

GI Endoscopy: Thriving on Innovation

(A#2010400048)

Written By Anne Staylor

Issue: MTI Jun. 2010

Section: Cover Story (Long Article)

Article Type: Technology Survey

Industry Segment: Supplies, Equipment and Devices; Supplies, Equipment and Devices/Surgical Equipment & Devices; Supplies, Equipment and Devices/Surgical Equipment & Devices/Minimally Invasive, Least Invasive

Therapeutic Categories: Gastrointestinal

Companies: Brigham and Women's Hospital; Columbia University; Fuji Photo Optical Co. Inc.; Fuji Photo Optical Co. Inc./Fujinon Inc.; Harvard University/Harvard Medical School; Karl Storz GMBH & Co.; National Institutes of Health; National Institutes of Health/National Cancer Institute; Olympus Optical Co. Ltd.; Smiths Group PLC; Smiths Group PLC/Cyrano Sciences Inc.; SpectraScience Inc.; superDimension Ltd.; Technical University of Munich; University of Kansas; University of Michigan; University of Warwick

Summary: Growth in the gastrointestinal endoscopy products market is being driven by advancements in GI diagnostics and screening technologies and growing adoption of high definition cameras and other enhanced imaging tools designed to improve diagnostic sensitivity and specificity in vivo, decrease the number of unnecessary procedures, and improve patient outcomes. Looking to the future, technological innovation will continue to impact growth in this market as emerging minimally invasive devices help redefine the diagnosis and treatment of GI disorders.

Further Analysis:	Title	Magazine	Issue	Article ID
	SAGES 2010: Barrett's Esophagus Still a Conundrum for Surgeons	<i>Medtech Insight</i>	May 2010	<u>2010400043</u>
	Colorectal Cancer: Meeting the Challenge	<i>Medtech Insight</i>	Sep. 2009	<u>2009400073</u>
	Scoping out Gastroenterology Start-Ups	<i>Start-Up</i>	Jul. 2009	<u>2009900159</u>
	Mauna Kea Technologies Takes Confocal Microscopy to the Tissues: An Interview with Sacha Loiseau	<i>Medtech Insight</i>	Sep. 2008	<u>2008400068</u>

Article begins on the next page . . .

© 2010, 2000 Windhover Information Inc.

No part of this publication may be reproduced or modified in any form, or incorporated into any information retrieval system without the written permission of Windhover Information Inc. (203-838-4401 ext. 232). This information is intended for the recipient only. Any further distribution is in direct violation of copyright laws.

GI Endoscopy: Thriving on Innovation

by Anne Staylor

In spite of a turbulent economic climate, the medical device market for gastrointestinal (GI) endoscopy products continues to thrive. According to statistics from the American Society for Gastrointestinal Endoscopy (ASGE), an estimated 20 million endoscopic procedures are performed annually in the US, and the total number of endoscopies have increased three- to four-fold since 1989. Driving this growth is an aging population, increasingly aware of the importance of early intervention and screening, and an increasing prevalence of gastrointestinal disorders, including inflammatory bowel diseases, colon cancer, Barrett's esophagus, stomach cancer, gastroesophageal reflux disease (GERD), diverticular disease, esophageal varices, and chronic liver disease, to name a few. Today, an estimated 60 to 70 million people in the US are affected by GI disorders. (*See Exhibit 1.*)

Exhibit 1

US GI Disease Statistics

- Prevalence: Affects 60 to 70 million people in the US
- Mortality: Causes 236,134 deaths per year (2004)
- Hospitalizations: Responsible for almost 14 million hospitalizations—9% of all hospitalizations
- 6 million diagnostic and therapeutic procedures (14% of all inpatient hospitalization procedures in 2002)
- Responsible for 72 million ambulatory care visits per year
- Cause of disability for 1.9 million people
- An estimated 146,970 new cases of colon and rectal cancer will be diagnosed in 2009 alone. Of the 20 million endoscopies performed each year, 70% are colonoscopies, which have increased 3-4 fold since 1989

Note: Data reflects most recent statistics available between 1990 and 2009.

SOURCES: National Institute of Diabetes and Digestive and Kidney Diseases; American Cancer Society; Medtech Insight

Growth in the market for GI endoscopy products is also being driven by exciting advancements in GI diagnostics and screening technologies and growing adoption of high definition cameras and other enhanced imaging tools designed to improve diagnostic sensitivity and specificity in vivo, decrease the number of unnecessary procedures, and improve patient outcomes. Looking to the future, technological innovation will continue to impact growth in this market as emerging minimally invasive devices help redefine the diagnosis and treatment of GI disorders.

Enhanced Imaging: Is Seeing Believing?

One of the most exciting areas of technology development for gastroenterology is in enhanced imaging modalities. Researchers are continually looking for new ways to improve the accuracy and diagnostic utility

of endoscopic screening methods, as standard white-light endoscopy (WLE) and random biopsies are somewhat limited in their ability to detect dysplasia and noninvasive cancers. Recent advances in biomedical optics are fueling new methods of in vivo detection and differentiation and are leading to increased diagnostic accuracy and a trend toward fewer, more targeted biopsies for screening Barrett's esophagus, ulcerative colitis, colorectal cancer, and other GI pathologies. (*Also see "SAGES 2010: Barrett's Esophagus Still a Conundrum for Surgeons*, Medtech Insight, May 2010 [A#2010400043] .)

Leading manufacturers have developed a variety of technologies to help detect and confirm neoplastic changes, and researchers are using multiple modalities to overcome some of the sensitivity and specificity limitations of individual techniques. Chromoendoscopy, narrow-band imaging, high-yield white-light endoscopy, Fuji intelligent color enhancement (FICE), and point enhancement technologies, such as confocal laser endomicroscopy (CLE), are examples of enhanced imaging technologies currently in use today. Manufacturers continue to improve detection capabilities by enhancing and refining wide field techniques and developing microscopic techniques and new characterization tools for in vivo characterization of tissue. Companies with current and emerging imaging modalities for gastroenterology include **Olympus Medical Systems Corp./Olympus Corp., Pentax Corp., Fujinon Inc./Fuji Photo Optical Co. Inc., Mauna Kea Technologies SAS, Karl Storz GMBH & Co. and SpectraScience Inc.**

At this year's Digestive Disease Week (DDW) meeting, held in New Orleans in early May, researchers discussed a variety of emerging technologies for GI imaging, including optical coherence tomography, endocystoscopy, spectroscopy-based devices, and molecular imaging. (*See Exhibit 2.*) While many of these are currently more academic than commercial endeavors, these techniques could eventually change the diagnosis and treatment of GI disease. But adoption of new imaging modalities and growth in this market will depend upon many factors, including the availability, accuracy, usefulness, safety, and cost of these technologies. And until the role of image enhancement tools is better defined, it remains to be seen how these technologies will ultimately impact the diagnosis and treatment of GI disease.

Exhibit 2

Emerging Technologies for GI Imaging

- Optical coherence tomography
- Endocystoscopy
- Elastic scattering spectroscopy
- Raman spectroscopy
- Fluorescence spectroscopy
- Reflectance spectroscopy
- Molecular imaging, fluorescent-tagged probes

SOURCES: "Advanced Imaging of Barrett's: Implications for Surveillance and Ablation," presented by Charles Lightdale, MD, Columbia University Medical Center, New York, NY, at DDW 2010; Medtech Insight

Confocal Laser Endomicroscopy

One imaging method that generated a lot of interest at DDW was confocal laser endomicroscopy (CLE), an emerging microscopic technique that uses extremely high magnification and resolution to provide in vivo histology or "optical biopsy" during endoscopic procedures. As a clinical solution, the technology is meant to

help bridge the gap between more imprecise macroscopic imaging technologies (such as magnetic resonance imaging, computed tomography (CT), positron emission tomography, high-resolution ultrasound, etc.) and microscopic techniques used in the clinical laboratory.

When used in gastroenterology, confocal microscopy allows physicians to zoom in on suspicious areas broadly identified by wide field techniques (such as narrow band imaging or chromoendoscopy) and conduct real time, in vivo microscopic evaluations of the gastrointestinal epithelium. By being able to differentiate normal versus abnormal tissue in real time, physicians can more accurately identify and select which lesions to biopsy during endoscopic exams, thus improving the diagnostic yield and minimizing the number of random biopsies performed during these procedures. The technology is commercially available both as a dedicated endoscope (eCLE, Pentax/**Optiscan Pty Ltd. Ltd.**) and as a probe-based device (pCLE, Mauna Kea Technologies). To date, CLE has shown promising results in the early detection of bile duct cancer, colorectal cancer, ulcerative colitis, and early cancer in Barrett's esophagus.

At this year's DDW, Mauna Kea Technologies' pCLE device, the *Cellvizio* System, received a boost when researchers presented positive results from the DONT BIOPCE trial (Detection of Neoplastic Tissue in Barrett's Esophagus with In vivo Probe-based Confocal Endomicroscopy). The trial is an international, multicenter, randomized controlled study that evaluated the sensitivity and specificity of *Cellvizio* when added to WLE and narrow-band imaging (NBI) in monitoring and detecting early esophageal cancer and high-grade dysplasia in patients with Barrett's esophagus. The findings of this study suggest that by adding *Cellvizio* to current endoscopic imaging methods, physicians can significantly improve their ability to accurately detect early esophageal cancer and dysplastic changes compared to standard imaging methods alone.

In the study, researchers from five leading centers (**University of Kansas, Mayo Clinic Jacksonville, New York-Presbyterian Hospital/Columbia University Medical Center, Nantes University Hospital** in France, and **Technical University of Munich**) led by the University of Kansas (Kansas City, Missouri) identified and marked suspicious lesions in 97 Barrett's esophagus patients using WLE, NBI, and four quadrant random locations (874 total lesions/locations marked). They then utilized *Cellvizio's* high resolution (one micron) probe to examine all suspicious lesions and random locations to make a presumptive diagnosis of benign or neoplastic tissue in real time. All locations were biopsied and reviewed by a central pathologist blinded to endoscopic or pCLE data. Pathology results confirmed 146 of the 874 total tissue samples to be early forms of esophageal cancer. Overall, the study showed that neither WLE nor NBI on their own or in combination was able to detect all precancerous and cancerous lesions during Barrett's esophagus surveillance. But by adding pCLE to NBI or WLE exams, physicians were able to identify *all* patients in the study with high-grade dysplasia or early esophageal cancer. When added to WLE, pCLE allowed researchers to identify 41 additional pre-cancerous or cancerous lesions, and when added to either WLE or NBI, physicians found 37 additional malignant sites.

The study also suggests that patients who test negative under all three modalities—WLE, NBI, and pCLE—can forego the tedious random biopsy process. In the study population, which typically has a higher prevalence of cancer than the mix of patients seen at community hospitals, the negative predictive value (NPV—the proportion of patients with a negative test who are correctly diagnosed) of pCLE was 95.6%. These findings correlate with results from an earlier study that showed that pCLE generated an NPV of 98.8% when conducted on a lower prevalence population (Pohl et al, *Gut* 2008). Based on the findings in the DONT BIOPCE study, 39% of patients could have foregone biopsies altogether, saving more than 330 biopsies out of 874 (37.8%).

Mauna Kea Technologies recently started enrolling patients in a large, randomized, controlled, multicenter outcomes study to confirm that *Cellvizio* helps physicians identify precancerous tissue that may have been missed during therapeutic interventional procedures for Barrett's esophagus. The CLEAN MARGIN study (Confocal Laser Endomicroscopy for Assessment of Neoplasia after Mucosal Ablation or Resection of Gastrointestinal Neoplasia) is expected to enroll 270 patients and is slated for completion in January 2011.

According to the company, *Cellvizio* delivers up to 12 microscopic images per second and can be used with almost any endoscope. At DDW, Mauna Kea showcased its second generation *Cellvizio* System, a more user-friendly version with cine review, a feature that allows physicians to record and stitch together a sequence of images for a larger field of view. The new *Cellvizio* System also allows physicians to export images to a memory stick for dictation and documentation. (*For more information on Cellvizio, see "Mauna Kea Technologies Takes Confocal Microscopy to the Tissues: An Interview with Sacha Loiseau," Medtech Insight, September 2008* [A#2008400068].)

Cellvizio has premarket notification 510(k) clearance from the FDA and the European CE mark for use in the GI and pulmonary tracts and has been commercially available since 2007. Since then, physicians have used the *Cellvizio* System in almost 6,000 patients worldwide and the company's installed base has grown to 40 hospitals in the US and 60 outside the US, according to Mauna Kea's CEO, Sacha Loiseau, who says the company continues to grow. "We've had 70% revenue growth between 2008 and 2009 alone. And right now, we are on a trend of very strong double-digit growth in the first four months of 2010, which we believe will continue for the remainder of the year." The company continues to expand its footprint into high growth markets and has partners distributing and marketing the system in more than 20 countries, including Europe. The firm recently started marketing the system in the Middle East and is currently awaiting regulatory approval for *Cellvizio* in Asia.

Like other companies with advanced imaging technologies, Mauna Kea still has some hurdles to overcome in order to gain widespread physician adoption of its technology for Barrett's esophagus. (*See Exhibit 3.*) One is the lack of a specific reimbursement code for endomicroscopy. Loiseau says the company has been working very actively in this area over the last several years and recently hired a director of reimbursement in the US. Some physicians have also expressed concerns regarding the cost of pCLE, although Loiseau says the technology has a clear potential for both improving health care and reducing costs.

Exhibit 3

Advanced Imaging in Barrett's Esophagus: Hurdles to Progress

- Device development and improvement
- Training
- Learning curves
- Quality control
- Intraobserver variability
- Costs
- Time
- Reimbursement

SOURCES: "Advanced Imaging of Barrett's: Implications for Surveillance and Ablation," presented by Charles Lightdale, MD, Columbia University Medical Center, New York, NY, at DDW 2010; Medtech Insight

In a panel discussion at DDW, one presenter said his hospital's analysis of pCLE found that the technology added \$700 per case and that he needed to perform seven biopsies in order to break even using the technology. Although Loiseau would not comment on this cost analysis, he says pCLE costs can be very hospital dependent and some people are not seeing the entire picture in terms of cost drivers. "If you look at the entire

equation, there's a reduction of random biopsies and savings in pathology costs, which is huge. But avoiding unnecessary procedures in general is a huge cost driver. If you can avoid just one colonoscopy, that's much more than \$700 in savings. And physicians are able to detect more lesions and ultimately improve patient care, which is very, very important," Loiseau asserts. Whether providers will buy into this argument remains to be seen, but cost reduction is certainly an important parameter, given the enormous costs currently associated with GI diseases. According to a recently published analysis, the total cost of digestive diseases to the US economy (both direct and indirect) eclipsed \$126 billion in 2004. (*See Exhibit 4.*) And both hospitalizations and ambulatory care visits for digestive diseases have risen steadily since 2000. (*See Exhibit 5.*)

Exhibit 4

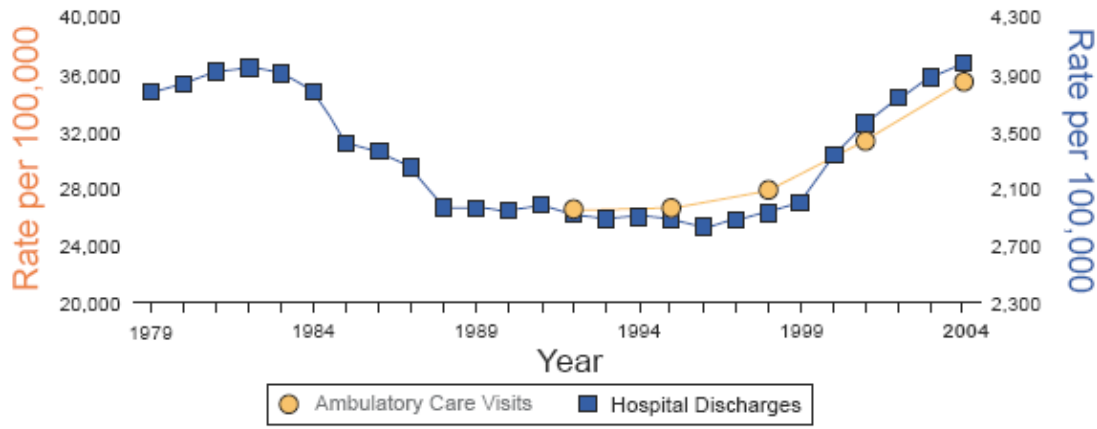
Costs of Selected Digestive Diseases in the United States, 2004 (\$ Millions)

Digestive Disease	Direct Costs (\$)	Indirect Costs (\$)	Total (\$)
GI infections	\$1,343.4	\$392.5	\$1,735.9
Esophageal cancer	597.3	1,975.4	2,572.6
Gastric cancer	487.5	1,415.0	1,902.6
Cancer of small intestine	123.8	159.9	283.8
Colorectal cancer	4,043.7	5,455.2	9,498.9
Liver cancer	261.2	1,318.6	1,579.8
Bile duct cancer	166.0	515.5	681.5
Gallbladder cancer	66.6	150.6	217.2
Pancreatic cancer	1,077.4	3,225.6	4,303.0
Other digestive cancers	1,618.0	1,490.9	3,108.9
All digestive cancers	8,441.5	15,706.7	24,148.2
GERD	12,125.0	515.0	12,639.9
Irritable Bowel Syndrome	949.8	57.5	1,007.3
Crohn's disease	1,071.0	227.9	1,298.9
Ulcerative colitis	767.9	100.1	868.0
All inflammatory bowel disease	1,838.9	328.0	2,166.9
Diverticular disease	3,569.3	471.9	4,041.2
Liver diseases	2,532.0	10,563.0	13,095.0
All digestive diseases	85,699.7	40,432.0	126,131.7

SOURCE: James E. Everhart and Constance E. Ruhl. Burden of Digestive Diseases in the United States, Part I: Overall and Upper Gastrointestinal Diseases; *Gastroenterology*, Volume 136, Issue 2, February 2009, pp 376-386

Exhibit 5

Age-Adjusted Rates of US Ambulatory Care Visits and Hospital Discharges for Digestive Diseases, 1979-2004



Barriers to progress can also include the time, learning curve, and training that is needed for physicians to become proficient and efficient with the technology. However, Loiseau doesn't see these as significant hurdles for *Cellvizio* and says the optical biopsy technique is actually easier than performing regular biopsies. "The beauty of the optical biopsy technique is it's noninvasive and very easy," says Loiseau. "Random biopsies are much more tedious because the field of view becomes bloody and you need to wash all the time. Physicians have told me they can perform a 10-centimeter quadrant examination in five minutes with *Cellvizio*, and there is no way they could do that with multiple random biopsies."

As far as training, the company says the vast majority of physicians trained on pCLE image interpretation can perform very well after reviewing about 50 pCLE sequences in a specific indication and the learning curve for probe manipulation is an estimated five to 10 procedures. According to Loiseau, a total of 150 physicians have been trained on the *Cellvizio* system to date.

The market potential for pCLE is huge. Approximately three million people in the US alone suffer from Barrett's esophagus. Endoscopic retrograde cholangiopancreatography (ERCP) is a market of 445,000 procedures each year and it can also be used for ulcerative colitis surveillance, which often involves 32 random biopsies. Biopsies are taken every 90 degrees and every 10 centimeters of the colon and yet the diagnostic yield of this procedure is very low. So being able to target biopsies at the correct location and avoid unnecessary biopsies is a great benefit in diagnosing this disease.

Mauna Kea is evaluating *Cellvizio* for other applications beyond gastroenterology and is sitting on several niche markets, each worth at least \$100 million. Pulmonary imaging has always been a second application for the technology, and the company recently completed a pilot study in urology for use in detecting bladder cancer, a condition with a high recurrence rate and a lifetime of surveillance for patients who have been diagnosed with the disease. Researchers at the **University of Michigan** are also evaluating pCLE for targeted imaging in combination with molecular agents to diagnose cancer, and Loiseau says pCLE will play a huge role in minimally invasive cancer surgery. The company also recently launched a research and development program in collaboration with French company **EndoControl Inc.** to develop a new type of robotic-assisted endomicroscope that will allow physicians to determine if GI cancer patients are appropriate candidates for surgery. The project received \$10.3 million in funding from the Industrial Strategic Innovation program of OSEO, a French governmental agency. (See "Market and Industry Briefs: Mauna Kea and EndoControl to Collaborate on Abdominal Imaging Robot," Medtech Insight, April 2010 [A#2010400035].)

Spectrophotometry

Another company with a point enhancement technology is San Diego-based SpectraScience. At this year's DDW, the publicly-traded company introduced the latest generation of its *WavSTAT* Optical Biopsy System, which employs a spectrophotometry technique called laser-induced fluorescence to optically illuminate and analyze tissue within the jaws of a standard biopsy forceps. The *WavSTAT* System uses an optical fiber to send cool, safe ultraviolet laser light into suspected tissue, where the light reflects back to the computer at different frequencies, depending on the type of tissue. For example, in abnormal tissue, cells look different optically and have a different spectrograph that the computer can interpret as either normal or abnormal. Physicians simply read the resulting indicator, which shows a green light for normal tissue and a red light for abnormal tissue. If the tissue is abnormal, they can also use the *WavSTAT* System to biopsy the tissue.

According to SpectraScience's CEO, James Hitchin, the technology has several benefits that make it unique in its field. " *WavSTAT* doesn't require physician interpretation as it just gives them the answer with a green or red light. No other technology gives an absolute answer. Also, it is both a therapeutic and diagnostic device, so it can remove tissue at the exact location where it is detected. Our technology allows physicians to identify where to biopsy rather than do it randomly. Good endoscopists have sensitivity in the 80% range but *WavSTAT* is an adjunctive tool that increases a physician's sensitivity to 96%," Hitchin says.

The technology reads cells at a depth of 100 microns, which can detect dysplasia at a deeper level than other image enhancement technologies; however, critics say with a specificity of only 75%, autofluorescence technology produces a high number of false positives. As far as the cost of the system, Hitchin says the *WavSTAT* retails for about \$40,000, and the cost of the disposables are around \$100 per case.

WavSTAT received FDA clearance in 2000 for detecting precancerous and cancerous tissue in the colon. The company subsequently made several upgrades to its original technology before introducing it at this year's DDW and launching it on the European market in September 2009. SpectraScience is planning a full-scale market launch in the US in late 2010. It is seeking additional patents for its technology and evaluating other applications as well, including esophageal cancer and Barrett's esophagus, irritable bowel syndrome, gastric cancer, and lung cancer. The firm currently holds 60 patents for its optical probes and underlying technology.

In November 2007, SpectraScience made a move to enter the cervical cancer market when it acquired the *LUMA* Cervical Imaging System, another type of autofluorescence technology that scans the surface of the cervix in 12 seconds. [W#200710187] The company says that when used as an adjunct to colposcopy (the current gold standard), the *LUMA* System will find at least 26% more high-grade precancerous cervical abnormalities than standard colposcopy in women with atypical squamous cell and low-grade squamous intraepithelial lesions Pap tests. Based on data from the National ALTS study, it is estimated that about 200,000 women with precancerous cervical disease go undiagnosed each year.

In terms of marketing its technologies, SpectraScience is expanding its distribution network in Europe and preparing for product introduction in the US, which will require a larger direct sales force or a strategic corporate partner.

Emerging Technologies for GI Disorders

Researchers at this year's DDW presented data on several emerging technologies that could potentially revolutionize the diagnosis and treatment of patients with GI disorders. These include image-guidance for flexible endoscopy, wireless biosensors and polymers for GI bleeding, and an "electronic nose" for noninvasive screening of patients with inflammatory bowel disease (IBD) and other disorders.

Advances in Image-Guidance

Keith Obstein, MD, of the division of gastroenterology, **Brigham and Women's Hospital** in Boston, presented initial human data on a new image-guidance system for gastroenterology that he says could potentially improve diagnostic accuracy and efficiency and shorten training times for physicians performing endoscopic ultrasound (EUS). The imaged-registered gastroscopic ultrasound (IRGUS) system uses preprocedure CT images and miniature ultrasound probe trackers to create a real-time display that shows the position of the endoscope within a 3D CT reconstruction of the anatomy, all while linking CT images to corresponding EUS planes for immediate comparison. Functioning as sort of a "human global-positioning system" for the endoscopist, IRGUS allows clinicians to more accurately identify anatomic structures and see precisely where they are in the body at any point in time for any given procedure. Although Obstein says the device could potentially be used for several applications, including ERCP, colonoscopy, natural orifice transluminal endoscopy, interventional procedures, and as guidance for biopsy procedures, the researchers chose EUS as the initial application for several reasons.

"There's a long learning curve with EUS," Obstein says. "EUS is complicated because there are subtleties in ultrasound interpretation, the fields of observation are small, and it can be challenging ascertaining probe position and orientation. So you can't just come right out of residency and be a fellow and be great at it. At the same time, advanced procedures like ultrasound require the ability to not only be functionally capable with an endoscope, but also to have the additional skill set of being able to interpret images. So instead of trying to find an application for a technology, IRGUS grew out of a clinical need. We looked at some of the problems we were having with EUS and we asked ourselves: 'How can we identify the organs better? How can we increase our efficiency? How can we make it safer? And how can we improve our diagnostic abilities?'"

In 2007, Vosburgh et al established the feasibility of the IRGUS system in porcine models and human trials are currently ongoing. To date, researchers have completed eight cases using IRGUS in humans with IRB (Investigational Review Board)–approved plans for enrolling a total of 25 patients. At DDW 2010, Obstein presented data on the first five patients enrolled in the study, which randomized patients with CT scan–identified pancreatic lesions to undergo either conventional EUS or IRGUS. According to Obstein, initial data suggest IRGUS has the potential to shorten EUS learning curves and broaden adoption of EUS among both novice and expert endoscopists.

"Our animal study demonstrated that IRGUS was able to significantly improve structure identification and timed tasked identification to a structure for both novices and experts. But the difference between novices using the image-guided system and experts without this system was not statistically significant. That means you could give this system to someone who has never used an echo-endoscope and within one day, while using the IRGUS system, they're at the level of someone who is an expert in conventional ultrasonography." These findings are being evaluated further in the human study, as researchers plan to assign eight patients to a portion of the study that compares novices to experts.

Although image-guidance has been used for years in neurosurgery and ear-nose-throat (ENT) procedures, Obstein says this is the first time image-guidance technology has been used in a flexible endoscope for GI applications. Unlike image-guided ENT and neurosurgery procedures, which involve image registration using immovable bony structures, the challenge for image-guidance using flexible endoscopy in soft tissue is that both the body and the endoscope move, which can compromise the accuracy of image-guided surgery based on preoperative images. And for gastroenterology, image guidance is further complicated by the use of insufflation and any change in patient position during a procedure.

To address these issues, Obstein says IRGUS mixes a dynamic registration process with sensor placement at hundreds of points on the body to develop exact coordinates that create an entire 3-D composite image of the body. A complex computer algorithm merges the CT scan with the 3-D composite image and locks them together. During the procedure, one composite display tracks the scope position within the 3-D anatomic

model along with the oblique CT scan slice in the exact plane and location of the EUS image. Obstein says the team is still refining IRGUS to improve the speed and accuracy of the system. The researchers have also been working to keep the system cost down, which Obstein says is currently under \$25,000.

The IRGUS project has received over \$1 million in funding over the past several years from a variety of non-industry sources, including the Department of Defense, the **National Institutes of Health**, the Center for Integration of Medicine and Innovative Technology, and the **National Cancer Institute**. And although Obstein would not comment regarding commercialization plans for IRGUS, he said the commercial potential for the device is significant. In theory, the device could be used in any patient who has already undergone a CT scan and who has an identifiable pathology that needs further evaluation using a flexible endoscope.

In addition to GI applications, image-guidance technology has been successfully used in a flexible endoscope for pulmonary applications. Minneapolis-based **superDimension Ltd.** has a commercially available flexible navigation system for lung applications. The company's *i-Logic* System uses *Electromagnetic Navigation Bronchoscopy* to provide minimally invasive access to lesions deep in the lungs as well as access to mediastinal lymph nodes.

New Techniques for Hemostasis

Meanwhile, researchers at **Harvard Medical School** and Brigham and Women's Hospital are evaluating new techniques for diagnosing and treating GI bleeding. Acute GI bleeding is a potentially life-threatening emergency and is still a common cause of hospitalization in the US, accounting for approximately 350,000 hospitalizations per year. Commonly used endoscopic techniques for treating GI bleeding include local injection, thermal coagulation, and argon plasma coagulation, as well as mechanical hemostatic methods, such as clips, elastic bands, ligation, and endoloops. However, rebleed rates following treatment can be as high as 20%, even after endoscopic intervention. Rebleeding is also a major cause of morbidity and mortality, with reported mortality rates as high as 10%. At DDW, Sohail N. Shaikh, MD, a developmental and bariatric endoscopy Fellow at Harvard Medical School, and colleagues presented studies describing two novel techniques for detecting and controlling GI bleeding and rebleeding.

One technique involves the use of endoscopically implantable wireless biosensors. Physicians implant the miniature biosensors along the length of the GI tract, where the sensors remain for a period of weeks, recording and transmitting data wirelessly as necessary to an external receiver attached to the patient. Using fluorescence detection capabilities, the biosensors detect fresh bleeding amid the gastric milieu and then transmit a wireless emergency signal to the e-mail or cell phone of designated medical personnel. Researchers tested the feasibility of the biosensors in ex vivo and in vivo animal models to determine the biosensor's sensitivity for detecting fresh blood and its ability to wirelessly transmit a signal through soft tissue while submerged in gastric contents. The biosensors were able to successfully detect acute hemorrhage in the GI tract and wirelessly send an emergency text message to the intended cell phone without incident. According to Shaikh, the technology is evolving and has applications for both upper and lower GI bleeding.

"Our first endeavors were just to develop technology that could discern blood from other substances," he says. "Through careful development of optics, diodes, and fluorescence technology, we were able to discern between hues and reflectance of old blood, new blood, or foodstuffs....Now we are working on a model that will downsize the biosensor from a centimeter to a millimeter scale, which would bring it down to about the size of a clip and allow physicians to deploy it transendoscopically. Once we get it to that size, it may have a great impact on the management of bleeding."

Shaikh says the biosensors can be set to various degrees of sensitivity so the wireless alarm will only go off when the biosensor detects a predetermined amount of fresh blood. In the study, the average estimated blood loss leading to biosensor activation was 30 cc (range: 10 cc – 75 cc). The biosensors are also designed to communicate with each other, which could potentially help physicians pinpoint elusive sources of rebleeding

within the GI tract. For example, when a bleed first starts, one biosensor may first detect a change of optics in that region and as the blood moves through the GI tract, the next sensor will detect it, then the next, etc. So the biosensors will track the pattern of detection and tell a physician where a bleed first started and how it is progressing in the GI tract. In addition to solving a clinical problem that "keeps us up at night," Shaikh says endoscopic placement of biosensors for GI bleeding surveillance could potentially limit morbidity, mortality, and health care costs associated with post hemorrhage supportive care and rebleeding.

Thermosensitive Reverse Phase Polymers

Shaikh is also working on a new endoscopic method of controlling severe hemorrhagic GI bleeding that is unique in that it can be performed without direct endoscopic visualization. In a study presented at DDW, Shaikh and his colleagues used EUS-guided intravascular polymer injections to achieve temporary hemostasis in porcine bleeding models using a new family of biocompatible polymers that rapidly transform from a liquid to a gel plug at body temperature. The gel plug dissolves over time (8 to 16 minutes in animal studies) and is reversible back to a liquid via cooling. According to Shaikh, using a gel plug to achieve temporary hemostasis allows the physician to gain more control of a potentially life-threatening situation.

"Any gastroenterologist will tell you the most worrisome bleeds are those that are arterial in nature...In the most severe scenario, you don't know where the blood's coming from, and you have a closed space, such as the stomach or duodenum, that fills up with blood and it is completely blinding. And if you can't see the source of a bleed, you can't address it," says Shaikh. "So using the ultrasound, you can identify the artery and then inject this polymer, which forms a temporary gel plug that allows the physician to get more control of the situation."

Developed by Massachusetts-based **Pluromed Inc.**, the polymer technology is currently being used outside the US in humans for stone fragmentation in the renal calyces as well as for preventing embolization during beating heart surgery. Pluromed's first products using this proprietary technology are *LeGoo* Internal Vessel Occluder for temporary occlusion of blood vessels, and *BackStop* for kidney stone removal.

Electronic Nose "Smells" Disease

Also at DDW, researchers from the **University of Warwick** in England presented the results of a pilot study evaluating the "electronic nose," a completely noninvasive screening method for detecting patients with inflammatory bowel disease and other medical conditions. Also called "artificial olfaction" or the "e-nose," the electronic nose is a novel device that employs an array of chemical sensors to sniff out the bio-odorant signatures characteristic of various diseases. Originally developed by **Cyrano Sciences Inc.**, a division of **Smiths Group PLC**, to sniff out explosives, food contaminants, and other compounds and to verify solvents and other chemicals, the e-nose uses gases emitted from feces and urine to create a "fingerprint" of the total chemical composition of a sample.

In the study presented at DDW, researchers used the device to analyze the gaseous profile of urine samples obtained from healthy volunteers as well as those with ulcerative colitis and Crohn's disease and then compared the differential response between samples. The e-nose was able to recognize and distinguish between disease groups based on the gaseous profile from the urine samples.

"This gives us a new insight into the nature of IBD and in time may allow us to identify the disease at an earlier, more treatable stage," said lead investigator Ramesh P. Aransaradnam, MD, gastroenterology consultant and senior lecturer at the University of Warwick. "This could prevent patients from having to undergo invasive procedures." He added that the test results may be able to help clinicians select the most appropriate treatment.

Anne Staylor is Senior Editor for *Medtech Insight* (e-mail: A.Staylor@Elsevier.com)