JOHNS HOPKINS
InsideTract

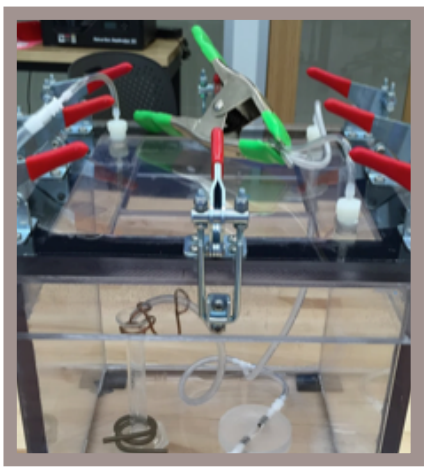
NEWS FROM THE JOHNS HOPKINS
DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY

WINTER 2015

JOHNS HOPKINS
MEDICINE

Pumped!

Ashish Nimgaonkar's mechanical pump has promise for patients with ascites.



Ashish Nimgaonkar's mechanical pump uses patient movement to move fluid out of the peritoneal cavity. Early prototypes demonstrated what Nimgaonkar calls "simple fluid dynamics."

Ascites—the buildup of fluid in the abdomen—may be a result of decreased liver function from cirrhosis of the liver that afflicts people as they wait for liver transplants. Water leaks out of blood vessels and into the peritoneal cavity with nowhere to go and no way to move.

"Until the patient gets a liver transplant, the only way to alleviate that fluid buildup and the pressure that it causes has been to drain the fluid manually every one or two weeks," says **Ashish Nimgaonkar**. "That's an expensive procedure, and the fluid buildup significantly impairs the quality of life for the patient."

Tapping several liters of fluid, says Nimgaonkar, also requires an infusion of albumin to help maintain cardiovascular and kidney function. "Albumin is made from human plasma, and it can be quite expensive. For every liter of fluid we pull from a patient, we infuse up to 8 grams of albumin."

But Nimgaonkar and his lab team have designed a mechanical pump that can move the fluid out of the cavity and into the bladder or stomach, where patients can eliminate it naturally themselves.

A PURELY MECHANICAL PUMP MADE OF SILICONE THAT USES THE PATIENT'S BODY MOVEMENT TO PUMP FLUID OUT OF THE PERITONEAL CAVITY

Nimgaonkar says a simple drain wouldn't work; there was nothing to propel the fluid from the cavity through the drain.

He designed an electrical pump, but the metal interfered with MRI. "People who are awaiting liver transplants have to get a lot of MRI scans done. Thus, a pump with metal in it wouldn't do."

Instead, Nimgaonkar designed a purely mechanical pump made of silicone and other MRI-compatible materials that uses the patient's natural body movement to pump fluid out of the peritoneal cavity. For people with ascites, the pump will be a life-changer.

"It's a biopowered shunt," says Nimgaonkar, who is testing the pump in animal models. "Body movement creates a pressure differential between the cavity with the fluid in it and the bladder or stomach. The pump senses the difference in pressure and drives the fluid from one chamber to the other."

Nimgaonkar, who has biomedical engineering degrees from Stanford, MIT and the Indian Institute of Technology, as well as faculty appointments at the Johns Hopkins Center for Bioengineering Innovation and Design and at the Carey School of Business, says that each patient visit to have fluid drained costs between $2,000 and $3,000. "We estimate that this will save the U.S. health system more than a billion dollars a year."

For his work with the pump, late last year Nimgaonkar received the inaugural Career Development Technology and Innovation Award from the American Gastroenterological Association and Boston Scientific. The pump continues to move closer to clinical trials, which Nimgaonkar expects within a few years.

He stresses that, more important than dollar savings, the pump offers patients a far better quality of life as they await liver transplant.

"Best of all, these patients don't have to get so sick." ■

Tony Kalloo

Patients Are the Mission

The breakthroughs in this issue of *Inside Tract* are all aimed in the direction of advancing patient care.

Inflammatory bowel disease is the topic of three of these stories.

Stephen Meltzer and his laboratory team are looking at a gene sequence that copies itself and jumps all around the genome. Meltzer's work is providing clues that this sequence could be associated with the early stages of cancer.

Steven Brant and two colleagues at other academic medical centers have published an article on the first-ever research on African-Americans and inflammatory bowel disease. The article offers us a first look at the origins of IBD in a population where its incidence is on the rise.

Alyssa Parian's research centers on a relatively new pathological finding. Serrated epithelial changes that we see in biopsies and through the endoscope are looking increasingly like new cancer markers. Parian and her colleagues will continue exploring this new pathology, but we're already using the finding as an early marker.

And finally, Ashish Nimgaonkar has designed a mechanical pump to help patients clear the fluid that can build up in the abdomen when their livers are failing. As they await transplant, the patients will be spared numerous hospital visits to drain the fluid.

As always, we welcome your thoughts, and we invite you to call on us if we can contribute to your practice.

African-Americans and IBD

A first-ever close look.

Inflammatory bowel disease is becoming more common in African-Americans. Steven Brant led a first-ever 10-year study of the genetics of IBD in African-Americans.

Researchers at the Johns Hopkins University School of Medicine this month published in the journal *Gastroenterology* the first major, in-depth analysis of genetic risk factors of inflammatory bowel disease in African-Americans.

The NIH-funded study is an intensive evaluation of the genetics of inflammatory bowel disease (IBD) in the African-American population.

Crohn's disease and ulcerative colitis affect as many as 1.6 million Americans. Patients with IBD have immune systems that attack their own intestines, resulting in inflammation. Recent years have seen a steady increase in reported cases of IBD in African-Americans.

"This study is the culmination of over a decade of work," says **Steven Brant**, director of the Johns Hopkins Meyerhoff Inflammatory Bowel Disease Center and corresponding author of the study. "We hope it's the first of many steps to better understand and treat these debilitating diseases."

IBD genetics have been evaluated in more than 1,000 studies in white and Asian—primarily East Asian—populations. Although the risk is slightly lower than that of white Americans, African-Americans are at significant risk for IBD.

> "THIS STUDY IS THE CULMINATION OF OVER A DECADE OF WORK. WE HOPE IT'S THE FIRST OF MANY STEPS TO BETTER UNDERSTAND AND TREAT THESE DEBILITATING DISEASES." **STEVEN BRANT**

The study evaluated more than 1,500 African-American patients with IBD—including 1,088 with Crohn's disease and 361 with ulcerative colitis—from 35 IBD centers across North America and used 1,797 African-Americans without IBD for comparison.

The primary goal of the study was to determine whether African-Americans share the same 163 separate genetic variations shown in white Americans as IBD genetic risk factors. A secondary goal was to identify novel regions of the genome, known as loci, causing IBD risk in African-Americans.

The researchers also examined if, within the majority of these IBD genetic loci, there are genetic variations that are of particular risk for causing IBD in African-Americans that are distinct from those identified in whites.

"We also studied whether there are regions of the genome that cause or protect IBD risk in African-Americans that arise from either their West African or European genetic ancestries," Brant says.

The study revealed that in African-Americans, as in whites and Asians, the dominant region for ulcerative colitis genetic risk in is the human leukocyte antigen (HLA) region, a region that is a major determinant of immune regulation and risks for other immune diseases, like celiac disease and type 1 diabetes. However, the specific variant associated with African-Americans in this region is the same as the variant most highly associated with Japanese and Korean

The Study: By the Numbers

1,500 African-American patients from **35** IBD centers across North America

The primary goal: to determine whether African-Americans share the same 163 genetic variations shown in white Americans as IBD genetic risk factors.

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ESOPHAGEAL CANCER

Trouble on LINE-1

There's growing evidence that jumping genes may contribute to esophageal cancer.

It sounds like the plot of a cyber thriller: Programming code copies and then wedges itself into other parts of the program.

But it's not a movie, and we're talking about genetic code, not computer code.

The retrotransposon long interspersed element-1, or LINE-1, is a chunk of code from the human genome that researchers believe has been copying itself and jumping around the human genome for hundreds of thousands of years. LINE-1, while not part of the human genome referencing sequence, is very common. It can be harmless, or it can cause mutations. And as Johns Hopkins researcher **Stephen Meltzer** and his collaborator, **Haig Kazazian**, have found, the jumping process occurs in cancer and precancerous parts of the body.

Meltzer and Kazazian discovered that the LINE-1 sequence occurs quite frequently in the premalignant tissue known as Barrett's esophagus.

"Retransposition happens very early, even in normal esophageal tissue," Meltzer explains. "It appears to occur pretty much at random. Then, some of these events become amplified in Barrett's esophagus."

Meltzer cautions against assigning cause-and-effect status to LINE-1, though.

"We don't know if they cause, or are merely passengers in, malignant progression," he states. "We haven't yet proven that they're carcinogenic."

He does believe, though, that LINE-1 is an early marker for premalignancy and cancer in the esophagus.

"Where there's a genetically unstable environment, like the one created by acid reflux, it's easier for these genes to jump," says Meltzer. "The damage and inflammation induced by acid are associated with LINE-1 retrotransposition. So, in a sense, this jumping is itself a good biomarker for a bad environment."

Meltzer suspects that this new biomarker might help detect the danger of cancer sooner than does the current histologic marker, Barrett's esophagus.

"We knew that many types of molecular abnormalities could occur, but this is a new kind of alteration we didn't know could happen occur in Barrett's due to GERD," Meltzer explains. "So, this represents a new potential mechanism. Whether it causes cancer is open to question. But we do know it occurs during the carcinogenic process and shows promise as an early detection biomarker." ■

Stephen Meltzer says LINE-1 is an early marker for premalignancy and cancer in the esophagus.

RESEARCH

Pathology Clue Could Be a Link **Between IBD and Cancer**

Alyssa Parian looks at serrated epithelial change.

Trying to determine the link between a particular pathology finding and colorectal cancer in patients with inflammatory bowel disease (IBD), **Alyssa Parian** and several Johns Hopkins colleagues performed a retrospective observation study.

Patients with the IBDs of chronic ulcerative colitis or Crohn's disease are at increased risk of colorectal cancer. Parian says that, like all cancers, the best treatment is early detection—or even before cancer develops.

"That's why we monitor our IBD patients as closely as we do with colonoscopies every one to two years," says Parian. "When we take biopsies we'd like there to be a specific marker to determine which patients will develop colon cancer and what we should do."

Since it was consistently recognized in 2000 by the Johns Hopkins pathology department, researchers have suspected the pathology finding of serrated epithelial change (SEC) could be a harbinger of dysplasia. But the link has been difficult to prove.

Parian's retrospective study looked at 187 Johns Hopkins Hospital patients whose IBD diagnoses were at least 15 years old.

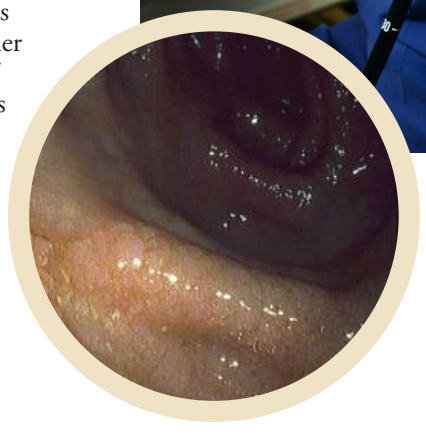
"The results suggest that there may be an association between SEC and dysplasia in IBD patients," Parian says. "In our study, patients with recurrent findings of SEC on biopsies were more likely to develop dysplasia."

She adds that patients with IBD with poorly controlled chronic inflammation, longer duration of disease and a concomitant diagnosis of primary sclerosing cholangitis were more likely to develop dysplasia.

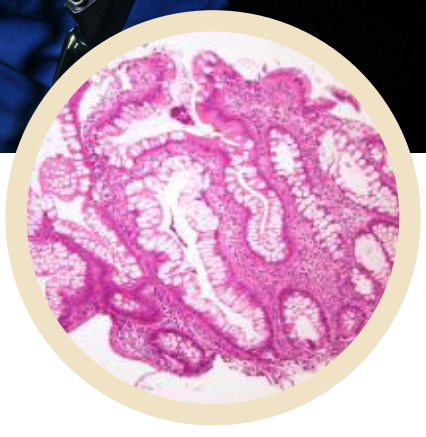
Parian believes the Johns Hopkins study is the largest study yet to look at SEC and the risk of dysplasia in those with IBD.

Still, she says, the topic needs more research. "The association between SEC and dysplasia remains just that; no path of causality has been delineated." She is involved in further controlled studies comparing the rates of dysplasia in patients with IBD with SECs and those with IBD without SECs.

Parian also notes some evidence of a unique genetic pathway for serrated lesions in IBD. "I think that's where we'll find some more definitive answers to this question." ■



Endoscopic picture of serrated epithelial change



Histologic picture of serrated epithelial change

African-Americans and IBD

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ulcerative colitis, and to a lesser degree ulcerative colitis in Europeans. It also is the same major risk variant in HLA for lupus in African-Americans, whose lupus risk is four times greater than white Americans.

The study did not find evidence for the major risk variant for European ulcerative colitis as having a role in the African-American population.

Identifying specific regions of the African-American genome that arise separately from the ancestral West African versus the ancestral European genome that are responsible for a portion of the genetic risk of IBD in the African-American population, the researchers found evidence for regions on four of the 22 autosomal (nonsex-linked) chromosomes as causative for IBD. For each of these regions, the IBD risk appears to come from the Caucasian ancestral genome that makes up 20 percent of the African-American genome overall.

In addition to Brant, the study was co-led by researchers at Emory University and Cedars-Sinai in Los Angeles. ■

ICD-10 Is Here

Please make sure to include ICD-10 codes when referring your patients to Johns Hopkins Medicine.

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Inside Tract is one of many ways the Johns Hopkins Division of Gastroenterology and Hepatology seeks to recognize and enhance its partnership with its thousands of referring physicians. Comments, questions and thoughts on topics you would like to see covered in upcoming issues are always welcome.

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JOHNS HOPKINS MEDICINE

NEWS FROM THE JOHNS HOPKINS DEPARTMENT OF GASTROENTEROLOGY AND HEPATOLOGY

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