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GASTROENTEROLOGY RESEARCH

UPDATE

DIVISION OF GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Inside This Edition

Message from the Chief

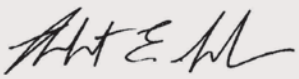
The single biggest problem in communication is the illusion that it has taken place.

— *George Bernard Shaw*

The ability to communicate has undergone a revolutionary change. In 2019, it is estimated there will be 4.7 billion cell phone users — 63 percent of the global population. The ability for the cell phone to bring in the outside world to even sheltered communities is, and will continue to shape our future. In the ultra-orthodox Haredi Hasidic communities there has been an increasing prevalence of "nonkosher phones" — phones which permit access to the Internet. As one might expect, increasing outside influence disrupts closed societies and threatens to bring about change. That is why authoritarian regimes restrict access to the internet — to control the peoples' dialogue. Digital communication is often measured in clicks or website hits, but that does not necessarily mean effective communication occurred. Studies suggest that internet users spend no more than 10 to 20 seconds on the typical webpage. Accessing a website does not mean you have absorbed its content, nor has it necessarily effectively communicated with you. In science, merely doing is not sufficient — we must communicate what we have done to be effective. The *Gastroenterology Research Update* is our attempt to bring you into our division and explore the research questions and clinical dilemmas we are addressing.

In this issue, we highlight our faculty's efforts led by **Dhiraj Yadav, MD, MPH**, **Kevin McGrath, MD**, and **David C. Whitcomb, MD, PhD**, in pancreatic cancer, pancreatic cysts, and chronic pancreatitis, respectively. **Yang Liu, PhD**, shares her ground-breaking efforts in high-resolution microscopy. We are trying to not only communicate but to communicate effectively. Welcome to our world and thank you for joining us.

To good health,



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New Research to Understand Pancreatitis, Diabetes, and Pancreatic Cancer

Two new studies, PROCEED and SHARP, will drastically change our understanding of pancreatic disease. **Dhiraj Yadav, MD, MPH**, professor of medicine in the Division of Gastroenterology, Hepatology and Nutrition is the primary investigator at UPMC and one of the national coordinators for these exciting initiatives.

"If we can identify who is at risk to transition to chronic pancreatitis, and, if we can know that by early diagnosis, then we may help them. Moreover, quantifying clinical outcomes and progression will provide tools to develop clinical trials to evaluate efficacy of novel treatments."

Dhiraj Yadav, MD, MPH

The PROCEED study (Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies) is one of four studies currently being conducted by the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). The CPDPC was established by the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases and is funded through a U01 grant. It is a multidisciplinary program designed to accelerate progress in the understanding of pancreatic diseases. The CPDPC comprises ten clinical centers — nine adult centers including UPMC, and one consortium of pediatric centers, including UPMC Children's Hospital of Pittsburgh — along with a data-coordinating center, which is located at The University of Texas MD Anderson Cancer Center.

The CPDPC is needed because there are large gaps in our knowledge of pancreatic disease, especially chronic pancreatitis. Despite substantial basic science research, there is not a good animal model of chronic pancreatitis, it has been difficult to translate discoveries into results for patients, and clinicians still lack effective therapies. As a result, treatment of chronic pancreatitis currently focuses largely on symptom amelioration, such as decreasing abdominal pain. Even though the total percentage of patients with pancreatic cancer who have experienced prior pancreatic problems is small, chronic pancreatitis is a risk factor for pancreatic cancer and is associated with a 13-fold increased risk. Additionally, about one percent of patients who become diabetic after the age of 50 will be diagnosed with pancreatic cancer within three years — an approximate eight-fold increased risk as compared with patients without new-onset diabetes. This pancreatogenic diabetic manifestation is referred to as Type 3c diabetes mellitus (T3cDM). The risk for pancreatic cancer is increased 33-fold in patients with both pancreatitis and T3cDM.

The CPDPC aims to understand how chronic pancreatitis, new-onset diabetes, and pancreatic cancer are linked. Additionally, the consortium will establish an annotated repository of biospecimens to allow for the identification and validation of biomarkers for risk stratification and early detection as a result of their collaborative efforts. The CPDPC has initiated three longitudinal studies to reach these objectives: 1) PROCEED; 2) NOD (new-onset diabetes), which will establish a cohort of patients with new-onset diabetes; and 3) INSPPIRE, the **In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n Search for a Cu**re** cohort study. The CPDPC also will perform studies to define and characterize pancreatogenic diabetes (T3cDM), including the DETECT (Evaluation of a Mixed Meal Test for **D**iagnosis and Characterization of **T**ype 3**c** Diabe**t**es Mellitus Secondary to Pancreatic Cancer and Chronic Pancreatitis) study, and the consortium already has more than 30 ancillary studies that are approved by its steering committee. Through these endeavors, the CPDPC will work toward the key goals of preventing pancreatitis progression, preventing diabetes progression, and identifying pancreatic cancer at an early, treatable stage.

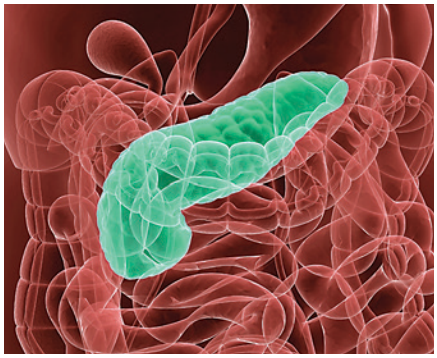
The PROCEED study, which Dr. Yadav oversees along with Darwin L. Conwell, MD, MS, from The Ohio State University School of Medicine, is the first longitudinal cohort study of chronic pancreatitis in adult subjects in the United States. The study will prospectively identify and follow a well-characterized cohort of patients with chronic pancreatitis in different disease stages. This will allow Dr. Yadav and his colleagues to accurately define the natural history of chronic pancreatitis and its associated complications. It will also allow them to estimate the risk of progression of suspected chronic pancreatitis to definite chronic pancreatitis and the risk of new-onset diabetes or exocrine pancreatic

dysfunction associated with chronic pancreatitis. Additionally, they will study how these risks are influenced by patient characteristics. The primary goals of PROCEED are to define disease progression, test the predictive capability of candidate biomarkers, and develop a platform to conduct translational and mechanistic studies of chronic pancreatitis. This groundbreaking approach should promote new strategies for diagnosis of chronic pancreatitis, new methods to monitor disease progression, and better treatment of chronic pancreatitis.

The PROCEED study will recruit patients who typify different stages of chronic pancreatitis as the current disease paradigm is understood. They will study patients with established chronic pancreatitis, patients with suspected chronic pancreatitis, those with chronic abdominal pain but in whom the pancreas appears normal, and control subjects who do not have pancreas disease. A linked repository of biospecimens (blood, urine, saliva, stool, pancreatic fluid, and pancreatic tissue) will be collected using standardized protocols. Dr. Yadav and his colleagues started recruiting patients to the PROCEED study in June 2017 and will begin recruiting control subjects soon. They have established one-third of their cohort. Of the 1,820 participants targeted, more than 600 patients have enrolled in the study. The PROCEED study will also facilitate additional research that will take advantage of the clinical and biological data and tissue samples collected, such as epidemiologic studies, genetic studies, biomarker analyses, and microbiome analyses. The consortium has more than 30 ancillary studies that are approved by its steering committee.

The PROCEED study is a conceptual framework that will accurately define the continuum of chronic pancreatitis and should facilitate the treatment of at-risk patients to prevent progression. According to Dr. Yadav, "If we can identify who is at risk to transition to chronic pancreatitis and if we can know that by early diagnosis or among patients who already have disease, if we know who is going to become a diabetic, who is going to develop malabsorption, who is going to develop cancer, then we could help those patients."

Developing an effective strategy for early detection of pancreatic cancer is essential to improve survival. A second longitudinal study of the CPDPC is the NOD (new-onset diabetes) cohort, which is headed at UPMC by Randall E. Brand, MD, Dr. Yadav's faculty colleague. In establishing the NOD cohort, the CPDPC is aiming for 10,000 participants 50 years of age or older with new-onset diabetes. Biosamples will be collected from this prospective cohort, and the patients will be followed clinically for three years. This longitudinal process will allow CPDPC researchers to estimate the three-year probability of pancreatic cancer in a patient population at increased risk and then use the cohort to assess biomarkers and screening approaches for detection of early-stage pancreatic cancer.



Although T3cDM differs from type II diabetes, there are no clinically validated methods to differentiate between these two diabetic presentations. The CPDPC will address this gap in knowledge with the DETECT study. This study will enroll ~450 patients with diabetes, chronic pancreatitis, and/or pancreatic cancer. Most patients in the study will have new-onset diabetes (within the last three years), but some will have long-standing diabetes and others will be nondiabetic. The patients will participate in a mixed-meal tolerance test, and changes in their glucose metabolism and hormone levels will be monitored over a two-hour period. The goal of the study is to identify a signature for T3cDM, which is associated with chronic pancreatitis and pancreatic cancer, which differs from that of type II diabetes.

UPMC centers are currently recruiting for all of these CPDPC studies. The CPDPC will develop significant resources for the study of chronic pancreatitis and its associated diseases, such as diabetes and pancreatic cancer for years to come. "This is a great opportunity for us to make discoveries and change the face of the disease," says Dr. Yadav.

Dr. Yadav also is the co-primary investigator on a major multicenter randomized controlled trial that could change the treatment of recurrent acute pancreatitis. Like the CPDPC, this SHARP trial (for SpHincterotomy for Acute Recurrent Pancreatitis) is funded through a U01 consortium grant (ClinicalTrials.gov Identifier: NCT03609944). The purpose of this study is to determine if a procedure called endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy reduces the risk of pancreatitis or the number of recurrent pancreatitis episodes in patients with pancreas divisum. Pancreas divisum is a congenital condition, found in approximately five percent of the population, and occurs when the dorsal and ventral pancreatic ducts do not fuse correctly, and the pancreatic secretions must exit through a smaller opening than is physiologically normal. It is believed that this small opening does not drain the pancreas very well, is a functional obstruction, and can cause attacks of acute pancreatitis. This rationale has been used by investigators to support the use of the ERCP procedure to enlarge the opening, but this procedure has risks. It can cause pancreatitis and other complications, e.g., scarring, and it may not help to resolve the patient's condition.

Although ERCP routinely is performed with the expectation of improvement, rigorous scientific data supporting this procedure is lacking. A randomized controlled trial was conducted previously but contained only 19 patients and was done more than 25 years ago. With Gregory A Coté, MD, MS, and Valerie M. Durkalski, PhD, from the Medical University of South Carolina, Dr. Yadav will now address this outstanding question in an appropriately powered clinical trial. The patients in the trial will be randomized to undergo either ERCP or a placebo procedure. All patients will undergo endoscopic ultrasound. The trial will enroll 234 randomized patients (117 per arm) and a 100-patient observation group comprised of patients

Continued on Page 13

Pancreatic Cysts and Cancer Detection

Kevin McGrath, MD, is a professor of medicine, director of the endoscopic ultrasound program, director of the gastroenterology endoscopy lab, and co-director of the Division's **Barrett's Esophagus Specialty Treatment (BEST) Clinic**. Dr. McGrath also focuses on pancreatic cancer and the evaluation and study of pancreatic cystic lesions through cyst aspirate analysis.

"We can look for and find cellular DNA shed into the cyst fluid, and then analyze the fluid for mutations to better diagnose the type of cyst and even predict the biological behavior in select cases."

Kevin McGrath, MD

In the BEST Clinic, Dr. McGrath collaborates on clinical care and research with Kenneth E. Fasanella, MD, assistant professor of medicine, BEST Clinic co-director, and program director of the gastroenterology fellowship. Jennifer Chennat, MD, associate professor of medicine, is a physician member of the BEST team as well.

Dr. McGrath's research priorities revolve around endotherapy for the management of Barrett's esophagus and superficial esophageal cancer, the evaluation of pancreatic cystic lesions and cyst aspirate analysis, and endoscopic ultrasound (EUS)-guided tissue acquisition.

Dr. McGrath's gastroenterology (GI) clinical practice places particular emphasis on therapeutic endoscopy, EUS for the diagnosis and staging of GI malignancies, pancreatic cystic neoplasms, and the management of dysplastic Barrett's esophagus and superficial adenocarcinoma via endoscopic therapies that include radiofrequency ablation, cryotherapy, and endoscopic mucosal resection. Dr. McGrath also routinely manages patients with esophageal strictures, eosinophilic esophagitis, and gastroesophageal reflux disease (GERD).

Pancreatic Cysts — Early Detection of Cancer Through Next Generation Sequencing

With the more widespread use of cross-sectional MRI and CT imaging modalities, incidental findings of pancreatic cysts are on the rise. It is estimated that between two and 25 percent of individuals in the United States may have pancreatic cysts, and the incidence increases with age. The questions become:

- What to do with these findings?
- How to discern who is at the highest risk of progressing to full-blown cancer?

"The most common type of cyst that is found in imaging studies is benign but is technically a precancerous form, the branch duct intraductal papillary mucinous neoplasm (BD-IPMN)," says Dr. McGrath. Because these are fluid-filled cysts, they cannot be biopsied in the traditional sense to obtain histological findings indicative of cancerous lesions. More than a decade ago, Dr. McGrath and other collaborators in the Division began working on ways to aspirate pancreatic cysts and detect which ones may be cancerous through a molecular analysis of the cyst aspirate. Researchers from the Division, including Randall Brand, MD, Georgios Papachristou, MD, PhD, Adam Slivka, MD, PhD, Asif Khalid, MD, Dr. Chennat, and Dr. Fasanella, have all worked on various aspects of pancreatic cancer and cyst fluid analysis for many years, and they have collectively made significant advancements in the basic science and clinical application of this analysis. Along with colleagues in the surgical field, and most notably molecular geneticist Aatur D. Singhi, MD, PhD, from the University of Pittsburgh Department of Pathology, these researchers have significant experience using molecular analysis to better manage cysts.

"We can look for and find cellular DNA shed into the cyst fluid, and then analyze the fluid for mutations to better diagnose the type of cyst and even predict the biological behavior in select cases. Dr. Singhi, with his notable expertise in the field and the use of next-generation sequencing technologies, is finding ways to look at multiple mutations at once and with high throughput. Dr. Singhi and his group have developed better diagnostic panels to distinguish cysts from one another. This enables us, as proceduralists, to have much more precision than in the past. We can now see which cysts are precancerous and need to be followed and which can be ignored," says Dr. McGrath.

This ongoing work also has led to the development of a panel of biomarkers that can predict the coexistence of high-grade dysplasia or even early cancer.

The BEST Clinic

The pre-cancerous condition of the esophagus, Barrett's Esophagus (BE), caused by chronic acid reflux carries with it a typically low cancer risk; however this risk is increased in patients with dysplasia. The BEST Clinic, run by Dr. McGrath and **Kenneth E. Fasanella, MD** (left), employs the latest endoscopic technologies for the diagnosis and treatment of Barrett's esophagus with dysplasia, such as narrow band imaging, endoscopic mucosal resection, radiofrequency ablation, and cryotherapy.

Drs. McGrath, Fasanella, and their clinic colleagues specialize in endoscopic diagnosis and treatment of low- and high-grade BE, and early esophageal cancer as a result of BE. Superficial cancers and nodular high-grade dysplasia are often treated with endoscopic mucosal resection. Radiofrequency ablation is the typical choice of ablative treatment for flat dysplastic BE.

"When we employ cryotherapy for treatments, for example in flat or nodular dysplasia, we have two technologies at our disposal — one is a spray cryotherapy with liquid nitrogen, and the other is a newer technology that we have begun using in the last year. This is a cryo-balloon therapy that uses nitrous oxide gas to inflate a balloon in the esophagus and ablate the target tissue," says Dr. McGrath.

"It is a continually evolving field and an exciting one in which to work because new biomarkers are being sought and found all the time, expanding our abilities to better detect cancer at earlier and earlier stages of development. All of our like-minded pancreatic researchers in the Division collaborate very closely, but I must call out the work of Dr. Singhi particularly. He is the mastermind behind cyst fluid analysis. Working with him has been a noteworthy collaboration for our group," says Dr. McGrath.

Critical Analysis

In 2016, the multidisciplinary group at UPMC published the findings of a study[1] undertaken to assess the clinical efficacy of the 2015 guidelines published by the American Gastroenterological Association (AGA) for the management of asymptomatic neoplastic pancreatic cysts.

As Dr. McGrath explains, when those guidelines were published in 2015, he and other researchers in the Division were troubled by the recommendations since, if followed, they would appear to miss a significant number of cases of high-grade dysplasia and early cancer.

"We set out to conduct a comparative study to test the AGA guidelines against our clinical practice procedures and analytical capabilities. This was one of the first studies to detect cancerous cases earlier through molecular analysis," says Dr. McGrath.

This study looked at a cohort of 225 patients who had cysts evaluated with EUS-guided fine needle aspiration between January 2014 and May 2015. The study compared the clinical findings with molecular analysis findings against what the AGA guidelines would have recommended for the same set of patients.

In essence, the AGA guidelines would have missed 45 percent of intraductal papillary mucinous neoplasms with adenocarcinoma or high-grade dysplasia compared to the UPMC testing and evidence protocols. The AGA guidelines in this cohort showed 62 percent sensitivity, 79 percent specificity, 57 percent positive predictive value, and 82 percent negative predictive value. The UPMC pathway using molecular testing of cyst fluid was able to detect advanced neoplasms with 100 percent sensitivity, 90 percent specificity, 79 percent positive predictive value, and 100 percent negative predictive value.

"We realized that the AGA guidelines were insufficient by comparison with our cyst management algorithm by a significant margin. Our collective work over many years has allowed us to devise our guidelines for use at UPMC based on our extensive experience and research. We incorporate aspects of guidelines from other entities such as the American College of Gastroenterology (ACG) and the AGA, but also rely heavily on our cyst fluid analysis and experience. Our research has proven its efficacy, and we use it actively in our clinical care pathways every day," says Dr. McGrath.

Much more pancreatic research is ongoing in the Division. These collective efforts are helping to transform the field and improve the odds against what for many is a devastating and incurable disease.

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Early Cancer Detection Using Advanced Spectroscopy

Super-resolution microscopy allows the visualization of biological molecules with nanometer resolution. **Yang Liu, PhD**, director of the Biomedical Optical Imaging Laboratory and an associate professor in our Division and the Department of Bioengineering, is advancing this technology to study DNA changes during colon cancer progression with striking results.

When applying super-resolution imaging to colon cancer samples, Dr. Liu can learn more about the clinical course of the patient, allowing her to address important questions using powerful imaging modalities.

Conventional imaging techniques are limited to ~200 nm resolution by the diffraction properties of light. Stochastic optical reconstruction microscopy (STORM) is a fluorescence-based technique for super-resolution microscopy that can image the subcellular structures in a single cell nucleus to a resolution of 20 to 30 nm. Cellular targets are labeled with fluorescently tagged antibodies. The key to breaking the diffraction limit is precise localization of the centers of sparsely distributed, single, fluorescent emitters. In conventional fluorescence microscopy, all the fluorophores glow at once, but the centers of individual fluorophores cannot be identified due to overlapping, diffraction-limited spots. Yet under certain laser settings and specific buffer conditions (i.e., no oxygen), only a subset of the densely labeled molecules are turned "on," making it easy to find the centers of individual fluorophores at a scale 10 times smaller than the diffraction limit. Dr. Liu and her colleagues image the same area multiple times, letting only a few interspersed molecules glow each time. These images are superimposed to yield a dense super-image with nanometer resolution. This established technology was recognized by the Nobel Prize for Chemistry in 2014.

Depth-resolved nanoscale nuclear architecture mapping (nanoNAM) is based on light interference and optical phase. The density of the compacted DNA changes the pattern of the light waves and can be quantitated. NanoNAM does not allow visualization of subcellular structures on a nanometer scale, like super-resolution imaging, but nanoNAM measures alterations to the intrinsic nuclear density with incredible sensitivity (1 to 2 nm). Because this advanced imaging can be performed on unstained human tissue samples, it is highly clinically applicable.

Using these two cutting-edge techniques, Dr. Liu examines chromatin structure to understand basic biology and cancer progression by criteria that are far more specific than a standard pathology examination. Chromatin packages DNA in the cell nucleus, and changes in the chromatin configuration determine the accessibility of the DNA. Chromatin must assume an open configuration for genes to be expressed. However, when DNA is less compact, it is more prone to damage from external factors and genome instability. These cells are then at a higher risk for cancer.

Dr. Liu and her laboratory recently applied STORM technology to mammalian cells and comprehensively characterized genome-wide, higher-order chromatin structures in single mammalian cell nuclei. Histone proteins organize chromatin and modifications to the histone proteins, namely acetylation and methylation, modulate their activity. Dr. Liu examined histone acetylation and methylation marks and their spatial proximity to assess the chromatin environment. Histone proteins with specific methylations or acetylations were labeled using fluorescently tagged antibodies. Dr. Liu found three distinct structural characteristics unique to higher-order chromatin: histone acetylation in spatially segregated nucleosome nanoclusters, histones with methylation associated with gene activation in spatially dispersed nucleosome nanodomains, and histones with methylation associated with gene repression in highly condensed large aggregates. The histone marks associated with gene activation spatially coincided with a more "open" or less compact chromatin structures and were localized in proximity to active gene transcription. Repressive histone marks spatially coincided with densely packed chromatin structure and were distant from areas of active gene transcription.

The characteristic structural features of each histone mark persisted even during cell division/mitosis, when the chromatin becomes highly compacted. With a 2018 National Cancer Institute grant, Dr. Liu plans to improve the throughput of her STORM techniques and standardize them so that they may be applied to routinely obtained clinical samples.

NanoNAM maintains the spatial and pathologic context of each cell nucleus and can serve as an adjunct to pathology, because it can be performed on unstained patient samples. Dr. Liu has capitalized on this to examine if changes to the nuclear architecture detected by nanoNAM can predict colon cancer progression. Many of the features that pathologists use to assess malignant potential are indicative of changes to the nuclear architecture (e.g., coarse aggregation of condensed chromatin, hyperchromasia, and nuclear pleomorphism), but these features are not sensitive enough to predict cancer progression. Using nanoNAM, Dr. Liu found a gradual increase in nuclear density heterogeneity during colon cancer progression. She then collaborated with Douglas Hartman, MD, in the UPMC Department of Pathology and obtained tissue samples from patients with colitis who underwent surveillance colonoscopy. Using nanoNAM, she compared nuclear density heterogeneity in samples from patients who went on to develop high-grade dysplasia or adenocarcinoma during follow up with nuclear heterogeneity in samples from patients who did not progress. This analysis was done on samples obtained from a first surveillance colonoscopy, when all of the patients had histologically normal tissue. Using nanoNAM, Dr. Liu identified changes in nuclear density heterogeneity, in the patients who would go on to develop high-grade dysplasia or cancer even though histologically their tissue showed no signs of dysplasia. NanoNAM may provide a new method to predict cancer progression. It is a promising approach to address the highly unmet clinical need of personalized risk assessment for patients.

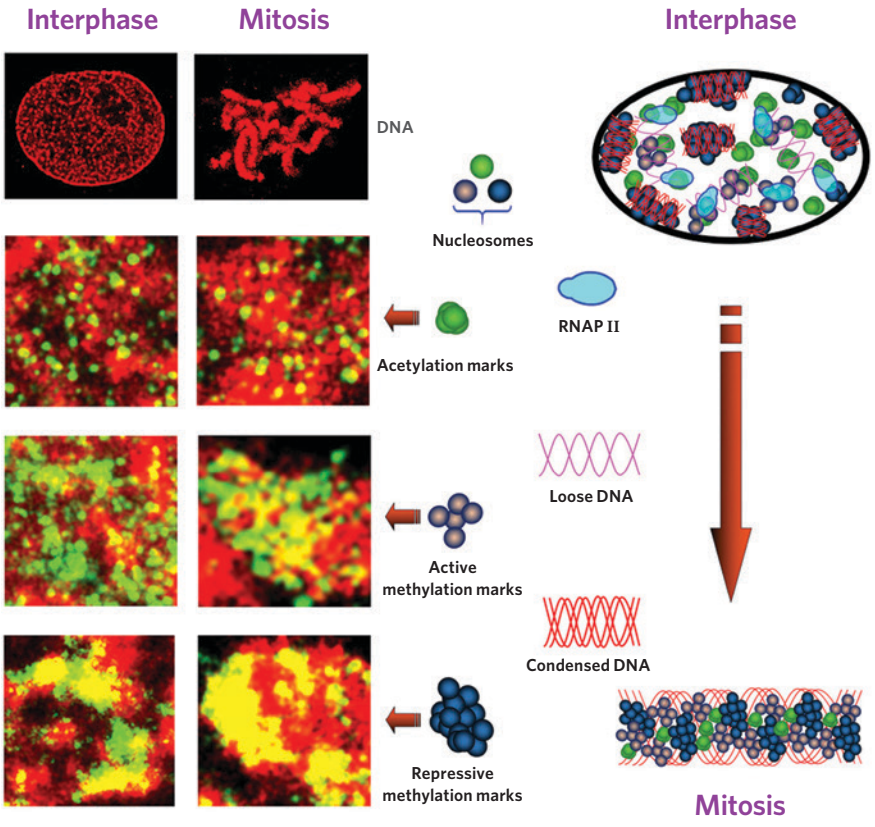

Figure 1. STORM imaging of higher order chromatin structures in mammalian cells. From Xu et al. Cell Reports 2018; 24: 873. doi: 10.1016/j.celrep. 2018.06.085. Used under the terms of the Creative Commons Attribution License (CC BY).

UPMC is an ideal place to perform this cutting-edge, translational research. Dr. Liu collaborates with Robert E. Schoen, MD, MPH, the Division Chief for Gastroenterology, Hepatology, and Nutrition, who has established a large tissue bank of colon cancer samples that includes a patient cohort with well-documented clinical outcomes. When applying super-resolution imaging to colon cancer samples, Dr. Liu can learn more about the clinical course of the patient, allowing her to address important questions using powerful imaging modalities.

By optimizing imaging technologies and developing them for clinical applications, Dr. Liu strives to detect cancerous changes early and to gain insight into which patients with precancerous colon tissue will develop cancer and why. Ultimately, this will aid clinicians to usher in the era of personalized medicine.

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Chronic Pancreatitis: A Model System for a New Paradigm in Medicine

David C. Whitcomb, MD, PhD, is the Giant Eagle Foundation Professor of Cancer Genetics, professor of medicine, cell biology and physiology, and human genetics, and director of the UPMC Precision Medicine Service.

Dr. Whitcomb's research career has been filled with numerous achievements and advances in the field of pancreas research and genetics, leading to the ongoing development and evolution to a state of precision medicine for the individual. Dr. Whitcomb's research program involves the study of pancreatic disease with a focus on modeling complex, multistep gene-environment interaction disorders that require a precision medicine approach. Dr. Whitcomb's multicenter, genotype-phenotyping hereditary pancreatitis and North American Pancreatitis Study II (NAPS2) programs, plus acute pancreatitis and pancreatic cancer studies using reverse engineering and predictive modeling approaches, serve as a foundation and pathway for treatment of diseases in multiple organ systems. He leads the Genomic Resource to Enhance Available Therapy (GREAT) study, to initiate the delivery of precision medicine for complex chronic disorders and their complications. Dr. Whitcomb also studies the pathophysiology of severe acute pancreatitis and pain genetics.

For Dr. Whitcomb, the current state of medicine — how it is practiced, how research is conducted, and the very foundation upon which medicine and research is built must evolve in order to provide better clinical care and outcomes for patients.

Below, Dr. Whitcomb discusses the main goals of his research programs, the challenges and complexities in dealing with complex chronic diseases, and how he uses chronic pancreatitis modeling to bring forth a paradigmatic shift in the provision of medicine. He is turning away from the prevailing and somewhat simplistic germ theory of disease to one of personalized medicine that is better equipped to deal with the underlying complexities and inherent challenges of preventing and treating chronic illness.

"A complex disease is one that requires a *combination* of two or more factors to cause the disease, where any factor alone is neither necessary nor sufficient to cause disease."

David C. Whitcomb, MD, PhD

Q: What has the traditional approach to chronic disease looked like?

A: Western medicine's traditional approach to medicine emerged in the 1800s based on the *germ theory of disease* whereby a single factor or agent causes a complex disorder to develop. The "scientific method" for finding the cause of a disease based on the germ theory is designed to find the one, single causative agent. This method has been refined over many years to rapidly and systematically identify a single causative factor using "null hypothesis significance testing" (i.e., form a hypothesis, test for association between the presence and absence of the factor versus the presence or absence of the disease, and choose the one factor with the lowest probability, e.g., $p < 0.05$ of *not* causing the disease). It is a method that works quite well in the world of infectious disease, such as when an outbreak of an unidentified virus or other pathogen occurs. However, most of the diseases that affect the population of the United States today are complex chronic diseases (CCD). A complex disease is one that requires a combination of two or more factors to cause the disease, where any factor alone is neither necessary nor sufficient to cause disease. If the combination of factors cannot be identified or removed, the disease becomes chronic. Roughly 75 percent of the total burden of health care costs comes from CCDs. The germ theory of disease and the scientific method of medical research simply fail for CCDs, so they continue with high prevalence. But worse still is the reality that physicians are trapped in the system by **tradition**, **dogma**, and **law**.

Tradition speaks to the historic foundations of medicine. Diseases are defined using the clinicopathologic approach focusing on the clinical signs and symptoms and/or tissue pathology. Examples are arthritis — inflammation of the joint, hepatitis — inflammation of the liver, or liver cirrhosis — atrophy and fibrosis. Diabetes mellitus is a syndrome, defined by fasting blood sugar measures over 125 mg/dL on two occasions without corresponding pathology in most cases (e.g., type 2 diabetes). The entire medical education system, electronic health record system, and all billing, coding and diagnostic criteria are based on a clinicopathologic framework.

Dogma describes the teaching of principles that are asserted by an authority as incontrovertibly true. The germ theory of disease is the dogma of Western medicine, and the scientific method is the dogmatic approach that discovers the etiology of diseases that are defined by clinicopathologic criteria. If inflammation is caused by infection, then this approach works. If it is inflammation without infection, then the scientific method typically fails to determine the cause, and the patient ends up with a CCD. Patients are then treated symptomatically or by suppressing their immune systems. There is no acceptable alternative paradigm.

Law refers to the government regulation of physician training and practice. The 1910 Flexner Report on medical education was commissioned by advocates of the germ theory to end medical approaches with *NO* scientific basis and to outline their idea of medical education and the scientific method. The report demonstrated that medical education in the United States and Canada was awful, and that the government needed to take control. Every state government accepted the recommendation that required a state license to practice medicine, and the candidate was only permitted to sit for the exam if they had graduated from a medical school that followed the curriculum set forth in the Flexner Report. Even today, over a century later, all medical schools must fashion their curriculum to teach the germ theory. And all clinical research is evaluated using the scientific method even though there are some major limitations.

Q: Why does this model not work for complex chronic diseases? What factors contribute to its ineffectiveness?

A: The primary problem is that the germ theory focuses on a strong external agent causing disease in a normal person. CCDs develop in people who have organs or systems that are NOT normal, so that a weak external agent causes disease. CCDs are difficult to study since the abnormality is typically not complete, but this malfunction affects the function of a system so that it begins to fail after injury or a suprathreshold level of stress. The organs and systems are complex machines, so that there is no one factor that causes dysfunction in all cases but, rather, many factors and in different combinations in different people. Furthermore, the body has amazing alternative and back-up systems, adaptive mechanisms, and regenerative capacities. It often takes two or more damaging factors, such as genetic variants that alter protein expression or function, to cause susceptibility to disease from weak external agents as well as additional abnormal systems to modify the disease severity or complications. Forming a hypothesis that only one factor causes the same syndrome in every person, as is done by physicians trained in the germ theory of disease, typically fails.

The problem with Western medicine can be explained by a simple example.

Suppose you bought a new car, but, unfortunately, there is a problem with the engine quitting at random times. There are two ways to get help to fix the problem. *A) Call the dealer and explain the problem.* The dealer will call Detroit, and the "epidemiologist" at headquarters will link your information with that of others with a similar make and model of car from around the world. They will look for similar circumstances, form a hypothesis as to the cause of the engine failure in this model, then work to find a fix — in some cases they identify a design flaw and order a recall months later to have a part replaced. Chances are that the recall will not fix your car and you are out of luck. *B) Go to a mechanic and explain the problem.* The mechanic has an online mechanical model of your car, including wiring diagrams and descriptions of the parts. Using standardized tools and procedures,

they quickly check the function of all of the parts linked to the engine, diagnose the problem in your car, and fix it the same day. Applied to medicine, the germ theory and the scientific method is Detroit. Personalized, precision medicine is the mechanic. But in medicine, there are no system-driven, mechanism-based functional modeling and testing tools for the "mechanic" so the patient is stuck with option A. Our group is developing the knowledge to develop the needed tools for option B.

Three examples of the failure of the scientific method to solve CCDs can be used to illustrate the point.

- The gold standard of evidence for the efficiency or effectiveness of disease treatment is the double-blinded, randomized control clinical trial (DBRCT). When this method is applied to a CCD, at least two major limitations of the germ theory are exposed. First, at the completion of the trial, the researchers discover that a therapeutic agent never works in everyone. An interesting number is calculated called NNT, or **n**umber of people that you **n**eeded to **t**reat to prevent one bad outcome. If the NNT = 5, then 4 of 5 will have the bad outcome! The second limitation of DBRCTs is that they have very well-defined inclusion/exclusion criteria that focus on the median, or most common, features of the disease. This practice *excludes* patients with the most severe disease *a priori,* so there is little or no guidance on how to help them! Furthermore, diseases with greater complexity require a higher number of patients for a clinical trial to demonstrate effective treatment (likely with a larger NNT), and, based on standard power analyses, these studies can only be done on very large populations at an enormous cost. In uncommon diseases, such as chronic pancreatitis, there are not enough patients to do these trials. So, traditional medicine offers no hope.

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- The second example is genetics. Genetics is clearly a major player in CCDs, but it does not fit into the classic clinicopathologic paradigm, except in the case of rare Mendelian disorders. Furthermore, they are not external agents hitting normal people but represent the basis of weakened defenses and responses with complex, self-regulating machines. After sequencing the human genome, it became possible to do genome-wide association studies (GWAS). A GWAS is a germ theory, scientific method approach where each polymorphism in the DNA (e.g., a single nucleotide polymorphism [SNP]) is tested starting at the top of chromosome 1 and proceeding SNP-by-SNP to chromosome 23. Chromosome 1 is independently tested to determine if that one SNP is the cause of the complex disease. What is being discovered is that CCDs such as inflammatory bowel disease have *hundreds* of SNPs associated with the disease, with none of them being necessary or sufficient as a cause, and with an association that is statistically significant (e.g., with 100,000 cases and 200,000 controls), but with a minimal effect (e.g., OR of 1.05 or less). This does not mean that genetics are not important, but that the data cannot be interpreted within the framework of the germ theory.
- The third example is evidence-based medicine. This is a method of looking backward at a series of DBRTCs that were based on older theories and methods or that were too small or poorly done to be convincing, and combining them to improve clarity and statistical power that results in stronger evidence of something. All of the problems of RCTs are retained, and there are seldom any further insights.

In addition to problems with the germ theory of disease, a fundamental problem of defining diseases is in the use of clinicopathologic definitions. CCDs are defined as syndromes, which are combinations of clinical signs and symptoms, abnormal laboratory values, and pathology findings. Nearly everything in medicine is defined this way, including the ICD-10 codes, electronic health records, and treatment plans. The problem with this approach is that, while it is important to define the pathology of the underlying disorder, it is even more important to be able to identify the underlying cause itself *before* pathological events result in irreversible features. Waiting until the disease is fully manifest and focusing on the symptoms instead of the underlying cause (which remains unknown) is unacceptable for the future.

This, in essence, is the status quo of medicine. What we have now is a system that spends massive sums of money to manage the downstream effects of out-of-control inflammation, or cancer, or diabetes when we should have been able to identify the problem when the person was younger, when they only had mild symptoms of disease or a subclinical disease that could be effectively dealt with or tamped down. Managing a disease to its downstream effects is incredibly expensive and is proving to be unsustainable in the long-term.

Q: Where do the solutions lie and how does your research model of chronic pancreatitis fit into this paradigmatic shift in medicine for which you advocate and are working to achieve?

A: The solution lies in abandoning the framework of the current system!

In order to address the problem in medicine, there must be an alternative framework. We may agree that the germ theory is not working, but there must be an alternative that is much better, or there is no point in changing. The goal of my research is to build and demonstrate the superiority of a new model referred to as personalized medicine.

I started with fundamental principles, and, for the last 25 years, have looked at one of the simplest organs in the human body — the pancreas. The pancreas has only three cell types: the acinar, duct, and islet cell. Each cell type performs one specific function. We know the molecular mechanisms that drive these cellular functions. They have been characterized and studied extensively. This allows you to build very simple predictive models of how cells normally work, what each of the pieces does, and how they interact with one another. The reason this is vitally important is that if one of the pieces is not functioning correctly and causes some of the problem, you can figure it out with a *reverse engineering* approach. This approach allows the underlying problem in individual patients to be studied. Furthermore, as any engineer can tell you, if you have a robust model, you can simulate the effects of multiple changes in any part of the system and determine both qualitative and quantitative outcomes based on thousands of conditions.

We can get to the core problem in a simple organ system like the pancreas, an organ that is protected from the environment within the human body. In a model of inflammatory bowel disease, for example, you would have to consider everything that has been in the intestines and colon, including all of the bacterial and fungal species, the environmental factors, everything over a lifetime. The same can be said for the using the lungs, or liver as organs that are exponentially more difficult to model. Everything someone breathes or ingests or has metabolized must be considered. In those organs, the possible confounding conditions or variables make it exceptionally difficult to model.

But the pancreas is different. Diseases of the pancreas generally start with acute inflammation. We can have a starting point within 10 minutes of disease inception. We know who progresses and who doesn't. We know in what ways they progress and how fast. We have the context for all of this in the pancreas. The simplicity of the organ itself makes it manageable to model CCDs such as chronic pancreatitis. Yet, it has taken us two decades of hard work, thousands of individual patients who were studied in detail, and the organization of effective working groups to crack the code.

Q: For modeling complex chronic diseases, you begin with a very simple model, ascertain the underlying principles of how the model works, and then, at some point in time, you can apply this model to other systems — interrelated systems — possibly rolling all the way up to the entire human body and its connected physiological processes?

A: In essence, that is correct.

Q: A shift to a new paradigm is not an easy or short process. What are the challenges you see and have experienced in developing your model of pancreatic disease and applying this to the thinking of any complex disease process?

A: The challenge is that you have to get physicians to switch to a new paradigm that has never been taught, and they have to learn to function in an entirely new way to make progress in the understanding of these diseases. Current systems are all built on the old paradigm, including the financial model, the diagnostic model, all the literature, all the pathology, all the laboratories, all the testing. Everything.

The other big problem is that the current system is not set up to connect all of the pieces efficiently or to involve the right people to interpret of the complex genetic information within the context of the clinical features and biomarkers. I am working on this problem as well.

Ultimately, I think it will come down to a financial crisis that will force a shift to this new paradigm. We're on a trajectory in this country and globally for unsustainable spending on health care that is expensive and less than effective. But once you have to have a new model in place that works and saves money, it will replace the old way of doing things. But the new model has to work. It is simply not good enough to just have an alternative way of doing things. It has to work better than the system it is replacing.

Q: How do you define personalized or precision medicine?

A: Personalized medicine is an alternate approach (to the germ theory) where physicians give the right medicine to the right patient in the right dose at the right time and always get a good result. This new approach is needed when a disease or syndrome is complex, when multiple etiologies lead to the same pathology with the same pathology leading to multiple outcomes, or when treatment effects are unpredictable, such as in CCDs. Precision medicine is needed for disorders that are functional in nature (i.e., no pathology) and for cancer. Precision medicine works because it focuses on underlying mechanisms, rather than only symptoms, but relies on modeling and simulation instead of epidemiologic inferences or RCT. It relies on progressive, mixed-disease models and not data-driven models from populations that were ascertained using clinicopathologic terms. Precision medicine includes analysis of multiple factors interacting within a single individual, and it can predict the best outcome in that individual based on a consideration of all the major variables.

Q: Can you elaborate on how your research has played a role in building this new model of how we should approach complex chronic diseases?

A: There was a beautiful paper in the *New England Journal of Medicine* in 1995 from Steer, Waxman, and Freedman, that I routinely quote. This publication was written in response to 100 years and untold millions of dollars of research. Their summary was that "chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment." And they were absolutely correct. My research for the last 25 years, and that of other like-minded clinical research colleagues around the globe, has been designed to upend that statement.

Twenty years ago, I began a study called the North American Pancreatitis Study II or NAPS2. The project was designed using a reverse engineering model to understand the complexity of pancreatic disease. We collected data from several thousand people and organized it to represent all of the puzzle pieces of pancreatic disease. Many questions were answered, one issue at a time, in a systematic way, until the full picture was eventually built. This approach has been the basis for revolutionizing pancreatic diseases, and it can be translated into other CCDs.

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Chronic Pancreatitis: A Model System for a New Paradigm in Medicine

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Consensus Statement Definition:

"Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress." In addition, "Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia. This definition recognizes the complex nature of CP, separates risk factors from disease activity markers and disease endpoints, and allows for a rational approach to early diagnosis, classification, and prognosis."

A big step forward in the area of pancreas medicine came with the updated definition of chronic pancreatitis to include precision medicine. Several of my international colleagues developed a consensus for a *mechanistic* definition of chronic pancreatitis to replace the old pathology-based definition from 1984. That work and the subsequent paper "Chronic Pancreatitis: An International Draft Consensus Mechanistic Definition on Chronic Pancreatitis" was published in the journal *Pancreatology* in 2016. This was a major accomplishment: getting a consensus definition essentially approved by all the major pancreas groups and thought leaders around the world.

In working through this definition over several years, we agreed that early on there is no disease, and, at the end, there is well-described end-stage disease with well-defined characteristics. The underlying process that linked the beginning of the disease with the end was missing. The new definition includes the essence of disease. It reflects abnormalities in the injury → inflammation → resolution → regeneration sequence originating in the duct or acinar cells, which only occur in susceptible people. This fits into the alternative to the germ theory of disease — namely the precision medicine model — without changing the name of the syndrome. This is very important for the field because the mechanistic definition tells you what the disease is and what it is not. Furthermore, diagnosis is not dependent on the end-stage features, so diagnosis and treatment can start immediately after the onset of symptoms.

In addition to this new mechanistic definition, we attempted to form a consensus on how to define early chronic pancreatitis. After three years of discussion with groups in Europe, North and South America, and Asia, we came to a consensus that it is impossible to diagnose early chronic pancreatitis using traditional approaches. Published in Spring 2018, this work tells us that we must switch to a different paradigm because the one we are using has failed to address the problem.

To improve communication and cooperation among leaders of the pancreas community, I host an international meeting in Pittsburgh each July called *PancreasFest. PancreasFest 2018* was another landmark meeting. Representatives from the NIH, FDA, industry, and pancreas colleagues from around the world assembled to discuss how to implement the principles of a new paradigm in pancreatic disease, preventing the development of a disease that cannot be cured and whose management is prohibitively expensive.

As a result of the work at *PancreasFest 2018,* three major new papers were developed to discuss consensus statements for the problems, opportunities, and approaches to acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis. We managed to form a consensus pathway that can be applied to pancreatic disease, and it was agreed upon by all the major players in government and industry. This was no small accomplishment, but it is still only a piece of the larger puzzle that must be worked out.

Q: What is on the horizon with your pancreas research?

A: At the last *PancreasFest,* we invited a number of key basic science researchers to attend the clinical sessions to hear the problems facing clinicians. The basic scientists are, of course, pursuing their research in a traditional way, and the animal models they are working with don't seem to help to devise medications to treat patients effectively. We still have no treatments for chronic pancreatitis and other chronic diseases, but we now can link the right animal model to the right subset of patients so that the models can be used to test the effectiveness (and potential side effects) of new treatments.

Another major advance realized at the last *PancreasFest* was the recognition that all of the stakeholders in pancreatic disease — the patients, physicians, researchers, NIH, FDA, pharmaceutical industry, the health care industry, and patient advocacy groups — must join forces to obtain results. Old partitions and divisions need to be demolished, and we must work together to solve this disease.

Further Reading

To learn more about Dr. Whitcomb's research efforts, please see the following links and references to published works that are discussed in this article.

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PancreasFest.Org

Pancreas.Org

Dom.Pitt.Edu/GI

Disclaimer: Professor Whitcomb is also co-founder and a consultant to Ariel Precision Medicine, a genomics and health technology company designed to move precision medicine into clinical practice. He has not been financially compensated but may have equity.

New Research to Understand Pancreatitis *Continued from Page 3*

who meet the study's inclusion criteria but who either refuse to be randomized (e.g., they want the procedure regardless) or whose physician does not want to them to undergo the ERCP procedure. The primary outcome measure for the study will be the time to the next attack of acute pancreatitis. A secondary outcome measure is the incidence of acute pancreatitis after the procedure (i.e., the number of attacks over time). Patient-reported outcomes, such as pain and narcotic use, hospitalizations, and quality of life, and whether chronic pancreatitis develops also will be examined. The study, which has been needed for 40 years, is now enrolling participants.

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2018 Sherman Prize Awarded to David Binion, MD

David Binion, MD, AGAF, FACG, is the recipient of a 2018 Sherman Prize for his analysis of "Big Data" to better understand inflammatory bowel disease (IBD) and to optimize treatment strategies for patients with Crohn's disease and ulcerative colitis. This $100,000 prize is awarded by The Bruce and Cynthia Sherman Charitable Foundation to advance IBD patient care. This is the second Sherman Prize for the UPMC IBD team. Eva Szigethy, MD, PhD, won the inaugural prize in 2016.

Dr. Binion is a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition. He is co-director of the IBD Center, director of the Division's Nutritional Support Service, and he leads IBD translational research efforts within the Division. Dr. Binion came to Pittsburgh in 2008, having been recruited by then division chief and current faculty member David C. Whitcomb, MD, PhD, to co-direct the IBD program. Dr. Binion has been a driving force in the transformation of the UPMC IBD Center into one of the leading programs in the United States during the last ten years.

Dr. Binion has extensive clinical experience with IBD, having personally cared for more than 2,000 patients with Crohn's disease and ulcerative colitis. Dr. Binion himself has suffered from Crohn's disease for nearly 40 years, an experience and journey that has shaped, informed, and focused his commitment to find cures for these diseases.

Dr. Binion's research efforts have been entirely focused on IBD from the time he was a medical school student. His work focused on defining the molecular and cellular mechanisms underlying human IBD, as well as identifying high risk groups of patients and developing improved treatment strategies. His research group helped to identify the devastating impact of the *Clostridium difficile* epidemic on patients with IBD.

As a young investigator, Dr. Binion was responsible for discovering how the microvasculature of the bowel is regulated and can be altered in chronic inflammation. His structured approach to IBD clinical care has allowed Dr. Binion to identify emerging clinical issues and subgroups of patients who have struggled with their disease. He has gained insight into the natural history of the disease in various patient subgroups, and he has published important findings regarding IBD and *Clostridium difficile,* autonomic dysfunction, chronic narcotic use, rapid abdominal re-operation, durability of biologic therapy, and permanent work disability. Since joining the Division, Dr. Binion also has collaborated extensively with the UPMC Small Bowel Transplant program, where 25 percent of the candidates have had severe IBD and short gut syndrome. Dr. Binion is leading local efforts with autologous stem cell reconstitution for severe and refractory Crohn's disease.

Dr. Binion has published more than 500 manuscripts and scientific abstracts centered on IBD, *Clostridium difficile,* and precision medicine. His laboratory has focused on the microvascular biology of the human intestine and big data analytics to define precision medicine in patients with IBD.

His research has been funded by the National Institutes of Health, the Crohn's and Colitis Foundation, and the U.S. Department of Defense. Dr. Binion also is a recipient of the Crohn's and Colitis Foundation's Premier Physician Award.

The Division expresses its congratulations to Dr. Binion on his 2018 Sherman Prize. This award is yet another mark of distinction in a career that has been devoted to improving the lives of IBD patients through groundbreaking research and compassionate clinical care.

UPMC Physician Resources

UPMCPhysicianResources.com is home to free CME courses, videos, news, and event listings for physicians. Below is a selection of current CME offerings in Gastroenterology, Hepatology and Nutrition. To learn more and explore additional content, visit **UPMCPhysicianResources.com/GI**.

Selected CME Course Offerings in Gastroenterology, Hepatology and Nutrition Include:

Frailty, Sarcopenia, and Liver Transplantation
Presented by Michael A. Dunn, MD

Management of Patients with Alcoholic Liver Disease
Presented by Ramon Bataller, MD, PhD

Live Donor Liver Transplant at UPMC: Changing the Paradigm
Presented by Abhinav Humar, MD

Psycho-Behavioral Approaches to GI Disease
Presented by Eva M. Szigethy, MD, PhD

Endoscopic Management of GI Bleeding
Presented by Adam Slivka, MD, PhD

ERCP Indications and Complications
Presented by Jennifer S. Chennat, MD

Nonalcoholic Steatohepatitis: Evaluation and Management
Presented by Jaideep Behari, MD, PhD

Diagnosis and Treatment of Esophageal Motility Disorders
Presented by David Levinthal, MD, PhD

Screening for GI Malignancy
Presented by Robert E. Schoen, MD, MPH

Inflammatory Bowel Disease: Evaluation and Management
Presented by Marc B. Schwartz, MD

Save the Date: PancreasFest 2019

The Division of Gastroenterology, Hepatology and Nutrition will again host the annual PancreasFest conference, **July 24–26, 2019**, in Pittsburgh, Pennsylvania. Please mark your calendar for this premier event, which brings together the world's foremost clinicians and researchers committed to learning and collaborating on translational studies of pancreatic diseases.

PancreasFest 2019 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 2019 will feature discussions on pancreatic cancer, pancreatic diabetes, and acute pancreatitis.

Course Directors

Randall Brand, MD
Walter Park, MD
Aliye Uc, MD
David Whitcomb, MD, PhD
Amer Zureikat, MD

Multicenter Investigator Meetings

- **CAPER** (**C**ollaborative **A**lliance for **P**ancreatic **E**ducation and **R**esearch)
- **INSPPIRE** (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis **I**n Search of a Cu**RE**)
- **APPRENTICE** (**A**cute **P**ancreatitis **P**atient **R**egistry to **E**xamine **N**ovel **T**herapies **I**n **C**linical **E**xperience)
- **PRIMO** (**P**rospective **R**esearch in **I**PMN **M**anagement and **O**utcomes)

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

Division News and Notes

Dr. Arteel Chairs AASLD Basic Science Forum

Gavin Arteel, PhD, co-chaired the Basic Science Symposium at The Liver Meeting, the national annual meeting of the American Association for the Study of Liver Diseases (AASLD) which was held November 9-13, 2018 in San Francisco, California. Dr. Arteel co-led "Matrix Biology and the Liver: Beyond Collagen and Fibrosis" with Rebecca Wells, MD, from the University of Pennsylvania. Dr. Arteel is a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition, where he also serves as the associate chief for basic science and is the pilot and feasibility core director for the Pittsburgh Liver Research Center.

Dr. Szigethy to Lead PCORI Grant

Eva Szigethy, MD, PhD, will be the principle investigator for a $6.3 million PCORI (Patient-Centered Outcomes Research Institute) grant, "Specialty Medical Homes to Improve Outcomes for Patients with Inflammatory bowel Disease (IBD) and Behaviroal Health Conditions". Dr. Szigethy submitted this grant in collaboration with the UPMC Center for High Value Health Care. Dr. Szigethy is a professor of Psychiatry, Medicine and Pediatrics, and is a faculty member with the Division of Gastroenterology, Hepatology and Nutrition, where she directs Total Care-IBD, the UPMC IBD medical home, and is the founder of the Division's Visceral Inflammation & Pain (VIP) Center. Dr. Szigethy also directs UPMC Behavioral Health through UPMC's Chief Medical and Scientific Office.

2019 Pittsburgh Gut Club

The Pittsburgh Gut Club is a gastroenterology education and networking series designed to bring novel and relevant subspecialty advancements to the greater Pittsburgh region. Gastroenterologists, physicians, and allied health professionals are encouraged to attend. All Gut Club dinner lectures will be held from 6 p.m. to 8:15 p.m. at the University Club, 123 University Place, Pittsburgh, Pennsylvania.

Sponsored by:
Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, UPMC Center for Continuing Education in the Health Sciences

Course Director:
Robert E. Schoen, MD, MPH
Professor of Medicine and Epidemiology
Chief, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine

Thursday — March 28, 2019

Endoscopic Treatments of Obesity

Reem Sharaiha, MD, MSc
Associate Professor of Medicine
Advanced Endoscopy and Metabolic Endoscopy
Weill Cornell Medicine
New York, New York

Thursday — May 2, 2019

The Changing Epidemiology of Liver Cancer

Fasiha Kanwal, MD, MSHS
Professor of Medicine
Chief, Gastroenterology and Hepatology
Baylor College of Medicine
Houston Veterans Affairs
HSR&D Center of Excellence
Michael E. DeBakey VA Medical Center
Houston, Texas

Monday — September 23, 2019

Are Newer Biologics Better Than Our Old Ones?

Maria T. Abreu, MD
Director, Crohn's & Colitis Center
Vice Chair of Research, Department of Medicine
Martin Kalser Chair in Gastroenterology
Professor of Medicine, Microbiology and Immunology
University of Miami, Miami, Florida

UPMC
LIFE CHANGING MEDICINE
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Pittsburgh, PA 15213-2582

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.**

UPMC PHYSICIAN RESOURCES

UPMC Division of Gastroenterology, Hepatology and Nutrition

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For consults and referrals, please call UPMC's 24-hour physician OnDemand service at **1-866-884-8579.**

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