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In recent years, colonoscopy has become a rite of passage into middle age for many Americans—a routine screening that must be undertaken every decade starting at age 50.

In all, four times as many Americans have colonoscopies and other endoscopic exams today than in the late 1980s. And the number is expected to rise as more people seek the early-warning reassurance that comes with screening for the cancer that causes the third largest number of cancer-related deaths in this country.

But as with any diagnostic tool, what is good today can be made even better tomorrow through research and translation of laboratory results to everyday clinical practice. Improvements in technology may also help encourage even more people to get screened—as half of those who should be getting regular colonoscopies aren’t.

The U-M Division of Gastroenterology is at the forefront of developing and applying new ways to create detailed images of the digestive tract that go beyond traditional endoscopes—while at the same time working to find new ways to use these same tools with new devices that can help see disease better, and perform procedures without the need for open surgery.

This past year was an especially active one for U-M in this field. With Grace Elta, MD (lower left), serving as the president of the American Society for Gastrointestinal Endoscopy, Laurel Fisher, MD (lower right), making contributions to the field of double-balloon and capsule endoscopy, and two major recruitments of young faculty with impressive translational research track records, the Division is becoming recognized on a national scale as a leader for endoscopic research.

Much of the focus by U-M faculty has been in three areas: advancing the ability to see and intervene in the small bowel; harnessing molecular and optical techniques to better distinguish abnormal tissue during endoscopy; and using the endoscope to treat conditions formerly considered manageable only by traditional surgery.

**Visionary endoscopists: Translating innovation into improved patient outcomes**

**Seeing the small bowel**

Routine colonoscopy and upper endoscopy revolutionized diagnosis and treatment more than a generation ago, but endoscopic diagnosis and treatment remained very limited, given its length and distance from instrument insertion. Certain imaging techniques, such as CT scanning, have been used in the past to see blockages, bleeding and other problems in the small intestine, though the images weren’t always clear and surgery was nearly always required to carry out any intervention.

Then, in the early 2000s, the first “pill cameras” came into widespread use. These miniaturized, self-contained devices could be swallowed, and store the images they recorded in their 25-foot journey through the digestive system. U-M first began offering “capsule endoscopy” in the early 2000s, as a way of detecting small-bowel problems that had remained undiagnosed and untreated. Now, a few years later, more than 1,200 patients have had this type of examination at U-M. However, when an abnormality was identified, the patient would then proceed to surgery, as the capsule currently has no therapeutic potential.

A new option, made available at U-M in 2007, lets physicians not only see the problem, but actually do something about it. Just as a colonoscopy provides both a view of the colon and the means to remove polyps, this new technique, called double-balloon endoscopy (DBE) (illustration below), does the same for the small intestine.

Fisher and her colleagues use DBE to cauterize lesions, and to perform biopsies of potentially cancerous growths and inflammatory lesions such as the ulcers from Crohn’s disease. U-M was the first Michigan hospital, and one of the first in the country, to offer the technique, which, as its name indicates, is based on the use of two balloons.
One balloon is attached to the end of a scope similar to that used in colonoscopies, while the other is attached to an overtube that slides over the endoscope. Once inflated, the balloons hold onto the sides of the bowel and “shorten” the small bowel by pleating it over the endoscope. This allows the scope to advance much further into the small bowel, allowing detailed visualization and therapeutic intervention with one device. Most often, the scope is inserted through the mouth, but it can also be passed through the rectum as well.

For patients who need biopsies to make the diagnosis, or a therapeutic intervention to stop bleeding, remove growths, or relieve obstruction, the combination of the capsule endoscope and the DBE is an incredible advance, says Fisher. She looks forward to another technology now on the horizon: a capsule endoscope capable of performing high-quality imaging in the colon. Although such a device remains in clinical trials, it may provide value for those patients who currently eschew colonoscopy and remain unscreened and at risk for colon cancer.

**Molecular imaging can enhance visual endoscopic diagnosis**

While a screening colonoscopy identifies pre-cancerous polyps and cancerous lesions in millions of patients, and has contributed to the decline in colon cancer deaths in recent years, there’s plenty of room for improvement. In fact, a recent report in the *Journal of the American Medical Association* puts the overall prevalence of non-polypoid neoplasms, which may be difficult to see with conventional colonoscopy, as high as 9.35 percent of the population.

And in the esophagus, where more than 15,000 cases of late-stage cancer are discovered each year, a screening tool to find pre-cancerous lesions (dysplasia) in high-risk patients (such as those with Barrett’s esophagus resulting from long-term acid reflux) is badly needed.

One of the most promising opportunities for enhancing the ability to distinguish normal from abnormal throughout the digestive tract is to combine the use of molecular probes with an imaging device. In 2007, U-M was fortunate to recruit a rising star of this field, **Thomas D. Wang, MD, PhD (left)**, from Stanford University, where he had led a team investigating this field. He arrived at the University of Michigan with a joint faculty appointment in Medicine/Gastroenterology and Biomedical Engineering, and began to establish his own laboratory.

The basic idea of this area of research is to find new ways to “tag” pre-cancerous cells using protein fragments called peptides in such a way that they can be seen during routine screening endoscopic procedures. But in order to tag the cells, researchers first identify specific molecules that are unique to the surface of cancerous and pre-cancerous cells and are not present on normal cells. Dr. Wang and his Stanford colleagues have been developing fluorescent-labeled peptides to target important biomarkers associated with pre-cancerous lesions for diagnostic and therapeutic purposes.

Once the abnormal areas are detected, they use the miniature confocal microscope to observe peptide-bound cells at high resolution, rivaling the information provided by a biopsy sent to the laboratory, but instead of waiting 3 days, the information is known in “real time” to the endoscopist. This “virtual biopsy” approach has great potential to not only improve the visual diagnosis but to help physicians treating early cancers be certain they have removed all of the abnormal tissue.

As he begins his first experiments at U-M, Dr. Wang’s research, published in *Nature Medicine*, shows that this technique is able to distinguish abnormal, or dysplastic, cells from normal ones more than 80 percent of the time. Further research in his lab and with University of Michigan endoscopists will lead to refinements of this approach and its application throughout the digestive tract.

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*Macroscopic in vivo imaging of high-grade dysplasia in Barrett’s metaplasia. Endoscopic images collected in vivo of the distal esophagus in a human subject with Barrett’s esophagus and high grade dysplasia on **A.** white-light endoscopy, **B.** narrow-band imaging (NBI), and **C.** fluorescence image with topically administered FITC-labeled peptide reveals increased intensity at the site of the lesion confirmed to be high-grade dysplasia on histopathology.*
Minimally invasive procedures with an endoscope?

No matter what kind of endoscope a physician wields, or from which direction she or he starts, the use of this technology has been mostly limited to imaging and interventions within the lumen, or top layer, of the digestive tract’s lining.

Until now.

In just the past few years, gastroenterologists and surgeons have begun exploring the potential of minimally invasive surgical techniques called NOTES, short for Natural Orifice Transluminal Endoscopic Surgery™.

The basic idea: introduce endoscopes into the abdominal or thoracic cavity by traversing through the lumen of gastrointestinal tract (esophagus, stomach, colon) and even the vagina. Then, with existing or novel endoscopic tools, perform surgical procedures without ever puncturing the skin.

U-M gastroenterologists and gastrointestinal surgeons are hard at work to develop tools and techniques that could be used in NOTES procedures. Most notably, recently recruited faculty member Richard Kwon, MD (right), and his U-M colleagues Radoslav Coleski, MD, and Cyrus Piraka, MD, are leading the effort to develop an effective way to check for leaks in the stomach or intestinal wall after a NOTES procedure has been performed. This is a crucial step in the application of NOTES, because leakage of contents from the digestive tract into the abdominal cavity could quickly lead to serious infections.

Working with Jonathan Finks, MD, of the Department of Surgery, and mentored by Grace Elta, MD, and James Scheiman, MD, the team is testing the use of inert, nontoxic, and inflammable sulfur hexafluoride gas as a way to make absolutely sure that the gastric closure is complete. Funding for this research comes from a grant from the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR), a joint initiative supported by the American Society for Gastrointestinal Endoscopy and the Society of American Gastrointestinal and Endoscopic Surgeons.

Kwon cautions that NOTES procedures are a long way off from supplanting traditional laparoscopic surgery for many conditions. The approach may also give a new option to patients who cannot withstand surgery—because of morbid obesity, bariatric surgery, burns, or other conditions.

The Developmental Endoscopy Animal Laboratory (DEAL) is at the forefront of new techniques and device development for not only transluminal procedures, but new device and procedure development as well. With a strong collaboration with the College of Engineering and industry partnerships, new devices are being invented and tested for broad application at this interface of endoscopy and surgery. The ability to tackle the rising obesity epidemic and remove large growths in the wall of the GI tract, for example, will require new devices and novel endoscopic procedures. This laboratory is a multifaceted research program, and is poised to create, modify, and implement these exciting new technologies. Our bench-to-bedside program is creating great excitement among clinicians and researchers alike, looking to reach its full potential to improve patient outcomes.

Topically applied peptides bind to (target) colonocytes within dysplastic crypts on confocal microscopy in vivo and demonstrate high fluorescence target-to-background ratio in comparison to normal crypts (background).