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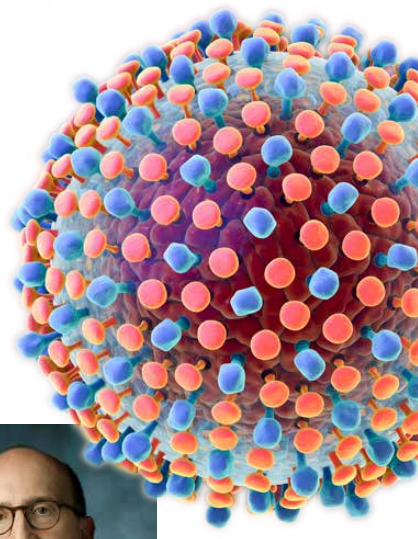
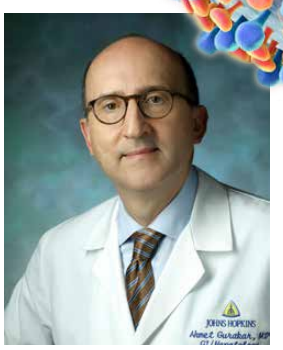
InsideTract

NEWS FROM THE JOHNS HOPKINS
DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY

WINTER 2019

JOHNS HOPKINS MEDICINE





Johns Hopkins Among First to Transplant HCV-Positive Livers Into HCV-Negative Patients

The intersection of a tragic epidemic and a new antiviral therapy has led to an important, if not entirely joyous, moment at Johns Hopkins.

As opioid overdose deaths continue to soar across the nation, many victims of the epidemic are sources of lifesaving organs for patients in need of transplantation. And with the advent of a drug that clears the hepatitis C virus from patients' systems, Johns Hopkins liver specialists and surgeons—already among the nation's leaders in transplant medicine—are helping even more patients who need donor livers.

"It's becoming more common that we transplant a liver from a donor who was hepatitis C positive into a recipient who is negative for the virus," says Johns Hopkins hepatologist Ahmet Gurakar. "The toll of the overdose crisis is tragic. But it would be doubly tragic if these otherwise healthy organs went unused."

Gurakar and colleagues in hepatology, transplant surgery and infectious disease early in 2018 published a study in the journal Liver Transplantation illustrating a successful HCV-to-nonHCV transplantation, followed by antiviral regimens.

The authors describe a 2015 case of a 57-year-old woman who had spent three years on the wait list for a cadaveric liver transplant. The woman's health was in sharp decline as her liver function decreased. Meanwhile, an 18-year-old man infected with the hepatitis C virus died of an intravenous heroin overdose. The transplant team explained to the woman that a donor liver had become available, making it clear that the donor had the virus and that, following the transplant, she would need to undergo weeks of antiviral therapy.

The transplant was successful and the antiviral treatment began 25 days after the surgery. Eight weeks later, the virus was undetectable in her system and her liver function was excellent.

Given the nature of the virus's transmission, it is common for intravenous drug users to be infected with hepatitis C. Now, with the availability of an antiviral medication that removes hepatitis from the system within a few months, Gurakar believes the potential exists for an expanded donor pool.

"Unfortunately, we're deep in the midst of an opioid crisis that is costing many young people their lives," he says. "Very often, despite an infection with the hepatitis C virus, these people had healthy, functioning livers."

Gurakar estimates that, as often as twice a month, he and his colleagues see donors who died of overdoses.

"It's very sad," he says. "Ideally, we would be able to get to these people sooner, whether with the drug that reverses overdose or, even better, by treating their addictions."

He adds that, as is the case with all organ donors, he admires the generosity of the donor families.

"The credit goes to those families," says Gurakar, "who are courageous enough to come forward and to donate on behalf of their loved ones. It's very humbling to consider."

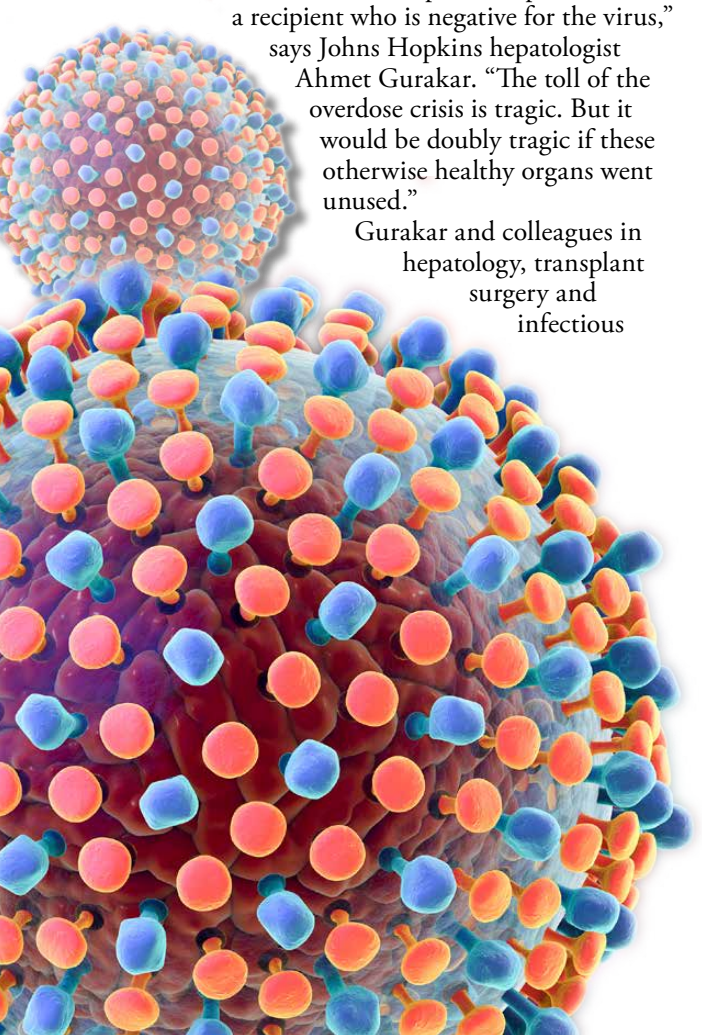
> "UNFORTUNATELY, WE'RE DEEP IN THE MIDST OF AN OPIOID CRISIS THAT IS COSTING MANY YOUNG PEOPLE THEIR LIVES. VERY OFTEN, DESPITE AN INFECTION WITH THE HEPATITIS C VIRUS, THESE PEOPLE HAD HEALTHY, FUNCTIONING LIVERS."
> — AHMET GURAKAR

The issue of transplanting livers infected with the hepatitis C virus is not without its complexities, says Gurakar.

"Obviously, outcomes data is limited," he says. "These are cases where patients are in end-stage liver disease and we need to get them the transplant to keep them alive."

Gurakar and his coauthors waited nearly three years to publish the case, keeping a close eye on the patient's progress and recovery.

"She's well," he says. "We've got good antiviral regimens now. These medicines changed the whole equation in the field of hepatology and liver transplantation." ■



Ahmet Gurakar and colleagues in hepatology, transplant surgery and infectious disease early in 2018 published a study in the journal *Liver Transplantation* showing a successful HCV-to-nonHCV transplantation, followed by antiviral regimens. Images shows 3D renderings of hepatitis C virus.

DIRECTOR'S COLUMN

Better Together: Collaboration at Johns Hopkins

Collaboration is the bedrock of so many parts of life at Johns Hopkins. Working with world-class experts on both research and clinical care is one of the things that I find constantly energizing at our institution. This edition of *Inside Tract* provides a few rich examples of the collaborative spirit that drives excellence in science, medicine and patient care at Johns Hopkins.

Ahmet Gurakar, for example, collaborates with transplant surgeons to give patients with end-stage liver disease another chance at life. As the opioid and heroin epidemic claims more and more lives in the US, some of those overdose victims carry the hepatitis C virus, but have otherwise healthy organs.

Gurakar discusses the transplantation of livers from donors who were positive for the hepatitis-C virus into recipients who do not have the disease.

When medical science engineers therapeutic genes to combat monogenetic diseases like hemophilia and cystic fibrosis, we've won only half the battle. The next challenge is the delivery of those genes to patients' systems so that they can replicate and replace faulty genes.

Florin Selaru and Vivek Kumbhari are collaborating on ways to deliver gene therapy endoscopically via the bile ducts. This promising new delivery method has enormous potential for the entire field of customized medicine.

Finally, we have two stories of innovation from colleagues at the forefront of therapeutic endoscopy.

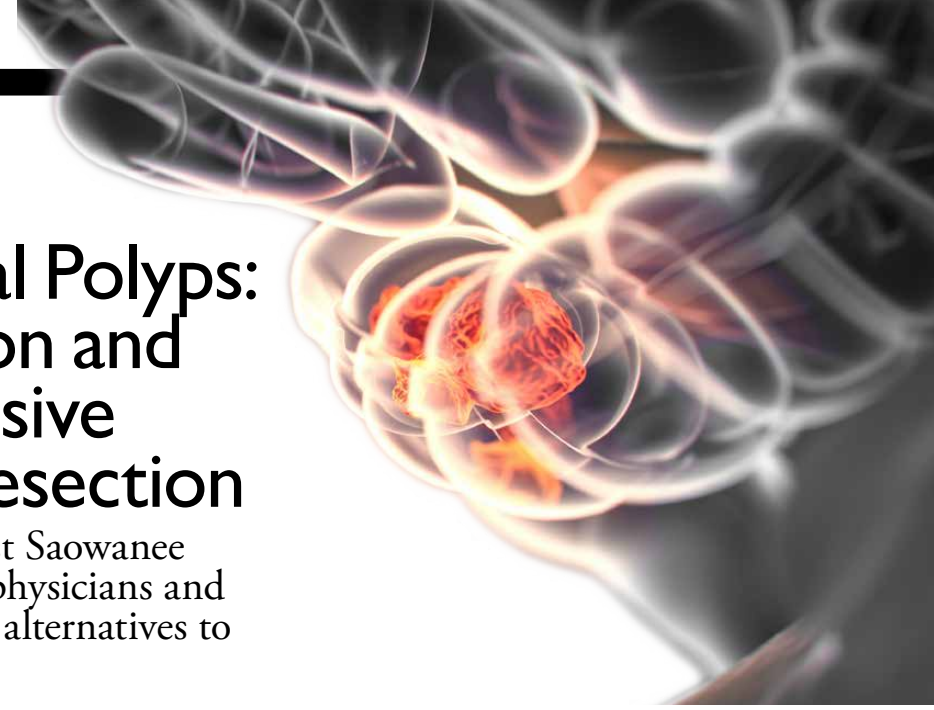
Mouen Khashab and his peers are training on the first FDA-approved flexible robotic endoscope, which is expected at Johns Hopkins in early 2019. For months, the team has worked to learn to use the new robotic scope which, Khashab says, will be an important weapon in Johns Hopkins' fight against colon cancer.

And endoscopist Saowanee Ngamruengphong collaborates with surgeon Sandy Fang on a minimally invasive approach to some of the most-difficult-to-resect rectal cancers. Her specialized training allows her to remove parts of lesions and tumors that sit in close proximity to vital organs, just millimeters at a time.

"My job is to dissect the lesion a tiny bit at a time, never going outside the GI tract," says Ngamruengphong. "When we have difficult cases, we work with our colleagues to come up with what's best for the patient. At Hopkins, our surgeons and our pathologists and oncologists – we all work together."

Tony Kalloo, Director
Division of Gastroenterology and Hepatology
Johns Hopkins University School of Medicine

CLINICAL INNOVATION



For Colorectal Polyps: Early Detection and Minimally Invasive Endoscopic Resection

Johns Hopkins endoscopist Saowanee Ngamruengphong wants physicians and patients to know there are alternatives to radical GI surgery.

Ngamruengphong teams with colorectal surgeon Sandy Fang to take a minimally invasive approach to some of the most difficult-to-resect rectal cancers. Ngamruengphong's training allows her to use an endoscope to remove parts of lesions and tumors that abut vital organs, a millimeter at a time. Image shows 3D representation of colorectal cancer.

Saowanee Ngamruengphong is on a mission to reduce the number of surgeries performed on patients who could benefit from less invasive procedures. "So many times, there are alternatives to things like proctectomy," says the Johns Hopkins gastroenterologist. "If the patient needs it, that's one thing. But let's see if there might be another approach."

Ngamruengphong teams with colorectal surgeon Sandy Fang to take a minimally invasive approach to some of the most difficult-to-resect rectal cancers. Her endoscopic submucosal dissection [ESD] training, undergone at Tokyo's National Cancer Center, allows her to use an endoscope to remove parts of lesions and tumors in the GI lumen, a millimeter at a time.

"So many patients in the United States with this large colorectal lesion undergo surgery, since that's what is recommended to them," says Ngamruengphong. "Even if it's successful, some of them have the whole rectum removed and have to live with an ostomy bag for the rest of their lives."

She notes a recent case of a woman with a large lesion on the anterior wall of the rectum. Ngamruengphong and Fang collaborated to remove the lesion while avoiding cutting through the wall and encroaching into the patient's vagina.

"Many bad things can happen in surgeries like this," says Ngamruengphong. "My job is to dissect the lesion a tiny bit at a time, never going outside the GI tract."

After her part of the removal, Ngamruengphong made way for Fang, who completed the procedure using a minimally invasive transanal technique.

Ngamruengphong and Fang published the case in the *Endoscopy* journal this year, noting that this approach was a first in the United States. She adds that the patient went home the next day and has recovered fully.

"When we have difficult cases, we work with our colleagues to come up with what's best for the patient," she says. "At Johns Hopkins, our surgeons and our pathologists and oncologists—we all work together."

In addition, Ngamruengphong is trained in a new endoscopic resection technique called endoscopic full thickness resection, or EFTR, where lesions in the colon are resected using a technique that gathers the lesion and the tissue around it bunched in a clip. She resects the tissue just above the clip, then snips off tissue containing the lesion.

"We can remove the whole thing, including

(continued on back cover)

RESEARCH

Johns Hopkins Researchers Deliver Gene Therapy Directly to the Liver

Fixing or replacing faulty genes has emerged as a key to unlocking cures for numerous devastating diseases.

But introducing those genes into live mammals has proven a challenge. The gene must be administered, it must reach its intended targets, it must get into the faulty or damaged cells, and then it must either disrupt or express a protein.

Johns Hopkins gastroenterologists Florin Selaru and Vivek Kumbhari believe they've taken a major step in the direction of helping patients with monogenic liver disorders by using an increasingly common endoscopic procedure to deliver the therapeutic genes to the liver via the common bile duct in large animal models. And they believe their novel method is safe and effective enough so that human clinical trials are not far off.

Thus far, patients with hereditary monogenic diseases like hemophilia, cystic fibrosis and Wilson disease have seen few benefits from gene therapy, as medicine has lacked a safe and effective way to introduce engineered genes to their systems.

Selaru and Kumbhari published a study this summer in the journal Gastrointestinal Endoscopy that describes introducing therapeutic genes to the liver by accessing the bile ducts using an endoscope.

"Until now, it hasn't been possible to perform liver-specific hydrodynamic gene delivery in a large animal model with direct translatability to human trials," says Selaru. Previous animal studies introduced the new genes through intravascular hydrodynamic injections which have a number of potential side effects.

"The technique was cumbersome, technically challenging, invasive and often led to severe cardiorespiratory problems in tested animals," Kumbhari adds. "There was very little progress in the direction of clinical trials."

The physician researchers used an endoscopic retrograde cholangiopancreatography (ERCP) technique

Johns Hopkins Among First to Offer Flexible Robotic Endoscopy

Thus far in the United States, robotic endoscopy has been limited to the sorts of things possible with a rigid scope and instruments.

"For therapeutic uses, the flexibility just hasn't been there," says Mouen Khashab, director of therapeutic endoscopy at The Johns Hopkins Hospital.

At Johns Hopkins, that's about to change.

"IT'S A MINIMALLY INVASIVE ALTERNATIVE TO SURGERY. FROM START TO FINISH, THE ROBOT GIVES THE PHYSICIAN CONTROL AND INCREASED EFFICIENCY AND PRECISION."

—MOUEN KHASHAB

Khashab and several of his colleagues at Johns Hopkins have spent months training on the first-ever FDA-approved flexible robotic endoscope.

"It's a minimally invasive alternative to surgery," he says. "From start to finish, the robot gives the physician control and increased efficiency and precision."

Controlled resection of superficial and deep tumors, Khashab says, will make flexible robotic endoscopy an important weapon in Johns Hopkins' fight against colon cancer.

When it comes to difficulties in therapeutic endoscopy, challenges posed by anatomy have largely been the main culprit.

Often, gastroenterologists recommend surgery in the case of larger tumors, not because mass can't be excised, but because of what that resection leaves behind. Manual endoscopic suturing of large holes left after resection often presents a challenge, especially in anatomically difficult areas of the colon.

"When a surgeon performs a full-thickness resection, that surgeon isn't concerned about the big hole he or she has just made," says Khashab. "It's right there and it's easy to suture."

But manually maneuvering a scope and its suturing device to close a hole can be difficult and unpredictable, says Khashab, who estimates that Johns Hopkins will offer patients the flexible endoscopy option by early this year.

"The robot will give us confidence that we'll have reliable closure after a procedure."

Though endoscopy has revolutionized the field of gastroenterology, there are still challenges. Intestinal folds can obscure a scope's field of vision, making it difficult for the endoscopist. Excessive force applied to intestinal walls and endoluminal linings can result in tissue trauma. And the controls of manually operated scopes are modelled after laproscopic surgical tools, which can cause ergonomic difficulties for the endoscopist.

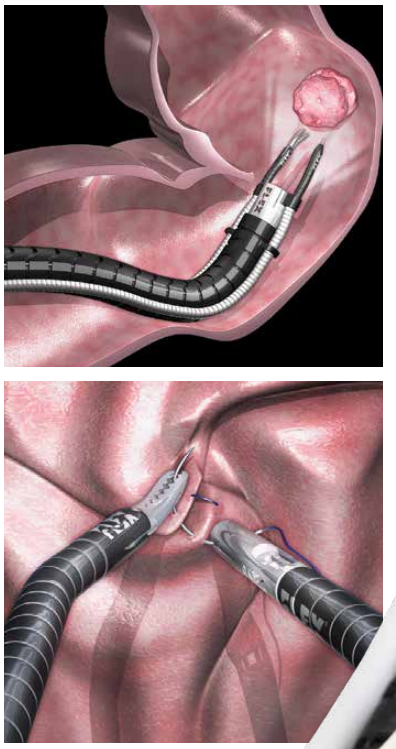
Robotics improve on each of those factors, even offering a more natural "feel" for the endoscopist, via haptic feedback and improved precision.

Khashab cautions that, because the technology is still in its infancy, flexible endoscopy won't replace surgery entirely.

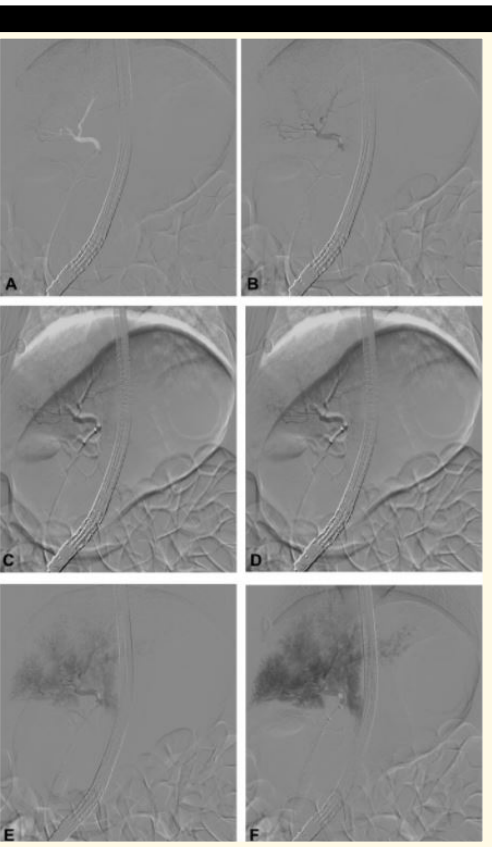
"The new scope is only able to reach 30 centimeters into the colon," Khashab says. "The manufacturers are working on making the robot better able to reach further, but they aren't there yet."

Still, he says, the new robotic system will be an option for many patients.

"We're very excited to start offering this as an alternative to surgery," says Khashab. "Greater precision and control are what make flexible endoscopy so promising." ■



Controlled resection of superficial and deep tumors will make flexible robotic endoscopy an important weapon in Johns Hopkins' fight against colon cancer. Images show rendering of robotic endoscopic resection.



Using an endoscopic procedure, Florin Selaru and Vivek Kumbhari delivered therapeutic genes to the liver.

Images A through F display fluoroscopic snapshots of a contrast injection into a bile duct using ERCP. The images were taken 3 seconds apart during injection of 30 mL of contrast dye at 2 mL per second. Image F shows the successful distribution of contrast dye, first into the right and then the left segments of the liver, without rupture of the bile duct wall.

to safely and successfully transduce engineered genes into hepatocytes in 12 pigs. The genes expressed the intended proteins in all 12 of the animals 21, 30 and 60 days from the time of the procedures.

"We're pleased with these results and we believe there's a great future for ERCP to deliver gene therapy," says Selaru. "In our study, we saw none of the side effects that accompany the intravascular injections. There was no biliary or liver injury. Our results indicate that gene therapy via ERCP is much less invasive, it's technically simple and it's safe."

ERCP uses a flexible endoscope to access the biliary tree. The endoscopist inserts the scope into the mouth of an anesthetized patient and guides the device down the esophagus, into the stomach and then to the duodenum. A smaller device comes out of the end of the scope and is guided by the endoscopist into the bile ducts. The procedure makes use of both a camera on the endoscope and X-ray to observe the bile ducts and, in this case, inject the therapeutic genes into hepatic cells.

Typically, hydrodynamic delivery of gene therapy has been difficult, due to the high volume of solution containing DNA molecules that needed to be injected rapidly into a vein. Ruptures and other vein injuries were common and, ultimately, the DNA missed its target and did not replicate successfully.

The Johns Hopkins researchers found, however, that a hydrodynamic injection into the bile ducts required a smaller amount of plasmids and led to no organ injury. And best of all, the genes replicated and expressed their proteins.

Selaru and Kumbhari chose pigs for their ERCP gene therapy study because of the animals' anatomic and genetic similarity to humans.

"Of course, at this point, we can only hypothesize that this procedure will be equally benign in humans," says Kumbhari. "But it appears that its safety profile shouldn't be a barrier to clinical trials." ■

For Colorectal Polyps: Early Detection and Minimally Invasive Endoscopic Resection

(continued from page 2)

margins," she says. "There's no hole to close up. It's already closed before we remove the lesion."

Ngamruengphong also has trained to spot gastric lesions early enough to avoid them becoming cancerous.

"Because stomach cancer is more common in Japan than in the U.S., they're better at spotting it," she says. "When I was a med student and a resident, I never saw early stomach cancer. But after I trained with the experts, I know what these lesions look like in their earliest stages."

Ngamruengphong describes a patient whose biopsy showed gastric cancer without suspicious lesions in the stomach. Before coming to her, the patient had had several ablations on a whole biopsied part of the stomach.

"They just ablated the whole area and that definitely didn't work," she says, noting that the lesion returned repeatedly, each time larger than before. Then the patient was recommended to undergo gastrectomy. "She came here and we were able to resect the lesion endoscopically using the ESD technique. It was an early gastric cancer, and the patient's doing well."

Too often, she says, gastric lesions are missed and are only spotted when they become advanced cancer.

"But when you see it and you treat it, it can be lifesaving." ■

CME

Third Annual HITEC Hopkins International Therapeutic Endoscopy Course

WHEN: April 3–5, 2019

WHERE: The Johns Hopkins Hospital and Johns Hopkins University School of Medicine, Thomas B. Turner Building Baltimore, Maryland, USA

For more information and to register: visit hitec-course.com

19th Annual Gastroenterology and Hepatology: Viva la Vida

When: March 12–15, 2019

Where: The Ritz Carlton, Cancun, Mexico

For gastroenterologists, hepatologists, surgeons, fellows, residents, physician assistants, nurses, nurse practitioners, and allied health professionals. Info and registration: bit.ly/V_L_V

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Gastroenterology and Hepatology Division Website
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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.

This newsletter is published for the Division of Gastroenterology and Hepatology by Johns Hopkins Medicine Marketing and Communications.

Johns Hopkins Medicine
Marketing and Communications
901 S. Bond St./Suite 550
Baltimore, MD 21231

Gastroenterology and Hepatology
Anthony N. Kalloo, M.D., *Editor*
Email: akalloo@jhmi.edu

Marketing and Communications
Justin Kovalsky, *Managing Editor*
Patrick Smith, *Writer*
Email: jkovals1@jhmi.edu
Lori Kirkpatrick, *Designer*
Keith Weller, *Photographer*

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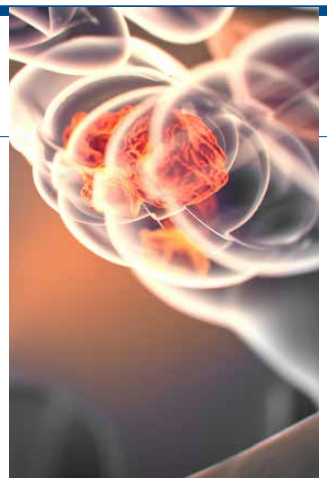

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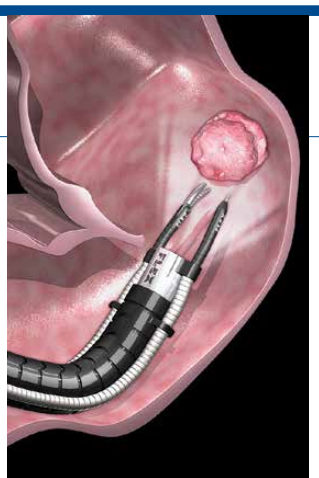

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