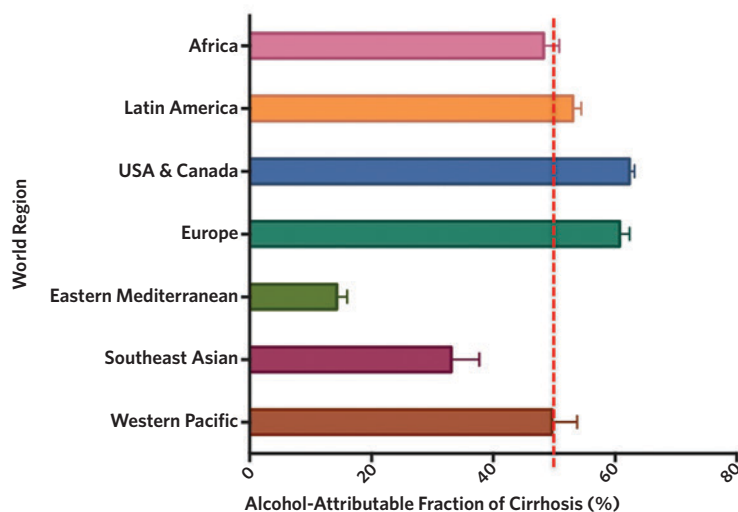


Figure 1.

Stein E, et al. *J Hepatol* 2016
With permission from the *Journal of Hepatology*

Pancreatic Cystosis: An Uncommon Manifestation of Cystic Fibrosis

A 14-year-old female with a history of cystic fibrosis complicated by recurrent respiratory tract infections and pancreatic exocrine insufficiency presented with a two-week history of jaundice associated with mild diffuse abdominal pain. Laboratory tests were notable for elevated total bilirubin to 7 mg/dL and elevated liver enzymes; alanine aminotransferase 460 IU/L; aspartate aminotransferase 208 IU/L; and alkaline phosphatase 427 IU/L.



Mohannad Dugum, MD, is a year III gastroenterology fellow with the Division of Gastroenterology, Hepatology and Nutrition.

A right-upper-quadrant ultrasound revealed diffuse mild biliary ductal dilation as well as multiple pancreatic cysts. Magnetic resonance imaging was then performed and revealed multiple large pancreatic cysts replacing almost the entire pancreatic parenchyma, as well as diffuse dilatation of the intrahepatic bile ducts, gallbladder, and common bile duct.

The patient was diagnosed with pancreatic cystosis, causing extrinsic compression of the common bile duct and leading to jaundice. As she was minimally symptomatic with no evidence of cholangitis, a trial of low-dose ursodiol was started with quick improvement in her total bilirubin level. She was to be monitored clinically and via serial assessment of bilirubin and liver enzymes. If symptoms or complications secondary to bile duct obstruction (i.e., cholangitis) arose, bile duct drainage or surgical resection of the pancreatic cysts would have been considered.

Cystic fibrosis almost always affects the pancreas, and the majority of patients have exocrine insufficiency. Pancreatic cystosis is a relatively rare entity characterized by replacement of the pancreatic parenchyma by multiple cysts of various sizes. This occurs in less than 10% of patients with cystic fibrosis.^{1,2} While the cysts can be quite large, patients tend to be asymptomatic and usually present during the second decade of life, when the cysts are detected incidentally on abdominal imaging.³ Symptoms develop as a result of mass effect, vascular compromise, or hemorrhage into the cysts; they include abdominal pain, nausea, and early satiety.⁴ Pancreatic cystosis is thought to arise due

to decreased bicarbonate transport that produces dehydrated pancreatic secretions with a high protein concentration. This causes pancreatic ductal obstruction, dilation, inflammation, and eventual cyst formation. Histologically, these lesions are true cystic lesions lined by epithelium with little to no pancreatic tissue between the cysts. Correlation between specific cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and pancreatic cystosis development has not been formally evaluated.⁵ Importantly, these cysts have no known malignant potential, and surgical intervention should be reserved for patients who develop significant symptoms or complications.⁶

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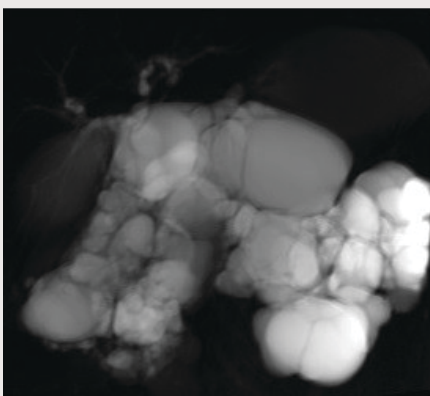
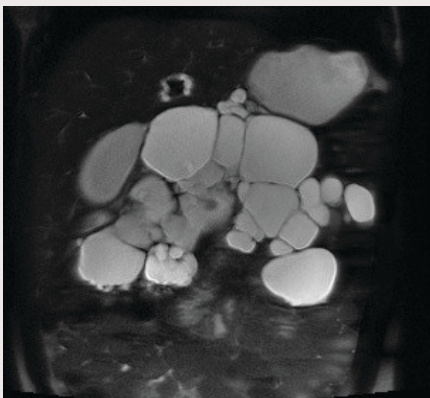


Figure 1. T2 weighted magnetic resonance imaging and magnetic resonance cholangiopancreatography show multiple large cysts replacing the pancreas.

Save the Date: PancreasFest 2018 July 25–27, 2018 – Pittsburgh, Pa.



PancreasFest is an internationally-accredited research and clinical conference designed for gastroenterologists, surgeons, oncologists, researchers, and interested medical professionals. Lectures and discussion groups will mix with investigative research meetings to further the multidisciplinary understanding and treatment of pancreatic diseases.

PancreasFest 2018 will feature discussions on pancreatic cancer, pancreatic diabetes, and acute pancreatitis. This annual conference draws more than 200 pancreatologists and physician scientists to Pittsburgh to advance pancreas treatments.

Collaboration among academic pancreas centers of excellence was discussed in the May 2017 Pancreatology publication, *Academic Pancreas Centers of Excellence: Guidance from a Multidisciplinary Chronic Pancreatitis Working Group at PancreasFest*.

UPMC GI in the Top 10 Again: U.S. News & World Report

UPMC Presbyterian Shadyside has been ranked as the 6th Best Hospital for Adult Gastroenterology and GI Surgery in the nation by *U.S. News & World Report*. Division chief **Robert E. Schoen, MD, MPH** says, “This ranking is a fitting tribute to the successful work of our gastroenterology and hepatology medical professionals, our surgery partners, the terrific patients, and all who work to support gastrointestinal health in western Pennsylvania and throughout the U.S.”

Division Welcomes New GI Colleagues

The Division of Gastroenterology, Hepatology and Nutrition welcomed new faculty in 2017, including **Ramon Bataller, MD, PhD**, section chief of medical hepatology; **Rohit Das, MD**, advanced endoscopy specialist; and **Robert Howland, MD**, psychiatrist with the Visceral Inflammation & Pain Center. Two previous GI fellows, **Anna Evans Phillips, MD**, and **Harkirat Singh, MBBS**, have also joined the Division as junior faculty. Dr. Evans Phillips continues to train as a clinical pancreatologist, and Dr. Singh is training in advanced endoscopy.

References

- This patient carried a diagnosis of neurofibromatosis type 1 (NF1), an autosomal dominant disease occurring in 1:3,000 births. Up to one quarter of NF1 patients will have abdominal sequelae. Neurofibromas, which are benign nerve sheath tumors, represent the most common abdominal lesion. Radiographically, neurofibromas appear as soft tissue masses (red arrow, Figures 1 and 2) with homogeneous attenuation equal to or slightly more than water, but less than muscle (blue arrow, Figure 1). Large plexiform neurofibromas arise predominantly in a parasagittal, sacral, or mesenteric distribution with a predilection for the small bowel and retroperitoneum. Abdominal neurofibromas are usually asymptomatic but can present with pain, obstruction, or bleeding. Debulking surgery remains the primary treatment for symptomatic disease. However, abdominal manifestations requiring surgery are rare, occurring in only 2.5% of patients.
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- Radiation therapy is contraindicated in the management of plexiform neurofibromas because of the malignancy risk. Compared to the general public, patients with NF1 have an increased risk for gastrointestinal stromal tumors, neuroendocrine tumors (particularly duodenal/perampullary), and malignant peripheral nerve sheath tumors, which represent the most common malignant neoplasms (lifetime risk of 7 to 12%). Malignant transformation of a neurofibroma may be signaled by a rapid increase in size, asymmetric attenuation, or the sudden appearance of a neurological deficit or pain. Interestingly, while this patient had extensive mesenteric involvement with displacement of normal bowel to the periphery (yellow arrow, Figure 2), her presentation was unrelated to NF1. An upper endoscopy ultimately revealed the cause of her presentation — a peptic ulcer.

What Is This? (Continued from Page 3)

ABOUT THE UPMC DIVISION OF GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

The Division of Gastroenterology, Hepatology and Nutrition is one of the leading centers for gastrointestinal clinical care and research in the country.

The UPMC Digestive Disorders Center is a comprehensive care program for patients that covers the full range of digestive health conditions including:

- Inflammatory Bowel Diseases
- Cancer Prevention and Treatment
- Functional Bowel Disorders
- Hepatic Disorders and Diseases
- Pancreatic and Biliary Diseases
- Nutrition Support

The Division also includes eight Centers of Excellence that provide specialized care for complex cases and conduct research on numerous fronts to better understand, and develop treatments for, disorders and diseases of the gastrointestinal and related systems.

Centers of Excellence

- Pancreas and Biliary Center
- Center for Liver Diseases
- Center for Intestinal Health and Nutrition Support
- Center for Women's Digestive Health
- IBD Center and UPMC Total Care-IBD
- GI Cancer Prevention and Treatment Center
- Neurogastroenterology and Motility Center
- Visceral Inflammation and Pain Center

To learn more about the UPMC Division of Gastroenterology, Hepatology and Nutrition, please visit UPMCPhysicianResources.com/GI.

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A \$17 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides more than \$900 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 80,000 employees, more than 30 hospitals, 600 doctors' offices and outpatient sites, and a more than 3.2 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. As UPMC works in close collaboration with the University of Pittsburgh Schools of the Health Sciences, *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, and UPMC International provides hands-on health care and management services with partners on four continents. For more information, go to UPMC.com.