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### CME Credit

**Disclosures:** Dr. Monga, Dr. Ganesh, Dr. Singhi, Dr. Slivka, and Dr. Cheng reported no relevant relationships with entities producing health care goods or services.

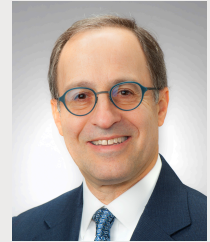
**Instructions:** To take the CME evaluation and receive credit, please visit [UPMCPHYSICIANRESOURCES.COM/GI](http://UPMCPHYSICIANRESOURCES.COM/GI), and click on Gastroenterology Digest, Fall 2019.

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The University of Pittsburgh designates enduring material activity for a maximum of 0.5 AMA PRA Category 1 Credit[s]<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Other health care professionals will receive a certificate of attendance confirming the number of contact hours commensurate with the extent of participation in this activity.

## Message From the Chief



*It was a cold December day in St. Petersburg when a blindfolded Fyodor Dostoevsky was about to be executed. The men were taken into the square, tied to pillars, and blindfolded. As the rifles were loaded, raised and aimed, a messenger arrived on horseback waving a white flag and telling the armed men to stop the execution, on direct orders from the Tsar. This was not a show of mercy. It had all been planned. Every last detail — from the blindfolds to the firing squad, to the extraordinarily convenient last-minute messenger — had been pre-arranged in a twisted form of psychological torture.*

A friend of mine experienced a similar event, though in a modern medical context. The initial diagnosis based on CT was stage IV kidney cancer with bone metastases. After seven different scans and various organ biopsies, including a drilled biopsy from the os pubis, all tissue samples were negative for malignancy. The PET-CT scan was also negative. Finally, after a radiologist eradicated all the colors from the PET-CT, a reprieve: Paget's Disease, a benign sclerotic bone disease. Like Dostoyevsky, at the last minute, while contemplating mortality with profound fear — saved.

Being a physician is both spiritually and financially rewarding. Instances where you have made a difference by correctly assessing a problem and providing a solution are recognizable. It's easy to take those moments for granted. Prescribing a PPI, detecting a cancer in the setting of iron deficiency, or even diagnosing a less common condition, such as achalasia, can be obvious to the initiated. Of course, for a patient who has no insight other than the problem they are experiencing, our analysis, investigation, and rendering of a solution can be perceived as miraculous, meriting substantial gratitude and admiration. While administering the right test and right treatment may often be routine, there is no escaping the humbling feeling of how little we know and how complex a machine the body is. A recent study estimated that about five percent of outpatient U.S. adults experience diagnostic errors, defined as missed opportunities to make a correct or timely diagnosis. Over half of these included the possibility of harm. A Johns Hopkins study in 2013, based on 35 million hospitalizations, estimated that 250,000 deaths stemmed from medical error, making medical error the third leading cause of death.

For Dostoyevsky or for my friend, how does one react to the trauma? A near death experience is a form of psychological torture that can induce depression, anxiety and PTSD. Alternatively, one can rebound from a death sentence with a renewed lease on life, maximizing every moment, living life with gusto and joy, and loving every minute of what you thought you'd never have.

Dostoyevsky boils down these two approaches in the novel *The Brothers Karamazov*, published shortly before his death, into the conflict between faith and doubt. Faith for him involved belief in God, which led to a love of mankind, kindness, forgiveness, and a devotion to goodness. Doubt referred to skepticism, which lent itself to the rejection of morality and an inner coldness and despair.

As physicians, a medical mistake, complication, or misadventure mirror all setbacks in life. All we can do after falling off the horse is get back on and try to do better. But getting back on must include rigorous attempts to understand and avoid making the same mistake. That is the essence of research!

It is my great pleasure to present another edition of *Digest*, where we share our research, and our attempts to learn and do better. Thanks for joining us.

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

# Pittsburgh Liver Research Center (PLRC) Obtains Digestive Diseases Research Core Center Designation

The Pittsburgh Liver Research Center (PLRC) has operated with support from UPMC and the University of Pittsburgh since 2016. Its mission is to bring Pittsburgh liver researchers together for meaningful collaborations and to build infrastructure to support their research with cutting-edge technology. The Digestive Diseases Research Core Center (DDRCC) designation from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) serves as validation for the high-quality work being done at the PLRC, and this honor will help to further the legacy of liver research and care in the Pittsburgh area.



**Satdarshan (Paul) Singh Monga, MD,** is the founding director of the Pittsburgh Liver Research Center and is an endowed research chair as well as the vice chair for the Division of Experimental Pathology at the University of Pittsburgh. He serves in leadership roles in the American Society for Investigative Pathology (ASIP) and American Association for the Study of Liver Diseases (AASLD). Dr. Monga is the editor-in-chief of *Gene Expression* and is an associate editor for the *American Journal of Pathology*, *Annual Review of Pathology*, and *Seminars in Liver Disease*. He is also the assistant dean and co-director of the *Medical Scientist Training Program of the University of Pittsburgh and Carnegie Mellon University*.

His research interests include personalized medicine in hepatocellular carcinomas (HCC), liver cell and tissue therapies, regenerative medicine, cellular and molecular signaling in liver development, liver regeneration, and liver cancer.

The PLRC's designation as a Core Research Center is an honor that only 20 research centers in the United States can claim. This designation and the associated five-year grant allow the PLRC to be sustainable and ensure that this research will continue to benefit patients with liver disease.

"This application required a herculean effort from PLRC leadership, and the PLRC is honored to have received this designation after only its first application," said Dr. Monga.

The PLRC also recognizes the incredible history of advanced liver research and clinical care within the broader Pittsburgh community, a community that the PLRC brings together and provides with important resources. To achieve the NIDDK designation, a center must have a history of integrating, coordinating, and fostering interdisciplinary cooperation among established investigators, who themselves must conduct high-quality research on digestive and liver diseases. The PLRC's members are recognized for their excellent research, which is enhanced by Pittsburgh's patient population and innovative research history.

## Liver Research and Care in Pittsburgh

For some time, Pittsburgh has been at the forefront of liver research. The country's first liver transplant program and first immunosuppressant therapies were developed in Pittsburgh through the work of Dr. Thomas E. Starzl, namesake for the Thomas E. Starzl Transplantation Institute. His innovative work created a platform that helped to draw researchers to the city,

especially those interested in immunology and liver transplantation, as well as researchers interested in regenerative medicine, stem cells, artificial liver devices, and the reparative qualities of the liver.

Other strengths of Pittsburgh research include the pathological diversity and sheer volume of liver patients in the area. The greater metro area has a high incidence of many advanced liver conditions, including chronic liver injury due to alcoholic and nonalcoholic liver diseases in adults and a high occurrence of liver tumors. Many adult and pediatric patients also present with the black boxes of liver diseases, such as primary biliary cholangitis and primary sclerosing cholangitis, and even rarer diseases, such as progressive familial intrahepatic cholestasis (a disease more common in Old Order Amish communities), alpha-1 antitrypsin deficiency, and other monogenetic disorders. Researchers are attracted to the ability to study the deeper mechanisms of these complex liver diseases, as well as liver functionality and regenerative capacities.

Until now, researchers from the University of Pittsburgh and UPMC have worked in relative isolation in many departments (e.g., pediatrics, surgery, medicine, and pathology), in addition to specialized institutes including UPMC Hillman Cancer Center and McGowan Institute for Regenerative Medicine. The primary goal of the PLRC is to bring these incredible researchers together in collaboration and to offer them cutting-edge research tools.

## Research Areas and Scientific Service Cores

To foster translational science, dynamic dialogue, and enhanced collaboration, the PLRC hosts monthly group round tables covering three topics: chronic liver injury, liver tumorigenesis, and regenerative medicine, which form the research base of the PLRC. During these roundtables, a researcher and a clinician are paired together by topics and are allowed to present and discuss the topics from their perspective. Additional education occurs through invited seminars from visiting professors with expertise in specific areas of liver health and disease. These educational activities are coordinated by PLRC's Enrichment Program under the leadership of Kari Nejak-Bowen, MBA, PhD.

Members also have free or low-cost access to a variety of scientific resources, an infrastructure that the PLRC has developed through four unique cores:

1. The **Advanced Cell Tissue and Imaging Center**, directed by Donna Stolz, PhD, supports liver research through the Center for Biologic Imaging, one of the largest optical imaging centers in the country. This center provides our members access to cutting-edge optical imaging equipment, with priority given to funded collaborations and joint outputs.
2. The **Biospecimen Repository and Processing Core** provides a centralized location for investigators to request tissues, cells, and tissue microarrays. A tissue utilization committee considers each request for tissues and determines specimen distribution based on project relevance and feasibility. This committee is led by David Geller, MD, co-director of the UPMC Liver Cancer Center, Richard L. Simmons Professor of Surgery, and Aatur Singhi, MD, PhD, a leading collaborator from the Department of Pathology.
3. The **Genomics and Systems Biology Core** provides primary genome and data analysis services to researchers seeking insight at the levels of RNA and DNA. Directed by Jianhua Luo, MD, PhD, and Takis Benos, PhD, this core provides integral technological resources for research and works to build a precision-medicine, biomarker-centered approach to liver disease treatments.

4. The **Clinical Component** is an essential element of the PLRC that serves as its conduit for translation and commercialization of research. The Clinical Component is led by Ramon Bataller, MD, PhD. Dr. Bataller and colleagues have assembled a team of clinicians from various disciplines to offer a direct clinical perspective to researchers at any stage in their project. This helps investigators to select clinically meaningful end-points, design a clinically consequential methodology, and to select appropriate human biospecimens.

Each core group has contributed to the success of the PLRC, and its directors are pivotal to this DDRCC designation and the success of this endeavor.

"I'd like to offer a special thanks to Dr. Bataller and to each of the core directors for their leadership and support to obtain this grant," said Dr. Monga.

## The Future of the PLRC

For the continued health of any research community, some percentage of resources must be dedicated to the pursuit of preliminary data in novel studies and to the development of new research talent within the community's networks. Under the direction of Gavin Arteel, PhD, and Paul Monga, MD, the PLRC funds novel initiatives and new investigators who are pursuing liver-related research through the Pilot and Feasibility grant funding program. The PLRC has supported many early University of Pittsburgh investigators from a variety of disciplines through annual, longitudinal mentoring.

The PLRC offers exciting new insights for investigators and clinicians, and our patients are provided with consequent new hope to overcome their diseases. The PLRC underscores that young researchers can advance their careers in Pittsburgh through program support for preliminary investigations. Critical PLRC mission components include the ability to establish proactive liver research leaders and resources and to invest in the future of liver care in Pittsburgh and around the world.

For more information about the PLRC and its innovative work, visit [LiverCenter.pitt.edu](http://LiverCenter.pitt.edu).

## UPMC Center for Liver Diseases at The Liver Meeting® 2019

Friday, Nov. 8 to Tuesday, Nov. 12

The UPMC Center for Liver Diseases was well represented at The Liver Meeting® 2019. Our physicians discussed a wide variety of clinical and basic science topics on every day of the conference.

Saturday, Nov. 9, we hosted a reception in collaboration with the Thomas E. Starzl Transplantation Institute and the Pittsburgh Liver Research Center. Thank you to all who attended and all who participated in our presentations. Please join us again next year.

For more information about our presence at the AASLD annual meeting, visit the **Featured News** section at [UPMCPhysicianResources.com/GI](http://UPMCPhysicianResources.com/GI).

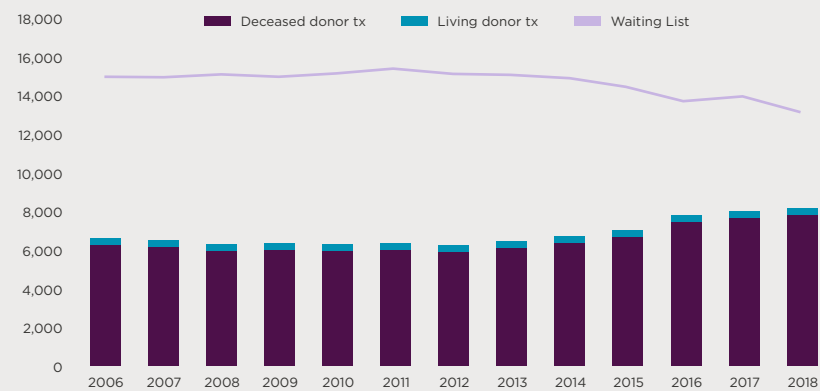
# When to Refer Your Patient for a Liver Transplant and the Benefits of Living Donation

In a short period of time, transplantation has progressed from an experimental procedure to the standard of care for patients with end-stage organ failure. With the establishment of the country's first liver transplant program in 1981, to performing our first adult living-donor liver transplant in 1999, to becoming one of the top and most experienced programs in the country for living donor transplants, physicians and researchers at UPMC have refined new therapies, giving hope to patients across the country and around the world.



**Swaytha Ganesh, MD**, is the medical director of the Living Donor Program at UPMC. She is renowned for her clinical expertise in treating a wide range of patients with liver disease with a specific interest in living-donor liver transplantation. Her areas of research include evaluating recipients and donors and assessing their ability for living donor surgery and developing disease management protocols in post-liver transplant patients with metabolic syndrome, hyperlipidemia, and systemic hypertension.

## CURRENT STATUS OF LIVER TRANSPLANT IN THE U.S.



A miracle of modern medicine, liver transplantation is the only definitive treatment for patients with end-stage liver disease. The one-year survival rate following a liver transplant ranges from 87 to 93 percent with the five-year survival rate being more than 75 percent. Unfortunately, due to the growing transplant waiting list (Figure 1) and hesitations among referring physicians to refer patients for a living donor transplant, many patients have a 15 to 20 percent chance of succumbing to their disease before making it to transplant.

### Indications for a Liver Transplant

A patient with liver disease and a high risk of decompensation is a candidate for a liver transplant. At UPMC, we are committed to providing liver transplant services to all patients who will benefit—even those with a low Model for End-Stage Liver Disease (MELD) score or complex cases who have been deemed high-risk and have been turned down for a transplant at another center.

A candidate for liver transplant may suffer from:

- Hepatitis C
- Hepatitis B
- Alcoholic liver disease
- Nonalcoholic steatohepatitis or fatty liver disease
- Primary liver cancers
- Primary biliary cirrhosis
- Autoimmune hepatitis
- Primary sclerosing cholangitis
- Acute liver disease from toxins including acetaminophen/Tylenol
- Alpha-1 Antitrypsin deficiency
- A failed prior liver transplant
- Polycystic disease
- Hemochromatosis
- Veno-occlusive disease
- Wilson's disease

### When to Refer for a Liver Transplant

Referral for a liver transplant should be initiated early, before the patient is too sick to be considered an appropriate candidate for transplantation. Early referral allows our team to address and resolve any pretransplant complications while the patient's liver disease is relatively controlled.

General indications for when to refer include continued progress of the patient's disease despite maximized medical therapies, development of a life-threatening complication such as hepatocellular carcinoma (HCC), or an increasingly unsatisfactory quality of life.

The MELD score determines how urgently a patient requires a liver transplant based on the likelihood of death within a three-month period. A MELD score of 10 or higher is a clinical indication of liver dysfunction. Patients with higher MELD scores have worse short-term prognoses and are given higher priority for the next available deceased-donor liver.

A patient's MELD score is based on:

- Serum creatinine
- Bilirubin
- International normalized ratio (INR)

### Living-Donor Liver Transplant for Patients With Low MELD Scores

Certain diagnoses or conditions carry a higher risk of death than the patient's MELD score may indicate. Some aspects concerning medical urgency for liver transplants are not accurately represented by a patient's MELD score, and the current MELD allocation system greatly underestimates the risk of waiting list mortality. Ongoing symptoms of liver decompensation such as loss of weight and muscle mass and ascites in the chest and limbs can reduce a patient's quality of life and, in some cases, may be life-threatening.

While patients with a MELD score less than 15 are often not listed for a liver transplant because their chance of receiving a liver through traditional allocation is so low, a living-donor liver transplant offers a life-saving option and the opportunity to receive a transplant sooner. By exploring a living donor transplant, patients with a low MELD score who should still be considered for a living-donor liver transplant include those with:

- Hepatocellular carcinoma
- Ascites requiring periodic large-volume paracentesis
- Hepatic hydrothorax
- Cholangiocarcinoma
- Significant life-altering HSE
- Multiple admissions for HSE, ascites, or GI bleeding
- Patients with decompensated cirrhosis whose overall health is continuing to decline

Early access to a liver transplant allows patients to avoid the considerable burden of chronic liver disease, which, over time, can lead to deteriorating health, multiple medical interventions, and hospitalizations.

### Partnering With Referring Physicians

Our understanding of the field of liver transplantation has allowed us to gain invaluable insight and experience in working with referring physicians. Throughout the transplant process, the referring physician remains an integral part of the patient's care by:

- Identifying patients with end-stage liver disease who will benefit from transplantation.
- Timely referral of those patients to the transplantation center.
- Assisting in the coordination of specialists in pretransplant evaluation.
- Continuing to medically manage the patient's care while he or she awaits transplantation.
- Collaborating with the transplant team in the long-term care and posttransplant care of the patient.

As an integral member of the patient care team, the referring physician will be continually updated about the patient's progress by a member of the transplant team. Continuous interaction with the transplant team can range from in-person and telephone interactions to email communications or teleconference sessions for physicians located remotely.

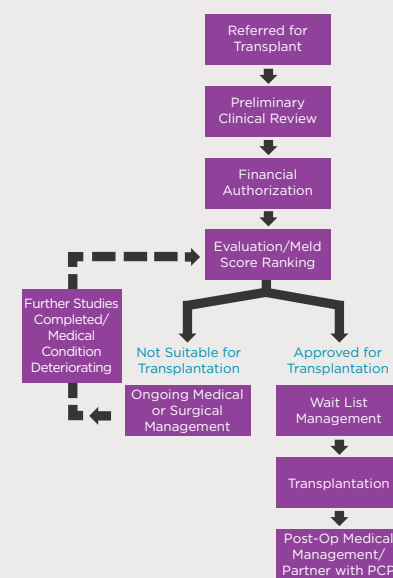
### About UPMC's Liver Transplant Program

One of the oldest and largest liver transplant programs in the country, UPMC has performed more than 6,000 adult liver transplants and more than 400 adult living-donor liver transplants. We believe that liver transplantation should be an option for any patient with end-stage liver disease who no longer experiences results with medical therapy.

Additionally, UPMC works with hospitals that have an existing liver transplant program and want to provide patients the option of a living-donor liver transplant. When partnering with another hospital, UPMC provides pre- and postsurgery consultation and training for clinicians, while the surgery itself occurs at UPMC.

For more information about our program and how to begin the referral process, visit [UPMC.com/LiverTransplantReferral](http://UPMC.com/LiverTransplantReferral).

### TRANSPLANT REFERRAL PROCESS



# Next Generation Sequencing (NGS) of Biliary Specimens Improves Preoperative Detection and Management of Malignant Bile Duct Strictures

The poor performance of current preoperative methods for differentiating between malignant and benign biliary strictures results in some patients undergoing surgical resection despite having benign strictures. Alternatively, this can result in a delay in the diagnosis of biliary cancer. Seeking a solution, Aatur Singhi, MD, PhD, and Adam Slivka, MD, PhD, developed a targeted NGS assay called BiliSeq. Testing endoscopic retrograde cholangiopancreatography (ERCP)-obtained biliary specimens against this assay offers clinicians a more reliable diagnosis compared to standard methods.



**Aatur Singhi, MD, PhD**, is an associate professor in the Department of Pathology and is a member of both the Gastrointestinal Pathology Center of Excellence and the Division of Molecular and Genomic Pathology. His research has a translational focus in the areas of gastrointestinal, pancreatic, hepatobiliary, and peritoneal pathology.



**Adam Slivka, MD, PhD**, is the medical director of the UPMC Digestive Disorders Center and is the associate chief of Clinical Affairs for the Division of Gastroenterology, Hepatology and Nutrition, where he also serves as a professor of medicine. His research interests include noninvasive diagnosis of pancreaticobiliary cancer, the development and testing of new drugs and devices used during ERCP, and the development of new strategies to treat pancreatitis and pancreatic cancer.

Benign biliary strictures are typically due to conditions such as sclerosing cholangiopathies, iatrogenic injury, and infection, while malignant strictures are related to carcinomas arising from the pancreaticobiliary duct cell, ampulla of Vater, and liver cancers. The preferred methods for pathologic confirmation during endoscopic retrograde cholangiopancreatography (ERCP) are bile duct brushings and forceps biopsies, but the sensitivity of these approaches to detect malignancy can vary from eight to 67 percent. Several ancillary detection techniques have been developed, including digital image analysis, KRAS mutation testing, and multicolor fluorescence in situ hybridization (FISH), but these methods also fail to produce reliable diagnoses due to the wide variance in sensitivity and, in the case of the latter method, a propensity for subjective interpretation errors, which can only be avoided by an experienced pathologist performing labor intensive work.

Distinguishing between the two is difficult, especially because certain conditions, like primary sclerosing cholangitis (PSC), are associated with benign strictures but are also associated with an increased risk of bile duct cancer and may harbor pre-cancerous changes.

The failure of current diagnostic methods for malignant biliary strictures often leads to repeated ERCP procedures and delayed clinical decisions that risk disease progression, and even more alarmingly, can lead to a high percentage of patients undergoing an unnecessary surgical resection. A more reliable method is required for preoperative diagnosis of malignant biliary duct strictures, and this serves as the motivation for this study of a promising new methodology involving NGS.

## NGS and Its Use in Previous Studies of Biliary Strictures

Sequencing of the human genome was once an expensive, time-consuming process, but the advent of NGS and the introduction of novel molecular diagnostics have created unparalleled opportunities for low-cost use of DNA sequencing in clinical and research environments. Consequently, our understanding of the genomic landscape of neoplasms arising in, or secondarily involving, the bile duct system has improved at an incredible pace in recent years.

These innovations have played a pivotal role in recent research studying the efficacy to distinguish between malignant and benign strictures. Bankov et al. published the results of an NGS assay that was used to test a retrospective cohort of patients and found a sensitivity of 81 percent. However, this study tested only 16 patients, did not evaluate biliary brushing specimens, and used DNA extracted from Formalin-Fixed Paraffin-Embedded (FFPE) tissue blocks for sequencing, resulting in such a low-quality of DNA that it had to be enriched before analysis. A more comprehensive assessment of NGS testing on bile duct specimens was reported by Dudley et al, which studied a cohort of 73 bile duct and eight main pancreatic duct brushing specimens, finding a sensitivity of 68 percent and a specificity of 97 percent. But even this larger study did not collect dedicated brushings for DNA isolation and extracted DNA from CytoLyt-preserved specimens. Unsurprisingly, 11 percent of their specimens had degraded to the point of failing NGS testing.

This previous literature has shown that NGS testing of bile duct strictures may have promise, but a more comprehensive study was required for definitive evaluation of the impact on patient management when genomic alterations are detected in bile duct specimens.

## Methodological Improvements and Results

In our study, we developed a highly sensitive, targeted NGS assay called BiliSeq in a laboratory with Clinical Laboratory Improvement Amendments certification and accreditation by the College of American Pathologists. Investigation centered on 28 genes that are commonly mutated, amplified, and/or deleted in malignant neoplasms involving the bile duct system.

During an initial training cohort followed by a validation cohort, a total of 163 biliary brushings and 172 biliary biopsies were collected for pathological evaluation. Rather than relying on DNA-extraction methods from processed pathology specimens that might have reduced the yield and quality of the genome, we performed a dedicated bile duct brushing and/or biopsy for each patient and submitted the resultant 160 brushings and 135 biopsies for BiliSeq testing.

NGS was performed prospectively as part of clinical care with a 10-day turnaround in the UPMC Molecular & Genomic Pathology (MGP) Laboratory. We then compared the results of NGS testing with the results of diagnostic pathology of 145 surgically resected specimens or biopsy specimens and with the results of further clinical evaluations on 75 of the patients. BiliSeq was found to have a sensitivity of 73 percent and a specificity of 100 percent, an improvement over pathological evaluation alone for detecting at least high-grade biliary dysplasia involving the bile duct. The combination of both pathological and BiliSeq testing brought sensitivity up to an incredible 83 percent while maintaining a specificity of 99 percent.

A preliminary observation from this study is the striking improvement in sensitivity that BiliSeq allowed for patients with PSC. These patients' strictures are typically caused by inflammation, so it is often challenging to procure a sample, and pathologic evaluation usually produces unreliable diagnoses. Routine cytologic evaluation tested at an eight percent sensitivity for PSC patients, but BiliSeq achieved a sensitivity of 83 percent for at least high-grade biliary dysplasia. This is compelling evidence to further explore the potential of BiliSeq to improve clinical outcomes for this high-risk patient population.

## Clinical Implications of Results

These results highlight the diagnostic applicability of NGS-based assays to ERCP-obtained biliary specimens in the early detection and management of patients with indeterminate bile duct strictures. For clinicians, this testing can grant the ability to avoid unnecessary resections and to make evidence-based clinical decisions before the disease progresses.

Our results also have implications for the growing body of literature around precision medicine. BiliSeq testing identified two patients with ERBB2 amplifications, a genomic alteration known to respond well to trastuzumab in conjunction with standard first-line chemotherapy. Both patients exhibited measurable radiographic responses and normalization of serum CA19-9, and both are currently alive and well thanks to the ability of NGS to provide a personalized, targeted treatment option. To learn more about these patients, visit [inside.upmc.com/deadly-diagnosis-precision-medicine](https://inside.upmc.com/deadly-diagnosis-precision-medicine).

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- For a full list of references, visit [UPMCPhysicianResources.com/GI](https://UPMCPhysicianResources.com/GI) and click on *Gastroenterology Digest*, Fall 2019.

## Division of Gastroenterology, Hepatology and Nutrition News & Updates



**David Levinthal, MD, PhD, received a national research award from the International Foundation for Gastrointestinal Disorders (IFFGD)** at the 2019 Digestive Disease Week (DDW) for his work as a basic/translational investigator. Dr. Levinthal's research focuses on treating patients with cyclic vomiting syndrome (CVS).



**James Squires, MD, received the 2019 Autoimmune Liver Disease Pilot Research Award from the AASLD Foundation** for his project "A Learning Health System for Pediatric Autoimmune Liver Disease Through Partnership with ImproveCareNow." Dr. Squires will utilize the tested model of a Learning Healthcare System (LHS) to decrease variability and improve care for children with autoimmune liver disease.



**Experts from the UPMC Liver Transplant Program, led by Abhinav Humar, MD, chief of The Division of Transplantation at UPMC, authored a report in *Annals of Surgery* that highlights advantages of living-liver donation.** In a retrospective analysis of surgical outcomes, they find numerous advantages of living-donor liver transplant compared to deceased-donor liver transplant, including better three-year survival rates and lower costs.



**Randall Brand, MD, received the National Pancreas Foundation's keynote "Courage Award" in Sept. 2019** in recognition of his advanced patient care and his valuable contributions to pancreatic cancer research. Our pathology colleague, Aatur Singhi, MD, PhD (see page 6), received NPF's "Nobility in Science Award" as well. Additional awards for "Compassionate Care" were presented to Beth Dudley, MS, MPH, CGC, Helen Carleton, RN, and Gail Smoulder, RN, CGRN, and staff member Joy Jenko Merusi, MA received NPF's "Professional Excellence Award".



**Paul Monga, MD is pleased to announce that the Pittsburgh Liver Research Center (PLRC) has been funded by the NIDDK through a P30 grant,** a grant that is only received by 20 Digestive Diseases Research Core Centers in the country. This prestigious five-year grant will allow the PLRC to continue to provide scientific resources and translational consultations to the research community in Pittsburgh. For a full explanation of the PLRC's activities, read the article on page 2.



**Marc Schwartz, MD, was recognized by the Crohn's & Colitis Foundation at its 2019 "Night of Steel" event** at Pittsburgh's Heinz Field on Saturday, Nov. 2. Dr. Schwartz was recognized for his outstanding patient care and his leadership in Pittsburgh's IBD community.

## New Online CME Courses

UPMC Physician Resources offers video CME courses in gastroenterology. New additions for 2019 include:

*Advances and Controversies in Colorectal Cancer Screening*  
**Robert E. Schoen, MD, MPH**

*System Modeling and Precision Medicine*  
**David C. Whitcomb, MD, PhD**

*Incorporating Genetic Testing into the Care of a PDAC Patient*  
**Randall E. Brand, MD**

*Gastroenterology Year in Review*  
**Kenneth E. Fasanella, MD**

*Hepatology Year in Review*  
**Naudia L. Jonassaint, MD, MHS**

To view these courses, visit  
[UPMCPhysicianResources.com/GI](http://UPMCPhysicianResources.com/GI).

## 2019 Annual Update in Medical Hepatology

Saturday, Dec. 7 • 7:30 a.m. to 2:30 p.m.

Thank you to all who attended the 2019 Annual Update in Medical Hepatology. This CME program was intended for experts in hepatology, gastroenterology, and abdominal and general surgery, referring primary care physicians, and other health care professionals with an interest in the treatment and latest research for liver disease.

At the event, our experts presented recent advancements and new innovations in highly active research areas. Topics included:

- An Integral Approach to Treat Alcohol-Induced Liver Disease
- Recent Advances in the Management of NAFLD
- Management of Complications of Cirrhosis
- Living-Donor Liver Transplant: the UPMC Experience
- Current Trends in Liver Transplantation

For more information, visit the **Featured Events** section at [UPMCPhysicianResources.com/GI](http://UPMCPhysicianResources.com/GI). Please join us again next year.

# Malignant Vascular Tumor of the Liver: A Cause of Liver Failure

Two years ago, while on his honeymoon, a 36-year-old male presented with spontaneous splenic rupture and liver lesions concerning for angiosarcoma. He did not respond to doxorubicin. He was later diagnosed with hepatosplenic T-cell lymphoma (HSTCL) on repeat liver biopsy and responded to chemotherapy including hyper-CVAD. He underwent stem-cell transplant (SCT) that was complicated by graft-versus-host disease and CMV viremia, although he eventually achieved remission.



**Debbie Cheng, MD**, is a gastroenterology fellow, Year II, in the Division of Gastroenterology, Hepatology and Nutrition.

The patient presented with two months of increasing abdominal pain and distension. A CT scan was notable for hepatomegaly and numerous lesions involving the liver, ribs, vertebra, and sacrum (see Figure 1). Bone marrow biopsies were unrevealing for malignancy. His liver function declined, and he was referred for liver transplant evaluation.

On exam, the patient was jaundiced and demonstrated massive hepatomegaly and anasarca. Labs revealed renal insufficiency, anemia, thrombocytopenia and coagulopathy, total bilirubin 33 mg/dL, AST 1336, ALT 378, and alkaline phosphatase 134 (IU/L). His course was complicated by rapid deterioration due to a large perihepatic hematoma with hemoperitoneum (requiring hepatic artery embolization), toxic epidermal necrolysis, disseminated intravascular coagulation, and, ultimately, multiorgan failure with septic shock. Given concerns for an aggressive malignancy, he was not deemed to be a candidate for transplant.

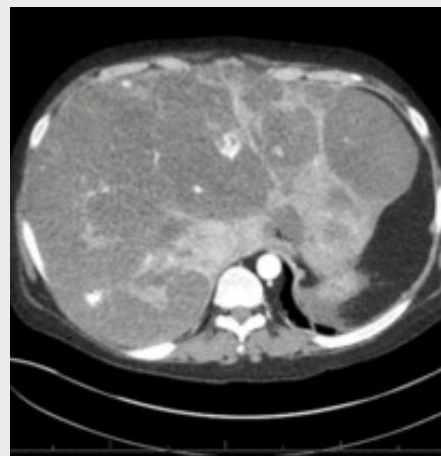
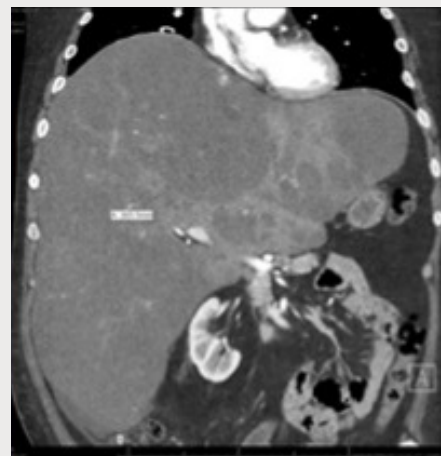
Postmortem analysis revealed a liver measuring 30 x 25 x 20 cm, weighing 7.0 kilograms with 90 percent of hepatic parenchyma composed of blood-filled vascular masses and confluent dark red hemorrhagic tumor nodules. Review of previously obtained biopsies by multiple pathology specialists diagnosed a malignant vascular tumor of the liver, representing either a hepatic angiosarcoma or hemangioendothelioma.

## Malignant Vascular Tumors of the Liver

Malignant vascular tumors of the liver include hepatic angiosarcomas (HAS), epithelioid hemangioendotheliomas (HE), and hemangiopericytomas. HAS is a high-grade tumor that can progress rapidly with metastases to areas including the spleen, lymph nodes, lungs, bone, and adrenals. It typically presents in patients 50 to 70 years of age and is more common in men. HAS is characterized by poorly defined hemorrhagic and necrotic nodules that are hypodense and do not enhance with contrast on imaging. These tumors may be associated with certain exposures, such as vinyl chloride, arsenic, and thorium. Clinical presentation may vary, and possible symptoms include abdominal pain, jaundice, ascites, and, rarely, Budd-Chiari syndrome. Fifteen percent of HAS patients present initially with acute spontaneous hemoperitoneum due to nodule rupture. Causes of death include liver failure and intra-abdominal bleeding. Microangiopathic hemolytic anemia and thrombocytopenia may result from damage when blood cells pass through tumor vasculature. On pathology, characteristic findings include variably differentiated tumor endothelial cells with severe nuclear atypia and frequent mitoses along dilated sinusoids. HAS and HE can have positive immunostaining for vascular markers, including ERG transcription factor, CD31, CD34, and Factor VIII antigen.

Surgical resection may be performed for HAS, but even with complete resection, patient survival is less than one year. Because of a high recurrence rate and poor survival posttransplant, liver transplantation is not recommended. Various chemotherapy regimens have been tested (including doxorubicin, ifosfamide, and paclitaxel), but there has been no proven effectiveness with these therapies.

Epithelioid hemangioendotheliomas (EH) are less common (incidence of less than 0.1 per 100,000) than HAS and are low-grade, although they frequently metastasize to the lungs, lymph nodes, peritoneum, bone, and spleen. Most commonly, EH affects individuals 40 to 50 years of age and is characterized by cellular infiltration of tumor cells in sinusoids and intrahepatic veins. Presentation can range from absence of symptoms to portal hypertension or hepatic failure with slow or rapidly progressive disease, however, a multifocal tumor with varying sized nodules is typical. In contrast to HAS, the tumor periphery may enhance with contrast and may retract the liver capsule with calcifications in 20 percent of cases. Pathology is characterized by neoplastic cellular infiltration with epithelioid-type cells of sinusoids and intrahepatic veins. Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive tumor more frequently seen in children. KHE may be associated with Kasabach-Merritt phenomenon, or consumptive coagulopathy with intravascular fibrin deposition with thrombocytopenia and purpura.



**Figure 1.** Hepatomegaly (measuring 36.5 cm craniocaudally, seen on left) with numerous confluent hypodense lesions.

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## The Division of Gastroenterology, Hepatology and Nutrition is honored and proud to welcome the following June 2019 gastroenterology & hepatology fellow graduates as GI colleagues:

**Jeffrey Dueker, MD:** Assistant Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition, UPMC Digestive Disorders Center, and the VA Pittsburgh Healthcare System - Pittsburgh, PA

**Diana Jaiyeola, MD:** Gastroenterologist, St. Luke's Gastroenterology Specialists and St. Luke's University Health Network - Philadelphia, PA

**Matthew Klinge, MD:** Hepatologist and Gastroenterologist, Bayfront Digestive Diseases at UPMC Hamot - Erie, PA

**Bassem Matta, MD:** Advanced Therapeutic Endoscopy Fellow, New York University Langone Health - New York, NY

**R. Warren Sands, MD, PhD:** Continuing studies as an Advanced ABIM Research Pathway Fellow - Division of Gastroenterology, Hepatology and Nutrition - Pittsburgh, PA

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