

your DIGESTIVE HEALTH

DEAR FRIENDS,

It is my pleasure to once again invite you to another issue of *Your Digestive Health*. This publication is designed to inform our patients and their families about the exciting progress we're making in diagnosing, treating, and preventing a variety of digestive diseases and disorders.

As Chief of the University Division of Gastroenterology, Hepatology, and Nutrition, I am fortunate to work with dedicated physicians, scientists, and staff members. You are undoubtedly familiar with the care our physicians provide, but we also take tremendous pride in our teaching and research programs.

While we continue to build on our successes in these areas, federal funding for medical research overall is on the decline. I hope, after reading the enclosed articles detailing the recent advancements made in our department, you will consider making a contribution in support of our efforts. Your gift would provide funding for research, patient care, and education, and would help us recruit and retain the promising scientists and top clinicians who will shape the future of our field.

To learn how to make a gift, please contact Gary Dubin at 412-647-9113 or dgary@pmhsf.org. And, as always, please know that regardless of your ability or inclination to make a gift, your continued care remains our *first* priority.

In good health,



David C. Whitcomb, MD, PhD

*Giant Eagle Foundation Professor
of Cancer Genetics
Professor of Medicine, Cell Biology &
Physiology and Human Genetics
Chief, Division of Gastroenterology,
Hepatology and Nutrition*

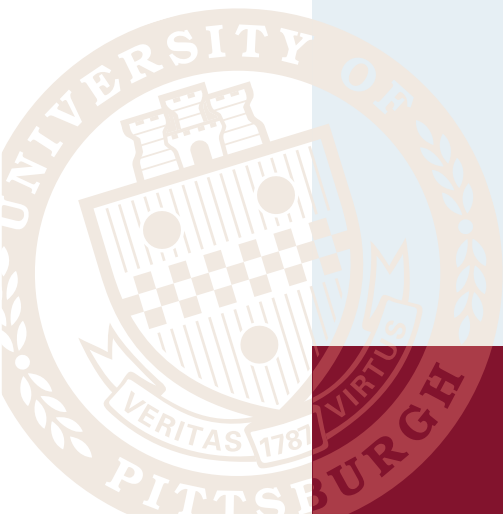
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David C. Whitcomb, MD, PhD
Executive Editor

Emily Martin
Managing Editor

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2008 ISSUE



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Promising New Blood Test Offers Potential For Early Colon Cancer Detection

Early detection and prevention of colon cancer have saved many individuals from the pain and suffering of one of life's most deadly diseases. However, the tests that either reveal or rule out cancer in the colon are no picnic.

As it stands now in the U.S., regularly scheduled colonoscopy, beginning at age 50, is among the most reliable ways to detect cancer or polyps, the precursor to cancer, within the large intestine. While colonoscopy is invasive and the preparation for it bothersome, polyps can be removed during colonoscopy, thereby significantly reducing the likelihood of pre-cancerous conditions moving on to full-fledged disease.

Colon cancer detection, however, has the potential to be completely revolutionized with the development of a

test that detects markers of colon cancer within the blood. "It has taken quite some time to reach this discovery," remarked Robert Schoen, MD, MPH, professor of medicine and epidemiology at the University of Pittsburgh School of Medicine and director of Colorectal and GI Cancer Prevention and Control Research for the University of Pittsburgh Cancer Institute. "About eight

years ago, I approached Robert Getzenberg, PhD, a researcher formerly with UPMC who is now the research director of the James Buchanan Brady Urological Institute and a professor of urology at the Johns Hopkins University School of Medicine. He had successfully developed tests for detecting bladder cancer, and I wanted to see if a similar type of test could be developed to identify the presence of colon cancer."

To support the investigation, Dr. Schoen and Dr. Getzenberg obtained funding from the National Institutes of Health (NIH) Early Detection Research Network (EDRN) to conduct preliminary investigation into the development of a blood test that could identify colon cancer. They had success in identifying markers that had the potential to be indicators of colon cancer and received additional funding to continue their research after five years of work. Interim data from the second round of funding were published in the June 2007 edition of *Cancer Research*.

"Our study involved more than 200 individuals," observed Dr. Schoen. "Some of the participants had colon cancer, some had polyps, some had normal results, some were people with insignificant polyps, and some were people with other types of cancer. We were looking at the levels of two specific proteins – CCSA3 and CCSA4 – in the blood samples taken from our participants. Within our sample group, the levels of both

proteins were significantly elevated in the blood taken from people with colon cancer. We also noted that the proteins were elevated, but less so, in people with advanced polyps. The proteins were not elevated in normal people or people with insignificant polyps, nor were they elevated in people with other types of cancer. Although these data are preliminary and are gathered from a relatively small, selected sample, we immediately recognized that this discovery could have huge ramifications."

Colonoscopy is still the definitive way to determine presence of cancer. However, a blood test could allow clinicians to better focus resources on those who really need colonoscopy. The test could help healthy individuals avoid needless colonoscopy that consistently produces negative results. Best of all, the blood test could become an easy-to-administer part of the normal physical at the doctor's office.

According to Dr. Schoen, "A blood test is profoundly less invasive than a colonoscopy and is an easy way to provide effective screening on a more universal basis. Currently we have screening participation rates of less than 50%. A blood test could go a long way toward improving that."

Still, there are many questions to be answered. More research needs to be done with larger screening populations to confirm the accuracy of the testing technique. Careful attention must be paid to identifying a cut-off level that correctly identifies those with disease, but which minimizes those with false positive tests. Beyond that, attention needs to be focused to how often the test should be performed.

We also need to determine if the readings produced by a tumor vary when a tumor is removed," said Dr. Schoen. At this point we don't know if the blood test can be used to monitor cancer treatment, or if it could be a harbinger to the return of cancer. From a biologic standpoint, we still need to figure out what the presence of proteins in the bloodstream means and see if this provides insight into how colon cancer advances."

Moving ahead, Dr. Schoen and Dr. Getzenberg will focus on fully characterizing the proteins and developing a more specific antibody for the sequence. Beyond that, the test will need to be evaluated in additional subjects and replicated across multiple centers.

"Every step of the way is a process of evaluation, and this won't happen overnight," summed up Dr. Schoen. "The research we have done so far has taken time, but it has enormous potential. If this blood test continues to produce promising results, it could result in a huge change in the way we approach detection of colon cancer."



NEW GENE DISCOVERIES DRIVE CUTTING EDGE RESEARCH

Crohn's Disease has challenged clinicians and patients for more than a century. Antoni Lesniowski, a surgeon from Warsaw, Poland, first noticed the condition in a few of his patients in 1904. The disease gained further prominence and its formal name in 1932 when Burrill Bernard Crohn, an American gastroenterologist, delved more deeply into the causes of a mysterious inflammatory condition that affected the small intestine, the large intestine, and the terminal ileum, the point where the small and large intestines meet.

A chronic immune-mediated disease, Crohn's Disease manifests itself in patients with debilitating gastrointestinal symptoms such as abdominal pain, diarrhea, and weight loss. Skin lesions, arthritis and eye inflammation can also show up as part of the disease. But the biggest questions that remained unanswered were why does this happen and what triggers the disease?

Now, thanks to the work of Miguel Regueiro, M.D., Associate Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Clinical Director of the Inflammatory Bowel Disease Program and Co-director of the Inflammatory Bowel Disease Center and Richard Duerr, M.D., Associate Professor of Medicine, Co-Director of the Inflammatory Bowel Disease Center and Director of the IBD Genetics Program, a new genetic link to Crohn's Disease – the *IL23R* gene – has been uncovered. Subsequently, *IL23R* has also been associated with other chronic

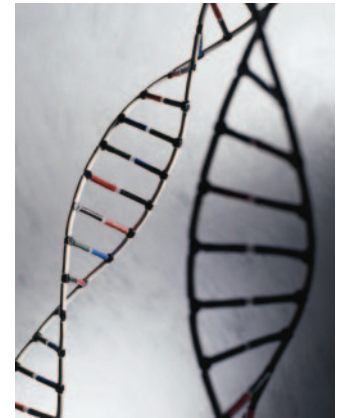
immune-mediated diseases including ulcerative colitis, psoriasis, and ankylosing spondylitis.

According to Dr. Duerr, "Research into the cause of Crohn's Disease has gone on for decades, but a new era of genetic research has really evolved within the last 15 years. Many of our preliminary investigations were based on knowledge gathered through the Human Genome Project, which was conducted in the 1990s. With the basic knowledge generated by these previous studies, we and other IBD genetics research groups focused on families with multiple members affected by IBD. We conducted genetic linkage studies to identify segments of the genome that are shared by affected relatives. Through those studies, we discovered several genetic linkages and were successful in identifying genetic risk factors in a few of the linkage regions. The chromosome 16, *IBD1* locus was identified in the mid 1990s as the first linkage region known to be connected to Crohn's Disease. Subsequently, in 2001, genetic risk factors for Crohn's were discovered in *NOD2*, a gene located within the *IBD1* linkage region. This was a major breakthrough, since it was the first gene that was definitively associated with Crohn's Disease."

The research, however, did not stop there. In 2003, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded Dr. Duerr's group and five other North American IBD genetics

research centers to work together as a consortium to unravel the complex genetics of IBD. After four years of DNA sample and data collection from patients and healthy controls, there was a large enough sample of study subjects to launch a genome-wide search for Crohn's Disease genes early in 2006. The new Crohn's Disease gene – *IL23R* – was discovered within six months, confirmed in additional groups of study subjects and then electronically published online in *Science Express* in October 2006, and published in *Science* magazine in December 2006. Dr. Duerr was the lead author and Dr. Regueiro played a leading role in recruiting and determining the disease characteristics or 'phenotypes' of patients included in this landmark study.

"The *IL23R* gene is strongly associated with Crohn's Disease," observed Dr. Regueiro. "Now that we know that, the questions are focused on what variations of the gene cause the disease and regulate the severity of symptoms. At this point, we don't yet know what the triggers for the disease are. We do know some people are genetically more susceptible than others, and those individuals may be at higher risk for an inflammatory immune response."



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FOCUSED RESEARCH UNLOCKS THE MYSTERIES OF PANCREATITIS

Pancreatitis is one of the most destructive and disabling afflictions an individual can face. Extremely difficult to treat, and often detectable only after considerable and irreparable damage has been done to the pancreas, the disease disrupts lives and careers, creates horrible pain that does not respond well to many therapies, and saps individuals of the energy needed to do even the most basic tasks. Until recently, it also came with a stigma – one that suggested that people suffering from this disease were drunkards or drug seekers, and that their lifestyles directly contributed to their conditions. This mindset, held by many old-school practitioners, added insult to injury while it denied suffering patients the care and pharmaceuticals they so desperately needed.

Fortunately, the mystery behind the disease, as well as the preconceived notions about its cause, are finally being firmly discredited by David C. Whitcomb, MD, PhD, Giant Eagle Foundation Professor of Cancer Genetics, Professor of Medicine, Cell Biology and Physiology and Human Genetics, and Chief, Division of Gastroenterology, Hepatology and Nutrition at UPMC. Within the past decade, he and his dedicated team of researchers and clinicians have made major advances to identify the genetic causes of pancreatitis.

“Pancreatic diseases are the most difficult to treat, and can result in the complete destruction of the organ. In 1996, colleagues from medicine

and pathology identified the first pancreatitis gene. Since then colleagues from the mathematics, epidemiology, cell biology, molecular biology and surgery areas here at UPMC and University of Pittsburgh partnered to successfully identify an additional gene mutation that causes pancreatitis,” commented Dr. Whitcomb. “This was a major step forward in understanding the disease. However, no two patients have the same DNA, and none with pancreatitis present their symptoms in exactly the same way. The course of the disease varies significantly from patient to patient, and some patients are in excruciating pain, while others show few symptoms at all. We needed more research to know why.”

Over the past decade, Dr. Whitcomb has worked closely with colleagues from around the country to collect DNA samples from people afflicted with pancreatic disease. With more than 2,500 samples gathered, he began work to determine what genetic factors and environmental triggers predisposed some patients to extreme levels of life-altering pain.

“There appear to be genes that are inherited in defective forms that prevent pain in some patients,” observed Dr. Whitcomb “As a result, a person can have pancreatic disease and never know it. Why this happens is unknown at this point, but it’s incredibly important to determine the cause. We want to find a

way to turn off the pain sensors in patients experiencing horrible pain, and ultimately give them their lives back. We have found a key gene that seems to be linked to the pain component of the disease, but now need to discover how it works, how it’s activated and how to control or prevent that activation response.”

Working through National Institutes of Health (NIH) grants, Dr. Whitcomb and his colleagues here in Pittsburgh began by looking at a dozen genes. “With each person there are 40,000 to 50,000 genes that code for proteins, have to be examined to see if they are linked to pancreatic disease. Furthermore, each gene has thousands of code letters in the DNA sequence that may contain one critical mutation,” he remarked. “While technology is continually improving, and it is now possible to look at thousands of genetic variants at one time, the investigations are extremely time consuming and

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but when you see your
granddaughter hurt or your child
hurt, that’s something else...*

require significant resources to support them. Once the lab work is done, you need to analyze the data. This, too, is time consuming and expensive. What this all boils down to is that you can only do as much research as your budget will allow at

any one time. This creates backlogs in the investigation process and keeps us from finding the answers we're seeking very quickly, which must seem like an eternity if you or your loved one has a pancreatic disease. With literally hundreds of genes to study, that translates into millions of dollars and many months, if not years, of work.

NIH funding is, however, only part of the fuel that powers Whitcomb's genetic investigations. Gifts from private individuals and corporate entities provide researchers with the resources they need to propel their investigations ahead. In addition, most private party gifts do not come with the restrictions that NIH grants typically do, and make financial resources available now, rather than three to four years from now as NIH grants typically do.

"Gifts from individuals provide opportunities for our researchers to follow the science and see where it leads," commented Adam Slivka, MD, PhD, Professor of Medicine and Associate Chief of Clinical Services for the Division. "If you're constrained by funding and tight project restrictions, you really can't get all the benefits out of your research."

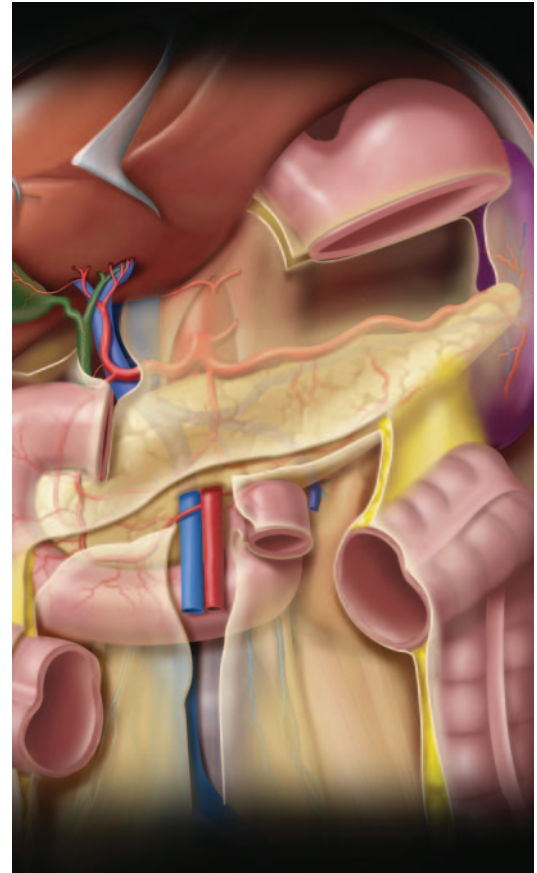
One of Dr. Slivka's patients, Vickie Hall, saw the potential in Dr. Whitcomb's research. In an effort to accelerate investigations into the cause of pancreatitis, and to hopefully prevent others from experiencing its extraordinary pain, she made a sizable contribution to support ongoing research at UPMC.

"It's one thing for you to hurt, but when you see your granddaughter hurt or your child hurting, that's something else," says Mrs. Hall, who has 15 family members – including herself, her youngest daughter, and her granddaughter – who have the disease with varying degrees of severity. Other family members have the gene but are asymptomatic.

Mrs. Hall and her husband, Bob, pledged \$25,000 to support hereditary pancreatitis research in Dr. Whitcomb's laboratory. She first met him in February 2005, when her granddaughter was brought to Pittsburgh to see Dr. Slivka. He introduced the Halls to Dr. Whitcomb, and the connection was forged.

According to Dr. Slivka, "Families that have faced this disease seem to have a better understanding of the situation. Having pancreatitis can be a miserable existence, as it takes away your vitality and freedom. It truly is a life altering disease. But now, research is helping us to figure out what's going on with these patients and how to care for them. I truly believe that real breakthroughs are not far out of reach. We've learned more in the last 10 years that we did in the previous 25 years. In medicine, that really says something."

That knowledge gained in the lab is also helping to change the negative perceptions about pancreatitis that were harbored by many practitioners. "At national meetings, five years ago it was nearly impossible to introduce new concepts," observed Dr. Slivka. "Now that's changing – there's a new guard coming in and they clearly see that this condition is genetically based and not the result of substance abuse. There is still a long way to go. We are seeing some translation of research into diagnostic techniques, but we haven't perfected



This illustration is printed with generous permission from Amirsys, Inc. Copyright © 2007 Amirsys, Inc.

any treatments yet. We're extremely close, but we still haven't arrived at the right answers. When we do, I think you'll see a whole new class of therapies and treatment protocols."

From Dr. Whitcomb's point of view, "It will take a couple million dollars to complete the mapping phase and to start focusing in on some answers. In fact, we are poised to do the entire project in eight months with about \$2 million. Once that phase is complete, we can then start work with the pharmaceutical companies to develop approaches that address individual genetic variations. When we reach that point, we truly will have accomplished something outstanding."

FACULTY NEWS

Randall E. Brand, MD, visiting professor of medicine, is a new gastroenterologist in our division specializing in pancreatic cancer and pancreatic diseases. He is interested in the early detection of GI malignancies including pancreatic cancer and cares for families with a strong history of pancreatic cancer. He has just been awarded a grant through the Early Detection Research Network to lead a multi-center effort of creating a



national reference set of blood specimens to be used as a resource for the development of biomarkers for the early detection of pancreatic adenocarcinoma. For more information about Dr. Brand or patient services in the Shadyside section of Pittsburgh, please call 412-623-3105.

James B. McGee, MD, associate professor of medicine, has been named the founding editor of the American Gastroenterological Association's (AGA) Online Education Program. As one of the premier gastroenterology associations in



the world, the AGA offers outstanding opportunities for global education through novel online initiatives. Dr. McGee will lead reviews concerning accredited education programs, physician recertification and related online projects. Online resources will be offered for both clinical physicians and research scientists.

In addition to his gastroenterology appointment, Dr. McGee serves as the assistant dean of Medical Education Technology and directs the Laboratory for Educational Technology for the University of Pittsburgh School of Medicine. Dr. McGee may be contacted at mcgee@medschool.pitt.edu.

Stephen O'Keefe MD, MSc has been awarded a major National Institutes of Health (NIH) grant entitled *Feeding and Pancreatic Rest in Acute Pancreatitis*. Dr. O'Keefe serves as a professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition, and his practice specializes in nutrition



support gastroenterology. This five-year NIH award involves a multi-center clinical trial comparing the effects of nasogastric versus distal jejunal feeding with pancreatic rest in patients with severe acute pancreatitis. This study will be coordinated by the University of Pittsburgh (Dr. O'Keefe as principal investigator) and will collaborate with seven other major academic gastroenterology programs in the U.S.

Kevin M. McGrath, MD, associate professor of medicine and director of the GI Laboratory and Endoscopic Ultrasound (EUS) Program, is expanding care for Barrett's Esophagus patients.



Barrett's Esophagus is a pre-malignant condition and is the main risk factor for esophageal cancer. Until now, acid suppression and surveillance have been the mainstay treatments for control of GERD (heartburn), which is the cause of Barrett's Esophagus.

Dr. McGrath and his endoscopic procedure team are now offering a new FDA-approved Barrett's Esophagus therapy, commercially known as the HALO ablation system. This system enables Dr. McGrath to more effectively treat problem areas in the esophagus through radio frequencies. The UPMC Digestive Disorders Center has used this new treatment since April 2007. The therapy is outpatient and is well tolerated, with minimal to no chest discomfort afterward. Referring physicians may call 412-648-9325 for patient treatment consideration.

WELCOME

The Division of Gastroenterology, Hepatology and Nutrition is pleased to welcome the following gastroenterologists to the Division of Gastroenterology, Hepatology and Nutrition:

David Binion, MD (as of 7/08) – inflammatory bowel disease subspecialty

Randall E. Brand, MD – pancreas and pancreatic cancer subspecialty

Michael A. Dunn, MD – general gastroenterology

Kenneth E. Fasarella, MD – esophagus and pancreas subspecialty

Andres Gelrud, MD, MMSc (as of 7/08) – pancreas subspecialty

Ian M. McGowan, MD, PhD – HIV/AIDS research & general gastroenterology

Ernest L. Sutton, MD, MPH – general gastroenterology

To learn about these physicians' clinical and research priorities, visit the Division's website, <http://www.dom.pitt.edu/gi>.

Ongoing genetic research, coupled with the discovery of the *IL23R* gene, is also changing the clinical perception of how inflammatory bowel disease progresses. "It's likely that inflammatory bowel disease represents a syndrome comprised of different disorders, all of which have unique mechanisms that result in similar phenotypes or clinically recognized conditions," commented Dr. Duerr. "It's likely that different groups of genes interact with various environmental triggers to produce inflammatory cascades resulting in chronic intestinal inflammation. The genes and the environmental triggers, as well as the severity and speed of the inflammatory cascades, can vary from person to person. In the end, however, the observable results of these events may not differ all that much from one inflammatory bowel disease patient to another."

To confirm these theories, significant work still needs to be done. According to Dr. Regueiro, most IBD genes should be identified within the next 5 to 10 years, which will lead to earlier and better diagnosis and stratification of patients. In the next 10 to 15 years, better treatments should be developed that will result in more effective inflammation control, less surgery and a better overall quality of life.

"Right now, we need to really understand what the *IL23R* gene means and how it works," remarked Dr. Regueiro.

Dr. Duerr concurred on the need for more research. "Currently, we don't know if the identified disease-associated genetic variants are the causative ones or just genetic markers for nearby causative variants. Because adjacent, closely linked genetic variants travel together as they are transmitted from generation to generation in the general population, more work needs to be done to determine which of the nearby, closely-linked, disease-associated genetic variants are the causative ones. To do that, we need to sequence the associated

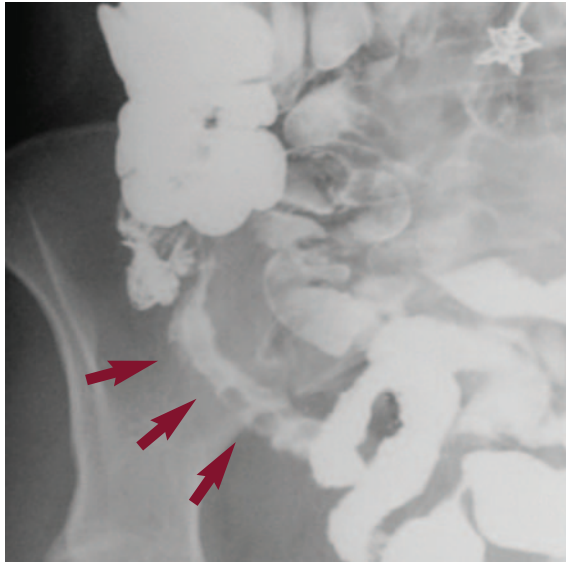
genes in affected individuals and healthy people from different populations to identify the full spectrum of genetic variants, compare the frequencies of these genetic variants in large numbers of disease-affected individuals and healthy controls, and determine which of the disease-associated genetic variants cause relevant alterations in biologic function. We will also need to determine functional links between the genetic variants and the environmental triggers."

It is also likely that the research will spur the development of an entirely new category of pharmaceuticals. "Biologics are clearly the wave of the future," commented Dr. Duerr. "Ultimately, we want to develop therapies that target specific immune pathways and address an individual patient's particular situation."

Dr. Regueiro agreed, "We want to get to the point where we can take a blood test, identify the problem and then prescribe the biologic medication that is best targeted to address the issues. We are not there yet, and the development

costs for pharmaceuticals are extremely high, but the future definitely looks promising."

In recent months, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) IBD Genetics Consortium, the Wellcome Trust Case Control Consortium, and a consortium of Belgian and French investigators have combined data and identified 74 distinct genetic loci that show strong evidence of association with Crohn's disease. More than 30 of these loci have been confirmed in subsequent replication studies. The international Crohn's disease genome-wide association study meta-analysis was highlighted as an abstract presentation in the plenary session of the American Society of Human Genetics annual meeting in San Diego in October 2007, underscoring the degree to which our understanding of the genetic architecture of Crohn's disease has and will continue to improve as research continues.



Barium study of a 19-year-old girl with Crohn's disease shows a nodular, inflamed segment of distal small intestine in the lower abdomen.

Dr. Chopra Wins PA State Hepatology Excellence Award

Kapil B. Chopra, MD, associate professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition's Center for Liver Diseases, has received the Commonwealth of Pennsylvania's 2007 Viral Hepatitis Award of Excellence for being an



excellent patient and physician advocate. This award is given annually to physicians showing outstanding clinical service. Dr. Chopra received this award through recommendations from his peers, patients and community health providers.

Dr. Chopra received the award at the 2007 Pennsylvania Viral Hepatitis Conference on October 19 of last year. At this conference, Dr. Chopra presented an educational talk entitled, *Managing Hepatitis C Treatment Failures and Defaulters*.

For more information about Dr. Chopra or the Center for Liver Diseases, call (412) 647-1170.

ATTENTION GOLFERS:

You can support the Division of Gastroenterology, Hepatology and Nutrition, and specifically the pancreas research of Dr. David Whitcomb, and enjoy your avocation at the same time by taking part in a golf outing organized by the Wayne Fusaro Pancreatic Cancer Research Fund. To date, the Fusaro Fund has raised more than \$144,000 in support of Dr. Whitcomb's research. This year's outing will

be held on **Monday, July 7, 2008** at South Hills Country Club, and we hope to see you there.

To reserve your golf spots or for information on sponsorship opportunities, please contact Gary Dubin at **412-647-9113** or Jill Fusaro at **412-828-7856**. Individuals, businesses and organizations are all welcome to participate.



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Digestive Health Network

Division of Gastroenterology, Hepatology and Nutrition

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