Message from the Chief

Dear Colleagues,

There is an old Hasidic story about Rabbi Eizik, son of Rabbi Yekel of Kraków, Poland. Rabbi Eizik had a recurring dream about a treasure buried in Prague under the bridge that led to the King’s Palace. Finally, Rabbi Eizik traveled to Prague but the bridge was guarded and he did not dare start digging. But he went to the bridge repeatedly until one day the captain of the guard asked him what he was looking for. Rabbi Eizik told him of the dream that brought him there. The captain laughed. “You wore out your shoes to come here? If I had faith in dreams I should have followed my recurring dream that told me to go to Kraków and dig for treasure under the stove in the home of Rabbi Eizik, son of Rabbi Yekel. Can you imagine how many Eiziks and Yekels there are in Kraków?” and he laughed again. Rabbi Eizik bowed, traveled home, and dug up the treasure from under his stove.

Where is the treasure? The answer is it’s right here, underneath us. Our division is outstanding with across the board excellence. Our future is to blossom that excellence further. We dedicate ourselves to training young investigators, to addressing critical scientific and clinical problems, and to recruiting new faculty who can spur us on. We have identified areas we know we want to expand and improve upon such as the microbiome and its role in GI and liver disease, mucosal immunology, personalized medicine, and outcomes research. We also look forward to seizing upon and exploring the latest discoveries yet to emerge. Thank you for being a part of our journey.

In this edition of Gastroenterology Research Update you’ll find news on our most recent colorectal cancer research efforts, as well as the work of David Binion, MD, and David Whitcomb, MD, PhD, who have secured major new grants from the U.S. Department of Defense for their big data work with inflammatory bowel disease and acute pancreatitis, respectively. Their new efforts hold great promise for radically reshaping how these illnesses are diagnosed and treated.

I would also like to take this opportunity to welcome Ramon Bataller, MD, PhD, to the Division. Dr. Bataller is our new chief of hepatology and brings with him the leadership skills and research prowess to reinvigorate and expand our clinical programs and translational hepatology research. More about Dr. Bataller and his work can be found further on in this newsletter.

I hope that you find the news and information in our ongoing updates to be beneficial, and I look forward to hearing comments and suggestions from you, our colleagues across the country.

Respectfully,

Robert E. Schoen, MD, MPH
Professor of Medicine and Epidemiology
Chief, Division of Gastroenterology, Hepatology, and Nutrition
University of Pittsburgh School of Medicine
Prediction Models for Personalized IBD Patient Care and the Role of Big Data Analytics

The past 20 years have produced a tremendous amount of discovery in the area of inflammatory bowel diseases. On the genetics and genomics front, virtually all of the risk polymorphisms associated with IBD have been discovered. The explosion of investigation into the microbiome in the last 15 years will decidedly expand upon the current evidence base and find new ways in which dysbiotic microbiomes in IBD patients play key roles in the initiation and perpetuation of disease and associated complications.

In the current clinical landscape, however, there’s a disconnect between all of the knowledge that has been accumulated on the genetic front for IBD and the translation of that knowledge into improved care and prognostication. And with microbiome research, the challenge now balances on the vast amount of data generated when characterizing the thousands or even tens of thousands of organisms living in the gastrointestinal tract. Understanding all the relationships and interconnected mechanisms at play in IBD pathology, and how diet and medications contribute to and affect the microbiome and disease course, reflect how this interconnected dance plays out on an individual patient level.

Embracing and Mining Big Data for New Discoveries

Our Division’s UPMC IBD Registry is a longitudinal and relational database housing complete information on more than 3,000 IBD patients who have been followed for nearly nine years. Two million laboratories, 15,000 pathology reports, every endoscopic procedure, medications — all resulting in a total prospective, multiyear natural history aggregated from the various EMR systems and fed from the nearly 500 outpatient clinics and two dozen hospitals within the UPMC system.

David Binion, MD, professor of medicine and co-director of the IBD Center has been working on the development, management, and use of the registry since arriving at UPMC in 2008. “If you think about the routine clinical care of individuals, the information collected is more or less unstructured clinical data. We have developed the ability to transform this unstructured clinical data into time-stamped metadata on a year-by-year basis. We can see how this information tapestry flows, and the trajectory over a multiyear period is enabling us to see patterns that would have remained elusive if we had limited our studies to a one or two-year timeframe. This multiyear, prospective natural history effort is an essential ingredient in understanding the associations between genetics and how patients present clinically in relation to various treatments over time,” says Dr. Binion.

The vast patient data repository available to Dr. Binion and his colleagues has allowed them to develop detailed clinical phenotypes of IBD, and has greatly expanded their ability to conduct disease outcome and treatment response research. The registry also likely holds the knowledge base necessary to create predictive modeling algorithms capable of high degrees of sensitivity and specificity, which is the focus of a newly funded research project led by Dr. Binion.

Developing Predictive Models for IBD

Dr. Binion’s newest investigation is funded by the U.S. Department of Defense, and will analyze IBD patient datasets contained in the UPMC IBD Registry to develop predictive, web-based modeling tools. Clinicians can use this data to identify patients who are likely to suffer from high-cost complications, such as enteric infections, as well as those who may respond poorly or not at all to anti-TNF biologic therapies. Dr. Binion is collaborating with several individuals and groups from across the UPMC and University of Pittsburgh systems on the study, including Marek Drodzell, PhD, in the School of Information Sciences, Mark Roberts, MD, MPP, with the Graduate School of Public Health, and Gong Tang, PhD, associate professor of biostatistics. Michael Dunn, MD, from the division is serving as a co-investigator on the grant with Dr. Binion.

“Our job is to find and understand these patterns, but more importantly translate them into useful clinical and diagnostic tools to reshape the provision of health care for IBD patients.”

David Binion, MD
The ability to predict in advance which patients are likely to suffer high-cost complications or to fail anti-TNF therapies has obvious beneficial implications to the patient and health care system alike. Only about 50 percent of patients have a sustained benefit to anti-TNF medications over a five-year period. Understanding who may not benefit from the therapy as early as possible in the disease course will lead to better patient care as well as likely cost savings over the long term.

“We believe that the registry has captured the data that will allow us to reverse engineer the factors that are associated with high-charge challenges. Our models could eliminate much of the trial and error process involved in the care of our patients. What we have essentially developed with our registry is a precision, personalized medicine platform that can be leveraged in many ways. Many discoveries await us in the data. Our job is to find and understand these patterns, but more importantly translate them into useful clinical and diagnostic tools to reshape the provision of health care for IBD patients,” says Dr. Binion.

References


Further Reading

Dr. Binion and his colleagues have recently published numerous studies using the UPMC IBD Registry. Below is a selection of these works for further reading.


New Research in Colorectal Cancer

Robert E. Schoen, MD, MPH, division chief and colon cancer researcher, has opened several new avenues of investigation into the treatment, detection, and surveillance of colorectal cancers (CRC). The first, under the support of a new NIH U01 grant, is examining the efficacy of early detection and monitoring of colorectal cancer via the use of circulating tumor DNA. ctDNA has received enormous attention in recent years for its potential as a noninvasive, blood-based biomarker test for cancer.

These so-called liquid biopsies hold great promise for faster, less invasive screening, especially for patients who must be assessed repeatedly over time for concerns of recurrent disease, such as with solid tumors within organs that cannot be safely and regularly sampled by biopsy, because doing so would subject the patient to undue burden or risk.

Dr. Schoen is partnering with Drs. Kenneth Kinzler and Bert Vogelstein at Johns Hopkins University in this new research, which will evaluate the use of ctDNA both as a primary screening modality for colorectal cancer and for patients under treatment or surveillance for recurrent disease. The studies will identify mutation markers as part of a plasma detection panel, and will assess their sensitivity and specificity with CRC subjects and disease-free control groups. In terms of monitoring, patients with stage III CRC will be sampled every three months for up to five years, with the resulting data permitting the assessment of ctDNA as a prognostic marker for disease-free survival and recurrence.

Machine Learning From Endoscopic Images

Capsule endoscopy, or the swallowing of a pill-sized camera for visualizing the small intestine, is now a routine diagnostic test. Application of capsule endoscopy to the colon, such as for the screening for colorectal cancer, is still in development, it holds the promise of a less invasive diagnostic technology. Distinguishing the findings of the captured images — normal versus pathologic — is at the heart of propelling the technology into more widespread use, assuming that accuracy, sensitivity, and specificity can be maintained. The heart of the problem is enhancing computer vision and analytic technology to develop machine learning approaches to aid in the diagnostic accuracy of capsule endoscopy for CRC. In effect, to create a computer-aided capsule endoscopy of the colon to assist with detection.

Dr. Schoen is partnering with Medtronic Inc. to advance in the development of machine learning algorithms to help differentiate between normal tissue and adenomatous polyps during capsule endoscopy. Dr. Schoen’s research team is providing thousands of de-identified endoscopic images and associated colonoscopy and pathology data to build the image bank that will be used to design recognition and detection algorithms.

The FORTE Study

A multicenter study called FORTE (Five or Ten Year Colonoscopy for 1-2 Non-Advanced Adenomatous Polyps) is being planned for 2018 in collaboration with the National Cancer Institute and its cancer cooperative group NRG Oncology. Fifteen thousand patients are planned for enrollment. Dr. Schoen will serve as the principal investigator for this national trial that seeks to determine whether a surveillance colonoscopy interval of five or 10 years is needed for subjects with one to two non-advanced adenomas found on colonoscopy. Approximately 30 percent of all colonoscopy exams detect a non-advanced adenoma, and that number is increasing because of improved methods for detection, and because endoscopists are being encouraged to identify even the tiniest adenomas. Current guidelines recommend that these patients return in five to 10 years, but there is no guidance on whether five or 10 years is needed. Additionally, data is emerging suggesting that small adenomas may not confer significant risk for cancer.

This randomized controlled trial seeks to establish evidence-based guidelines for the application of surveillance colonoscopy timing.

References and Further Reading

Modeling Acute Pancreatitis as a Predictor of Organ Failure in Trauma and Critically Ill Patients

With funding from the U.S. Department of Defense (DOD), David C. Whitcomb, MD, PhD, is investigating how some cases of acute pancreatitis (AP) lead to a systemic inflammatory response syndrome (SIRS), which can lead to vascular leak syndrome (VLS) and subsequent progression to multi-organ dysfunction syndrome (MODS).

This sequence occurs in approximately 10 to 20 percent of acute pancreatitis cases. Roughly 50 percent of patients with SIRS recover. The other half progress to VLS and MODS, and these patients have a mortality rate that approaches 30 percent.

The aims of Dr. Whitcomb’s research are to identify the likely constituent biomarkers driving the SIRS and MODS processes. He and his colleagues have already identified angiopoietin 2 (Ang-2) as a culprit in the development of vascular leak syndrome (VLS). VLS is triggered by a SIRS which is a part of the process leading toward MODS. They are also studying the possible role of the inflammatory cytokines tumor necrosis factor alpha (TNFa) and IL-1 in SIRS. Ultimately, Dr. Whitcomb’s research seeks to develop predictive models using machine learning techniques and algorithms to assess an AP patient’s lab values and biomarker findings to predict their relative risk of progression into SIRS and MODS. The utility of such a predictive model would provide clinicians with advance warning and insight into a complex diagnostic and treatment scenario.

Like AP, certain cases of traumatic injury and critical illness — burns, battlefield trauma, and sepsis — often exhibit a similar systemic inflammatory response which leads to multi-organ failure. The hypothesis is that once the mechanisms and biomarkers driving the inflammatory response are known and understood in AP, this evidence could be studied and applied to other categories of critically ill or trauma patients who exhibit similar inflammation and organ failure pathways, including members of the military injured during combat. While the DOD has a vested interest in this research to potentially benefit its service members, Dr. Whitcomb indicates that applications could extend well beyond the battlefield to critical illness and trauma care for the entire population.

Dr. Whitcomb’s research team and his partners in the Division working on the project (Georgios Papachristou, MD, PhD, and David Binion, MD) have made steady progress in the three years since the study’s inception. Several papers are in development or have been submitted for publication that detail aspects of the research, including the role of activin as a driver of severe acute pancreatitis in both animal models and patients, and how certain fatty acids that are broken down in the blood stream by pancreatic enzymes contribute to vascular leak syndrome and, ultimately, organ failure. “What we are learning is that we are really dealing with not one single condition, but multiple discrete pathways that are proving to be causative,” says Dr. Whitcomb.

“Modeling Acute Pancreatitis as a Predictor of Organ Failure in Trauma and Critically Ill Patients” by David C. Whitcomb, MD, PhD

References and Further Reading

Acute Pancreatitis as a Model to Predict Transition of Systemic Inflammation to Organ Failure in Trauma and Critical Illness. Principal Investigator: David C. Whitcomb. DOD Award Number: W81XWH-14-1-0376. For additional grant information, visit cdmrp.army.mil.
New Faculty Profile: Ramon Bataller, MD, PhD

Ramon Bataller, MD, PhD, joined the Division of Gastroenterology, Hepatology, and Nutrition in May 2017 as professor of medicine and chief of medical hepatology. Previously with the University of North Carolina at Chapel Hill, Dr. Bataller’s research focuses on epidemiological, clinical, and molecular aspects of alcoholic fatty liver disease.

Dr. Bataller also is a primary investigator in one of four NIH-funded consortia seeking to identify the molecular targets responsible for disease pathogenesis and novel treatments for alcoholic hepatitis, the most severe form of alcoholic liver disease. Dr. Bataller’s research has identified that a systemic inflammatory response as part of the alcoholic hepatitis disease course is likely driving the induction of renal failure and other complications. Identifying which molecular signatures emanate from the liver and cause the inflammatory response may lead to more effective, targeted therapies.

Further research by Dr. Bataller seeks to better understand the regenerative mechanisms of the liver in relation to alcoholic hepatitis — when, how, and why the regeneration process fails, leading to acute and dramatic decompensation and liver failure. Past work also has shown that persistent alcohol intake is the main determinant of long-term survival in patients with alcoholic hepatitis.

In the clinic, Dr. Bataller sees patients with alcoholic and non-alcoholic fatty liver disease, as well as those with cirrhosis of the liver. Since arriving at UPMC, Dr. Bataller has begun to work on developing programs aimed at better assessment of therapy in patients with advanced disease. He will focus on screening and detection of alcoholic liver disease in its early stages, when treatment and lifestyle changes can have a greater impact on long-term morbidity and mortality.

“One of the big problems and challenges with this disease, and one I will be working on at UPMC, is the need for better detection and management of patients with early-stage alcoholic liver disease. Alcohol use and abuse is greatly under-reported in our society, and screening for it is not nearly as robust as it needs to be. Coupled with the rising rates of obesity and cardiovascular disease, increasing percentages of the population are at higher risk for both alcoholic and non-alcoholic liver diseases, and they are at a higher risk for an earlier onset of disease,” says Dr. Bataller.

References and Further Reading
2017 State-of-the-Art (SOTA) Lecture Series

The SOTA lecture series is a twice-weekly didactic lecture featuring faculty experts discussing key areas of gastroenterology and hepatology medicine.

This year’s series includes 20 lectures, all of which will be available for CME on UPMCPhysicianResources.com.

Topics and speakers from the 2017 series include:

• Hereditary GI Disorders — Randall E. Brand, MD, and Beth Dudley, MS
• Evaluation and Management of Nonvariceal UGI & LGI Bleeding — Adam Slivka, MD, PhD
• Complications of Cirrhosis — Kapil B. Chopra, MD, and Shahid Malik, MD
• Viral Hepatitis — Michael A. Dunn, MD
• Inflammatory Bowel Disease Management and Evaluation — Mark Schwartz, MD
• Screening for GI Malignancies — Robert E. Schoen, MD, MPH
• Chronic and Acute Pancreatitis — Georgios I. Papachristou, MD, PhD
• Psychobehavioral Approaches to GI Disease — Eva M. Szigethy, MD, PhD

Save the Date: PancreasFest 2018

The Division of Gastroenterology, Hepatology, and Nutrition will again host the annual PancreasFest conference, July 25–27, 2018, in Pittsburgh, Pennsylvania.

PancreasFest 2018 is the annual pancreas 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, pancreatitis, and pancreas-related complications, such as diabetes and obesity.

Course Directors

Nathan Bahary, MD, PhD
Randall Brand, MD
Sohail Husain, MD
Georgios Papachristou, MD, PhD
David Whitcomb, MD, PhD
Herbert Zeh, MD

Multicenter Investigator Meetings

• CAPER (Collaborative Alliance for Pancreatic Education and Research)
• INSPIRE (International Study Group of Pediatric Pancreatitis In Search of a CuRE)
• APPRENTICE (Acute Pancreatitis Patient Registry to Examine Novel Therapies In Clinical Experience)
• PRIMO (Prospective Research in IPMN Management and Outcomes)

For more information, or to register for the conference, please visit PancreasFest.com.

IBD UNITE

The Division of Gastroenterology, Hepatology, and Nutrition has developed a new educational seminar specifically for IBD patients. Called IBD UNITE (Unify, Network, Inspire, Treat & Educate), this one-day course includes tracks for both adult patients and teens and their parents, and is designed to provide attendees with education and support through lectures, exhibits, breakout sessions, and moderated Q&A sessions.

The first IBD UNITE event is scheduled for Saturday, March 24, 2018, at UPMC Presbyterian.

Course topics include:

• Overviews and news about the latest treatment advances
• Behavior and psychiatric components of IBD
• Transitioning to adult GI care
• Social aspects related to living with IBD and other relevant topics in IBD treatment and management

Patient referrals for attendance at this free event are welcome.

Full course details and registration information will be available in the near future by visiting: https://www.dept-med.pitt.edu/gi.
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
- Pancreatic and Biliary Diseases
- Functional Bowel Disorders
- 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.