Advanced Technologies for Gastrointestinal Endoscopy

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Annu. Rev. Biomed. Eng. 2012. 14:397–429

First published online as a Review in Advance on May 22, 2012

The *Annual Review of Biomedical Engineering* is online at bioeng.annualreviews.org

This article's doi: 10.1146/annurev-bioeng-071811-150006

1523-9829/12/0815-0397$20.00

Keywords

capsule, magnet, technology, wireless, wireless capsule endoscopy, video capsule endoscopy, flexible endoscopy, colonoscopy, robotic endoscopy, robotic capsules

Abstract

The gastrointestinal tract is home to some of the most deadly human diseases. Exacerbating the problem is the difficulty of accessing it for diagnosis or intervention and the concomitant patient discomfort. Flexible endoscopy has established itself as the method of choice and its diagnostic accuracy is high, but there remain technical limitations in modern scopes, and the procedure is poorly tolerated by patients, leading to low rates of compliance with screening guidelines. Although advancement in clinical endoscope design has been slow in recent years, a critical mass of enabling technologies is now paving the way for the next generation of gastrointestinal endoscopes. This review describes current endoscopes and provides an overview of innovative flexible scopes and wireless capsules that can enable painless endoscopy and/or enhanced diagnostic and therapeutic capabilities. We provide a perspective on the potential of these new technologies to address the limitations of current endoscopes in mass cancer screening and other contexts and thus to save many lives.

Contents

1. INTRODUCTION

Each reader of this review is likely to know someone who has experienced a disease or disorder of the gastrointestinal (GI) tract. Diagnosing and treating these maladies is challenging for many reasons, but a history of technological innovation has continually improved the ability of physicians to help their patients. The earliest flexible endoscope, completely based on optical fibers, was presented at the American Gastroscopy Society annual meeting in May 1957 by Basil I. Hirschowitz (1) and described in a 1954 *Nature* paper by Hopkins & Kapany (2). Since these beginnings, endoscope technology has continually improved. Driven by breakthroughs in electronics, materials science, computation, sensing, and actuation, many novel GI devices, diagnostic techniques, and treatments have recently emerged. The purpose of this review is to discuss these new approaches and devices, beginning with the current clinical standards of care.

However, we first consider an example illustrating the pervasiveness of GI tract disease and the drawbacks of current treatments, which have inspired some of the technological innovations described below. Cancer occurs with high incidence in the large intestine and is life threatening, striking more than 140,000 in the United States each year and killing approximately 50,000, according to the American Cancer Society (**http://www.cancer.org**). A distinguishing feature of this cancer is that it is one of the few that can nearly always be prevented because it typically starts with a small, benign growth named a polyp. If the polyp is identified in its early asymptomatic stage, it can be removed, precluding the onset of cancer and resulting in a 5-year survival rate of almost 90%, compared with 5% when identified later (3). However, detecting and removing polyps is currently accomplished by inserting an endoscope into the colon, which is an unpleasant procedure. Because of this, only 62.9% of Americans comply with screening guidelines, meaning that an estimated 22 million in the United States alone are foregoing recommended screenings (4).

This information naturally leads to the question: How many lives could be saved if a technique more "patient-friendly" than colonoscopy were to be developed? Just as a screening process well tolerated by patients has resulted in the plummeting of cervical cancer–related deaths in the past generation [the Pap smear has reduced cervical cancer–related deaths by approximately 74% since its introduction in 1941, according to CervicalCancer.org (**http://www.cervicalcancer.org**)], a more agreeable procedure for routine colon cancer screening may save many lives, simply by encouraging people to comply with screening guidelines. There have been efforts to create such

an alternative screening test for GI cancer, including digital rectal examination, sigmoidoscopy, barium enema, and fecal occult blood testing, but the effectiveness of these continues to lag endoscopy dramatically (e.g., 33% false-negative rate for fecal occult blood testing; 5% false-negative rate for colonoscopy). Thus, a secondary purpose of this review is to provide an updated collection of results and perspectives that we hope will assist future researchers who take on the crucial public health challenges of developing better screening procedures for GI cancer and other diseases and disorders of the GI tract.

In this review, we first discuss anatomy and provide examples of various pathologies of the GI tract, and then present the state of the art in flexible endoscopy for diagnosis and treatment of GI diseases. Next, we introduce a set of advanced technologies for flexible endoscopy that are either already available or close to clinical trials and have the potential to reduce patient discomfort and increase diagnostic yield. Finally, we address wireless capsule endoscopy as a potential solution for mass screening of GI diseases, discussing potential research paths that may eventually make this novel approach practical for clinical use as a replacement for standard endoscopy.

1.1. Gastrointestinal Tract Anatomy, Pathologies, Diagnoses, and Therapies

The GI tract presents many challenges for diagnosis and therapy delivery owing to its length (9 m) and varying diameters. Responsible for the digestion and absorption of food and the removal of solid waste from the body, it consists of the mouth, pharynx, esophagus, stomach, small intestine, and large intestine (5). Most of the GI tract (i.e., from the esophagus to the large intestine) is a collapsed muscular tube, which stretches (i.e., distends) when liquid or food passes through it.

Proceeding downward from the mouth and pharynx, we reach the esophagus, a hollow muscular tube approximately 25–30 cm in length and 2–3 cm in diameter. Gastroesophageal reflux disease (GERD) is the most common esophageal pathology [affecting 20% of the US population (6)], in which stomach acids irritate the esophageal wall and cause painful heartburn. In severe cases, a gastroscopy is conducted to detect any complications including a hiatus hernia, Barrett's esophagus, or cancer. The latter two are typically confirmed by histological analysis and thus require biopsy sampling.

At the base of the esophagus is the stomach, a 25-cm-wide collapsed saclike chamber able to expand its volume from 0.1 liter to 4 liter to accommodate food or liquids. The internal wall of the stomach is coated with mucus for protection, as strong peristaltic contractions mix the food with gastric acid and digestive enzymes, fostering mechanical and chemical digestion (5). Among the most common stomach diseases are peptic ulcers, crater-like lesions in the mucous membrane that expose the stomach wall to the caustic contents inside the stomach. Patients suspected of having ulcers typically undergo an upper GI endoscopy to identify the ulcer and rule out gastric malignancy [which occurs in 2.7% of gastric ulcers (7)].

At the base of the stomach is the small intestine, a 6-m-long tube with a diameter of approximately 3 cm. Smooth muscular contractions mix nutrients with digestive juices secreted here and slowly propel material along (5). Among the common small intestine disorders is the condition in which mucosal cells fail to produce specific enzymes, resulting in the inability to digest certain foods (e.g., lactose intolerance). Celiac disease is a chronic disorder in which the mucosa of the small intestine is damaged by gluten, resulting in the inability to absorb nutrients. Biopsy continues to serve as the gold standard for diagnosis of this and similar diseases. However, given the invasive nature and cost of a biopsy, antibody tests are often used to identify individuals with a high probability of having celiac disease (8).

Material exits the small intestine into the large intestine, a 1.5-m-long muscular tube with four sections: the cecum, colon, rectum, and anal canal. The large intestine decreases in diameter

gradually from the cecum (7 cm) to the sigmoid (2.5 cm) and terminates in the rectum (13 cm) and the anal canal (4 cm). The large intestine's major function is the absorption of water, and it also houses a variety of bacteria that play an important part in digestion (9). Diverticular disease (in which mini-hernias occur in the intestine wall) occurs in 50% of people over the age of 60. Some cases result in bleeding, ulceration, and infection and require urgent therapy with antibiotics and/or surgery (10). Other disorders of the large intestine include chronic inflammation, which increases the risk of colorectal carcinoma, ileal disease, ulcerative colitis, and Crohn's disease (1).

1.2. Current Clinical Techniques for Gastrointestinal Endoscopy

Now that the main anatomical and pathological features of the GI tract have been highlighted, we briefly describe standard techniques for GI endoscopy. We pay particular attention to the limitations that have inspired the innovative devices discussed in Sections 2 and 3.

1.2.1. Bowel preparation and patient sedation. Bowel preparation is required to remove the contents of the GI tract, enabling visual endoscopic inspection. Usually, preparation involves a clear liquid diet (no alcohol and beverages containing red or purple dye) and the ingestion of a laxative solution (e.g., polyethylene glycol electrolyte lavage solution) on the day before the procedure (6). Although certainly not pleasant, this process effectively rinses the colon. Upper GI endoscopy does not require this form of preparation because material passes quickly through the stomach and duodenum (11).

Although many GI endoscopic procedures can be performed without sedation (12), sedation with pain relievers and sympathetic patient management can improve patient tolerance and acceptance, increasing technical success rates. Standard monitoring of sedated patients undergoing GI endoscopic procedures includes recording the heart rate, blood pressure, respiratory rate, and oxygen saturation to avoid risk of cardiac or respiratory problems, which account for more than 50% of all reported complications (12). It is also worth mentioning that a major cost component of GI endoscopy relates to sedation administration (13).

1.2.2. Standard endoscopic procedures and different types of flexible endoscopes. The endoscopes used for the examination and treatment of the GI tract consist of three main parts: the control handle, the insertion tube, and the connector. The control section, held and moved by endoscopist's left hand, has the following features:

- Two control dials that deflect and also lock the instrument tip in place;
- Separate buttons for suction, air or water insufflation, and image capture; and
- An entry port for the working channel.

The insertion tube, controlled by the endoscopist's right hand, is a flexible shaft with at least one embedded working channel, suction and air/water channels, and control wires for tip deflection. The tip of the insertion tube of a typical endoscope contains a digital imager [either a charge-coupled device (CCD) or a complementary metal-oxide semiconductor (CMOS) sensor] for color image generation (standard resolution of 400,000 pixels), a light guide illumination system, an opening for the air/water channel, and a water jet to clear the lens. Finally, the connector section attaches the endoscope to the endoscopy tower, which commonly contains an image processor, a 100–300-W white-light source with electrical power supply, air or CO_2 source, and water (14). Because endoscopes must be cleaned and sterilized between patients, they are designed to be completely waterproof and resistant to chemicals. **Figure 1** shows a standard flexible endoscope and a set of flexible instruments that are discussed in Section 1.2.3.

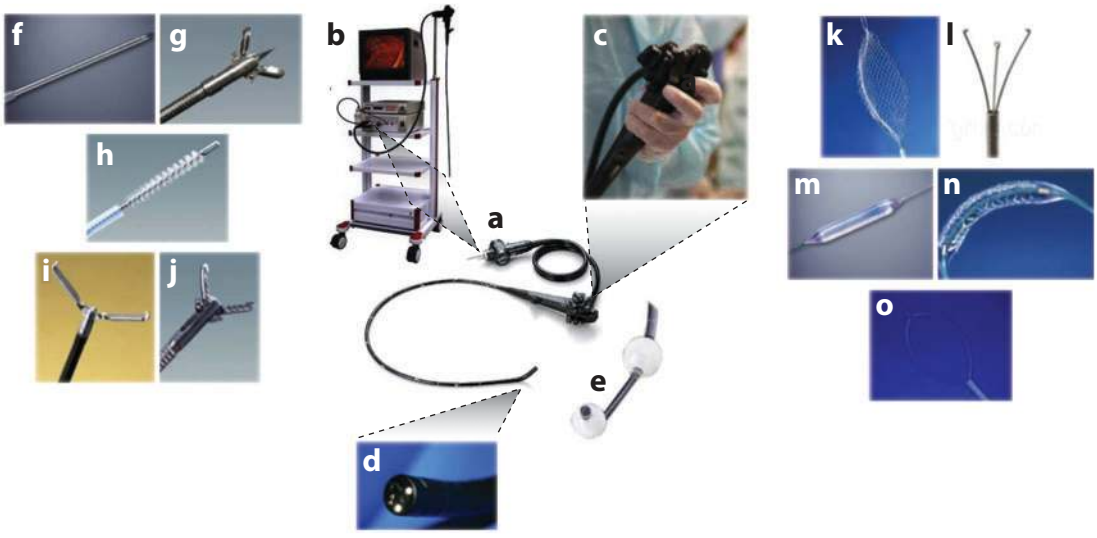

Figure 1

A typical flexible endoscope and examples of flexible tools: (*a*) a standard flexible endoscope, (*b*) an endoscopy tower, (*c*) the control handle, (*d*) the steerable tip, (*e*) a double balloon enteroscope, (*f*) a biopsy needle, (*g*) biopsy forceps, (*h*) a cytology brush, (*i*) a rat-tooth grasping forceps, (*j*) an alligator grasping forceps, (*k*) a net, (*l*) a tripod grasper, (*m*) an expandable balloon, (*n*) a metal stent, and (*o*) a hot snare.

In upper GI endoscopy, an overtube is usually inserted by the application of gentle pressure to overcome the sphincters that separate each part of the GI tract. After this intubation, flexible endoscopes can be easily inserted for examination of upper GI organs (esophagus, stomach, and duodenum) in approximately 20–30 min (1). Gastroscopes have variable insertion tube lengths (925–1.1 m), insertion tube diameters (4.9–12.8 mm), and channel sizes (2.0–3.8 mm). Ultrathin insertion tubes for unsedated peroral or transnasal esophagoscopy (5–6 mm in diameter) are available with tip deflection of one or two degrees of freedom (DoF). These devices may also have small instrument channels (1.5–2 mm) but have inferior diagnostic capabilities in comparison with standard endoscopes (15). Duodenoscopes are side-viewing endoscopes available in standard and therapeutic versions with long insertion tubes (approximately 1.25 m) and variable diameters (7.5–12.1 mm) and channel sizes (2–4.8 mm).

Enteroscopy, endoscopic examination of small intestine, is usually performed with an oral or nasal approach to resolve problems of obscure GI bleeding. Enteroscopes are forward-viewing endoscopes with a working length ranging from 1.52 m to 2.2 m, a channel diameter of 2.2 mm to 3.8 mm, and an insertion tube diameter of 9.2 mm to 11.6 mm (14). One of two main procedures can be used to complete the examination: (*a*) a standard push technique with manipulation of the abdomen wall by an assistant or changes in patient position (alternating lateral and supine positions) or (*b*) a Sonde technique that requires a specialized scope with an inflatable balloon, which anchors the instrument in place during shortening maneuvers while facilitating insertion by exploiting GI peristalsis (1). (The balloon can be single or double; single-balloon enteroscopy and double-balloon enteroscopy yield similar results.)

Lower GI endoscopy can be used to view the entire large bowel in most patients. Bowel insufflation by air or CO_2 facilitates insertion and withdrawal of the scope and distends tissue folds so that the entire surface can be examined (1). A colonoscope is a forward-viewing endoscope inserted through the anus. It is available in pediatric and adult models with different insertion tube lengths

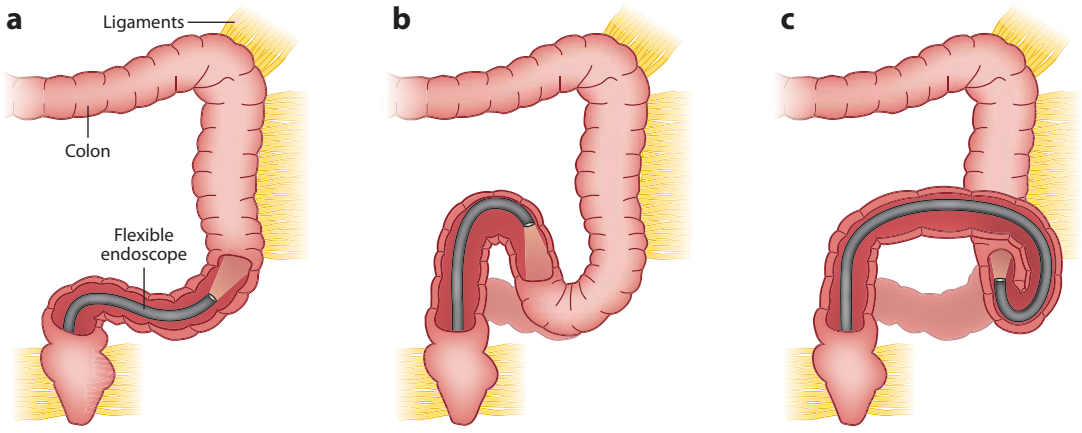

Figure 2

Endoscope flexibility problem in colonoscopy. (*a*) Desired situation: A colonoscope follows the curves of the colon. (*b*) In practice: The tip pushes against the colon and stretches it until the colon and its surroundings provide sufficient resistance to force the colonoscope to bend. (*c*) Pain-inducing bowel looping: Pictured is a typical loop shape (an N-loop) that can occur during colonoscopy. Because of the sharp bend at the tip, the flexible endoscope cannot advance. Adapted from Reference 21 with permission from IEEE.

(1.33–1.7 m), diameters (11.1–15 mm), channel sizes (2.8–4.2 mm), and channel numbers (1 or 2). The distal portion of the tube is flexible to allow the endoscopist to negotiate curves in the colon, whereas the shaft is stiff to enable pushing and reduce looping of the bowel (see **Figure 2** for a definition of looping). The sigmoidoscope—a relatively short, forward-viewing flexible or rigid endoscope designed only for examination of the distal colon and rectum—has variable insertion tube lengths (700–790 mm), insertion tube diameters (11.3–12.8 mm), and channel sizes (3.2–4.2 mm) (14).

1.2.3. Endoscopic instruments and procedures. Many flexible devices can be used with endoscopes to perform diagnostic or therapeutic tasks. These are introduced through the working channel(s) in the endoscope and are manually operated by an assistant endoscopist. We do not attempt to comprehensively catalog the available tools here; instead, we focus on the most widely used examples to explain the basic expectations an endoscopist will have of new endoscopic devices, in terms of tissue interaction.

During a GI examination, the endoscopist will routinely wish to acquire a tissue sample from visible lesions or areas of mucosa that differ from their surroundings. Biopsy forceps are widely used for this purpose in GI endoscopy (16). Alternative options consist of aspiration needles, cytology brushes, or balloons (17).

Furthermore, a variety of instruments are designed to remove polyps. A cold snare can be used to remove small polyps (<6 mm), whereas a hot monopolar snare can be used to cauterize the base of a polyp to prevent bleeding. Endoloops are used to constrict large polyp stalks prior to polypectomy or to treat esophageal varices. Nets or grasping forceps (e.g., alligator, shark and rat tooth, tripod, W-shaped) can be used to remove polyps but are more often used to remove various foreign objects from the GI tract (1). When inoperable or recurrent GI malignancies obstruct a portion of the GI tract, expanding metal stents can be inserted to reopen the intestine as a palliative approach. It is also possible to use pneumatic balloons to open simpler bowel and esophageal strictures (1).

1.2.4. Limitations of standard gastrointestinal endoscopy. Complications associated with endoscopy are related mainly to sedation and analgesia, with cardiorespiratory problems being the

most common [0.03% to 20% incidence (18)]. Bleeding can also occur (0.2% to 2.1% incidence), as well as occasional perforation [0.1% incidence (14)], which is a serious complication requiring emergency open surgery to correct. Bleeding and perforations are usually caused by large forces applied to the GI wall [>54 N in the colon (19)]. Lastly, another possible complication is infection [0.2% incidence (20)].

Given the efficacy of GI endoscopy and its fairly low complication rates, the main clinical challenge is one of distribution, which is limited by indignity, pain, and fear of sedation side effects (13). In upper GI endoscopy, pain is not a major problem because the esophagus is almost straight, so sedation is typically not required. In colonoscopy, however, the curves that the scope must traverse require that a colonoscope be both stiff enough to avoid buckling and compliant enough to follow the colon. In practice, this means that the scope deforms the colon wall at corners (21), causing pain. Looping (see **Figure 2**) has been shown to be responsible for 90% of the pain episodes in colonoscopy and increases the chance of tissue damage and perforation (22). Some special maneuvers can be applied to minimize this effect, but these make colonoscopy a difficult procedure to learn and master (23). Despite these techniques, even expert endoscopists cannot always prevent all difficulties because the endoscope cannot be simultaneously perfectly stiff and perfectly flexible (21).

Other limitations of current practice include the fact that biopsy samples must be processed off-line rather than intraoperatively. If the biopsy is positive, the pathology must then be treated during a second endoscopic procedure in which the same spot must be located again, if possible.

1.2.5. Virtual colonoscopy as an (imperfect) alternative. The most direct approach to reduce the invasiveness of flexible endoscopy is to eliminate the instrument. This can be achieved with virtual endoscopy, a technique based on using a computed tomography or magnetic resonance imaging (MRI) scan to inspect the GI tract (24). The colon is visualized using segmentation and surface or volume rendering to identify polyps and diverticula, among other maladies. Meticulous bowel cleaning is still required, as is heavy insufflation, but anesthesia is not required. The procedure takes 15 min, with 19 to 25 min for radiological interpretation (24).

Inadequate colonic inflation or excess fluid or stool retained within the colon leads to false-positive diagnoses, but recent advances in imaging and software analysis (including fecal tagging and fluid subtraction) have enhanced the clarity of the images (25). Unfortunately, traditional colonoscopy is still required to biopsy or remove any lesion/polyp found. A study of 1,233 asymptomatic adults who used experienced radiologists, stool and fluid tagging, and three-dimensional (3D) imaging reported a sensitivity (proportion of positive cases correctly identified) and specificity (proportion of negative cases correctly identified) of 93.8% and 96%, respectively, for polyps at least 10 mm in diameter, and 88.7% and 79.6% for polyps at least 6 mm in diameter (26). Results indicate that virtual colonoscopy is diagnostically comparable with traditional colonoscopy only for large, nonflat polyps greater than 10 mm in diameter (24).

The main strengths of virtual endoscopy are its noninvasive nature, its ability to clearly illustrate the spatial locations of objects, and its ability to enable visualization of the entire colon, even in the presence of stenotic lesions. Drawbacks include the following: Colon preparation is still required; there is a risk of perforation due to overinsufflation; radiation exposure is an issue, in the case of computed tomography; some flat or sessile lesions (which account for approximately 30% of all lesions) cannot be shown; and it is impossible to deliver in situ therapy or sample tissue (24). Owing to these limitations, despite initial predictions a number of years ago, virtual endoscopy has not yet replaced GI flexible endoscopy (27). It does not seem likely to do so in the foreseeable future, given that the US Preventive Services Task Force (28) and most insurance companies have not endorsed it for screening average-risk individuals.

1.2.6. Replacement criteria for alternative technologies. The fact that virtual colonoscopy has yet to replace traditional colonoscopy—despite its initial promise—inspires an analysis of the requirements for new technology to replace flexible endoscopy. Shifts in surgical and endoscopic techniques may be driven either by the physician who operates the device or by the patient who receives diagnosis and treatment from it. An example of patient-driven paradigm change is laparoscopy, in which the reduced invasiveness compensated for the increased procedural complexity for the physician. In contrast, an example of operator-driven change is the adoption of the endoscope along with the innovations that have led to its ability to maneuver, collect tissue samples, and provide high-quality visualization. Patients were not demanding these capabilities, but physicians observed that they would be able to deliver better care to their patients if they had them.

With these examples in mind, it is possible to identify general design guidelines for new GI technologies that could replace flexible endoscopy. Such considerations can be subdivided into three categories: absolute requirements, requirements for the foreseeable future, and advantageous qualities that may not be strictly required. In the absolute requirements category, we can identify three items:

- **High diagnostic accuracy.** As correctly underscored in Reference 21, a new device must provide diagnostic capability at least equal to that of current flexible endoscopes if the former is to fully replace the latter.
- **Low complication rates.** It is doubtful that any device that increases the risk of intestine perforation or other major complications (even slightly) would replace endoscopy.
- **Economic viability.** If financial costs of a new technology are not comparable with or lower than those of endoscopy, it is unlikely that the technology will be accepted. This is due to the high demand for endoscopic procedures, which will continue to grow because of aging world populations and public health campaigns encouraging screening compliance. Because endoscope costs can be amortized over many procedures, any single-use replacement technology faces significant cost challenges.

Beyond the above three absolute requirements are several other elements that will be required for the foreseeable future (i.e., unless dramatic and unforeseen technological breakthroughs are made). These elements would be required of any new technology that seeks to displace endoscopy in the short to medium time horizon:

- **Visualization.** Until automatic diagnostic methods improve dramatically in terms of both differentiation of various kinds of disease and accuracy in diagnosing all types of pathologies, any new technology seeking to replace flexible endoscopy must provide a user-controllable, clear, color view of the mucosa.
- **Tissue interaction.** In lieu of dramatic leaps forward in image-based diagnosis, tissue samples will have to be collected for diagnostic purposes. Also in lieu of breakthrough treatments that can be administered either systemically (e.g., novel drugs) or from outside the body (e.g., high-intensity focused ultrasound, which can be targeted toward the surgical site much more accurately than is currently possible), the use of endoscopes will be necessary to access the surgical site to deliver therapy.

Lastly, a novel technology seeking to replace flexible endoscopy will probably need to have several other qualities. Although not strictly required, these qualities would be advantageous to speed adoption of the technology:

- **No bowel preparation requirement.** A technology with no bowel preparation requirement would likely be rapidly adopted owing to pressure from patients. Although this is not a

requirement for a new technology to displace flexible endoscopy, it would be a significant advantage.

- **Elimination of pain/discomfort.** A significant reduction in invasiveness, pain, and/or discomfort for the patient can be expected to result in patient-driven adoption and to finally enable mass screening. Furthermore, preventing the need for sedation would decrease the cost of a single colonoscopy.
- **Short learning curve.** The easier the device is to learn to use, the more physicians will want to use it. However, as with the adoption of laparoscopic surgery, extremely compelling advantages in the level of invasiveness or the extent of diagnostic or therapeutic efficacy can outweigh some increase in complexity of use.
- **Scalability.** Scalability is desirable to enable the same instrument to be adapted to the different regions of the GI tract and/or to different sizes of people (e.g., pediatric populations).

2. ADVANCED FLEXIBLE ENDOSCOPES

2.1. Toward Mechanisms Enabling Painless Flexible Colonoscopy

Several colonoscope modifications (**Figure 3**) have recently been presented to prevent application of excessive force on the colon wall and to prevent looping. These devices can be categorized into two groups: those designed for visual inspection, and those that contain internal channels for interventional tools.

2.1.1. Diagnostic-only advanced flexible endoscopes. An example device in the category of diagnostic flexible endoscopes is the CathCam, whose technology has been supported/sponsored by Ethicon Endo Surgery, Inc. The CathCam is a nonsterile, disposable, multilumen catheter with a working length of 1.8 m and a diameter of 11 mm. Vision and illumination are provided by a 3-mm camera with six light-emitting diodes (LEDs). The catheter is designed for single use, whereas the camera is reusable and is mounted into the catheter tip prior to the procedure. The channels of the CathCam accommodate the cables of the video camera and provide suction, irrigation, visualization, instrument delivery, and guide-wire delivery (the guide wire is used to insert the device). This device has demonstrated a 30%–40% peak force reduction in bench-top experiments and in live pigs, compared with standard colonoscopes (29).

Another advanced diagnostic flexible endoscope is the Aer-O-Scope™ (GI View Ltd., Ramat Gan, Israel), which is a pneumatic, skill-independent, self-propelling, and self-navigating disposable colonoscope (30). The device is composed of a rectal introducer, a supply cable, and an endoscope embedded within a scanning balloon that serves as its vehicle. The rectal introducer is a hollow silicone tube (1.7 m in length, 19 mm in diameter) with a silicone balloon (80 mm in diameter) attached to its outer surface. The introducer is inserted into the rectum with its outer balloon, and the endoscope and its vehicle balloon are passed through the hollow tube of the introducer. The silicone balloon on the introducer seals the anus to prevent gas leakage. CO_2 is insufflated between the two inflated balloons, and gas pressure advances the vehicle balloon, the endoscope, and a trailing supply cable. The supply cable on the endoscope/scanning balloon is a flexible polyurethane multilumen catheter, 5.5 mm in diameter, that is coated with a hydrophilic material, which supplies the electro-optical capsule (the scope) and its vehicle balloon with electricity, air, water, and suction. The Aer-O-Scope is intended to be used for screening and diagnostic purposes and therefore does not have a working channel for accessories.

Yet another approach is inchworm locomotion, inspired by observations of geometer moths (31). Inchworm locomotion is used in the Endotics® System (Era Endoscopy s.r.l., Pisa, Italy).

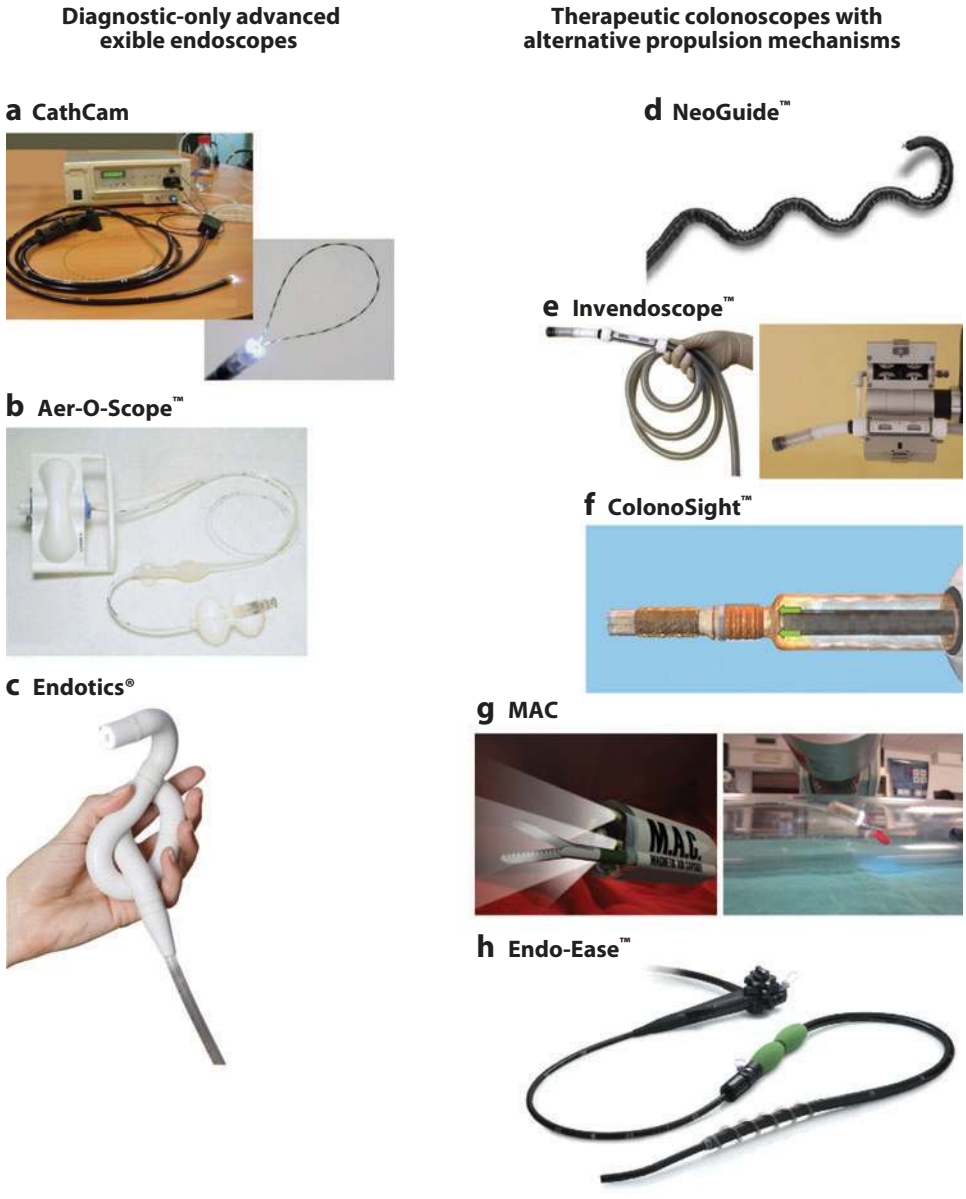

Figure 3

(*a*) The CathCam system. Reprinted from Reference 29 with permission from Elsevier. (*b*) The Aer-O-Scope™ system. Reprinted from Reference 30 with permission from Elsevier. (*c*) The Endotics® System (32). Image courtesy of Era Endoscopy. (*d*) The NeoGuide™ system. Reprinted from Reference 22 with permission from Macmillan. (*e*) The Invendoscope™ system. Reprinted from Reference 33 with permission from Elsevier. (*f*) The ColonoSight™ system. Reprinted from Reference 35 with permission from Elsevier. (*g*) The MAC system (36). (*h*) The Endo-Ease™ overtube over a pediatric colonoscope. Reprinted from Reference 37 with permission from Elsevier.

The disposable robotic probe has a head, a steerable tip, a flexible body (17 mm in diameter), a thin tail (7.5 mm in diameter), and a control box with an electropneumatic connector. The head hosts both a vision system (including a camera and LED light source) and channels for water jet and air to provide rinsing and suction/insufflation, respectively. The operator can steer the head of the robotic colonoscope 180° in every direction; elongate the body of the probe to move it forward along the intestine; and control rinsing, insufflation, and suction. A semiautomatic sequence of actions is implemented to move the probe like an inchworm, whereby two vacuum anchors located in the proximal and distal ends of the device are sequentially actuated between extensions and retractions of the central body. A human study (32) with 71 unsedated patients demonstrated that this system has a diagnostic accuracy comparable with that of colonoscopy and does not require sedation. However, in 13 cases (18%), the device was not able to reach the cecum, and procedure duration was longer than standard colonoscopy.

Concerning the replacement criteria listed in Section 1.2.6, it is evident that the lack of tissue interaction makes it impossible for diagnostic-only devices to completely replace traditional colonoscopes. Only prospective comparative outcome trials will be able to determine conclusively whether a first test with a diagnostic-only device followed by conventional colonoscopy will be preferable to performing conventional colonoscopy initially. Currently, 15% to 25% of patients with polyps subsequently have to undergo a conventional colonoscopy for polypectomy (33).

2.1.2. Therapeutic colonoscopes with alternative propulsion mechanisms. A first subset of advanced therapeutic colonoscopes consists of shape-retention devices, which are essentially tubes that are initially flexible and can be stiffened when desired. Several examples of devices utilizing this principle are described in Reference 21, but only the NeoGuide™ from NeoGuide Systems Inc. (a company based in San Jose, California, that was acquired in 2009 by Intuitive Surgical of Sunnyvale, California) has reached clinical trials. It consists of a 173-cm-long endoscope composed of 16 8-cm-long independent vertebrae, and it tapers from 20-mm diameter at the base to 14 mm at the tip, with a 3.2-mm working channel. Each segment can assume a circular shape in a desired direction, much as a conventional colonoscope tip can. As the human operator pushes the device into the colon, its shape changes under computer control, so that the shaft follows the trajectory of the tip in a follow-the-leader manner, minimizing colon wall interaction forces. Biopsies and therapies are conducted with the scope in passive mode, in which the shape and stiffness of the scope are the same as those of a standard colonoscope. An initial clinical trial on 10 sedated patients revealed a looping rate of 40%, with "extensive" looping in three of the four cases, but the entire intestine up to the cecum was reached in all patients (22).

Another computer-aided colonoscope is the Invendoscope™ (Invendo Medical GmbH, Kissing, Germany), which is 210 cm long and consists of an internal endoscope surrounded by several layers, beginning with a 10-mm-diameter sheath. The sheath is covered by double layers of an inverted sleeve that provides the propulsion mechanism. Eight drive wheels in the driving unit grip the inner layer of the inverted sleeve and rotate, causing the inner layer to move forward and making the colonoscope elongate at a position 10 cm below its tip. The overall objective of this mechanism (similar to that of the NeoGuide) is to minimize scope-colon interaction forces and hopefully remove the sedation requirement. The Invendoscope has a 3.2-mm working channel, allowing biopsy specimens to be taken and therapeutic procedures to be carried out, and is disposable. A first clinical pilot study on 34 healthy volunteers demonstrated that the Invendoscope was able to reach the cecum without any sedation in 82% of cases (33). This result was confirmed by a prospective single-arm study on 61 healthy volunteers undergoing screening colonoscopy, with a cecal intubation rate of 98.4% and fewer than 5% of patients requiring sedation (34).

Another disposable, self-propelling device is the ColonoSight™, based on IntraPull and ProtectiScope technologies by Stryker, Inc. This colonoscope has three working channels: a 3.7-mm-wide channel for suction and insertion of accessory tools, a channel for irrigation, and a channel for insufflation. A disposable sleeve anchored at the proximal end of the device envelopes the endoscope, protecting it from contamination. The IntraPull mechanism generates a force close to the tip of the scope by pumping compressed air inside the sleeve as a foot pedal is pushed. The material of the sleeve does not allow radial expansion, so the increased pressure inside the sleeve creates a force directed toward the tip of the colonoscope; the tip is pushed forward as the folded part of the sleeve is deployed. The maximum force generated is 4.9 N (0.5 kgf), versus a push force of up to 44 N (4.5 kgf) for a conventional scope. Pilot prospective clinical studies on 178 participants reported a success rate of 90% in reaching the cecum with no major complications (e.g., bleeding or perforation). All the patients were sedated as is routinely done in traditional colonoscopy, so no data about the pain associated with this technique are available (35).

With the exception of the Endotics System, control of tip deflection in all of the above (and in traditional endoscopes) is accomplished by wires running through the length of the device. That no thinner devices have been reported indicates that these wires (combined with optics and working channels) appear to impose a lower bound of approximately 10 mm on colonoscope outer diameter. However, as noted by Tumino et al. (32), pulling rather than pushing the endoscope might enable a dramatic reduction of shaft diameter. In a study by Valdastri et al. (36), magnetic steering and control were applied to an endoscopic device containing a tip-mounted magnetic camera (diameter 11 mm, length 26 mm) connected to an external control box by a 5.4-mm-diameter multilumen soft tether. This connection was used for insufflation, passage of a flexible tool, activation of a lens-cleaning mechanism, and operation of the vision module. The external magnet was held by a 7-DoF robotic arm controlled in real time by the endoscopist. A magnetic field sensor was also embedded in the device head to enable localization and closed-loop control. This method of generating a magnetic pull force at the tip allows the tether to be as small and light as possible and means that it does not have to push against the colon wall; consequently, bending stiffness and mass can be significantly reduced without a reduction in diagnostic or therapeutic capabilities in comparison with a standard colonoscope. The device has been tested in animal trials with promising results, and human trials are planned.

One final noteworthy locomotion mechanism is designed for cecal intubation (rather than painless endoscopy) in cases in which standard colonoscopy has failed. The Endo-Ease™ from Spirus Medical Inc. (Stoughton, Massachusetts) (37) consists of a 90-cm disposable flexible plastic overtube with a 5-mm soft spiral thread at its tip. The overtube is designed with a 13-mm inner diameter to carry a variable-stiffness pediatric colonoscope. Clockwise rotation of the overtube, which mimics the motion of a corkscrew, pleats the bowel onto the external surface of the tube. A preliminary clinical trial on 22 patients with incomplete colonoscopy because of redundant colons reported a cecal intubation rate of 92% with a median time of 14.2 min and no complications.

2.1.3. Summary and perspectives on painless flexible endoscopes. A common theme in reducing the pain associated with standard colonoscopy appears to be shifting the location of propulsive force application from the base of the device outside the patient (i.e., pushing) to the tip of the colonoscope (i.e., pulling). The latter can result in a better alignment of the direction of the applied force with the desired direction of forward tip motion. Several devices have demonstrated that this method can reduce forces applied to the colon wall during insertion, and these reduced forces are believed to correlate with reduced pain and a reduced risk of colon perforation. Diverse methods for applying tip forces have been proposed, ranging from pneumatic pressure (30, 34, 35) to robotic locomotion (32) to magnetic fields (36). Although it remains to be seen which of

these technologies will achieve market penetration and widespread clinical use first, replacing the stiff instrument body with a thin tether (32, 36) appears advantageous.

An alternative approach toward reduction of looping involves showing the current 3D shape of the scope as the endoscopist advances it into the colon. ScopeGuide® CF-H180DL, a commercially available endoscopic system from Olympus (Tokyo), integrates magnetic tracking into a standard colonoscope and provides a real-time rendering of the scope shape in free space on a secondary display. A recent study comparing this platform with standard colonoscopy reported a significantly shorter time for the instrument to reach the cecum and significantly lower pain intensity during the examination (38).

With regard to shortening the learning curve, computer-aided or computer-guided techniques (22, 30, 32, 34, 36, 38) have the potential to make colonoscopy easier; nursing staff may even be able to conduct the examinations. Such ease of use would enable the technology to meet the increasing demand for the procedure that will likely result from (*a*) the growing older population and (*b*) the willingness of more of the population to undergo screening owing to a reduction in real or perceived pain and discomfort.

A significant common disadvantage of both conventional and novel colonoscopes is the need for bowel preparation. An innovative device addressing this is ClearPath™ from EasyGlide, Ltd. (Kfar Truman, Israel) (39), which consists of a control cabinet and a disposable unit. The control cabinet includes a peristaltic pump, a controller, and a pinch valve that enables control of suction. The disposable element consists of a multilumen, custom-made, extruded tube. This has two channels, one that supplies water for irrigation and one that provides suction, and a head that attaches firmly to the tip of the colonoscope. When attached, ClearPath adds approximately 6 mm to the diameter of the colonoscope. Water for irrigation flows through four 0.6-mm nozzles in the distal head, and debris are evacuated through a single 18-mm^2 cross-sectional aperture. Preliminary animal trials on partially prepared pigs demonstrated effective intraprocedural colon cleaning with no immediate mucosal damage, acute complications (e.g., perforation), or delayed adverse consequences.

An alternative approach for cleaning the colon during colonoscopy is proposed by Fritscher-Ravens et al. (40). It consists of a disposable soft-tipped catheter with a water jet spray that can be advanced, under direct vision, through the accessory channel of the scope into the fecal matter. This way, when water is pumped through, even impacted stool can be broken up into slurry. The catheter tip has four radial nozzles through which the water is pumped. The water and the broken-up stool are then flushed or suctioned out of the colon into a collection system. Trials on unprepared colons of anesthetized pigs demonstrated the effectiveness of this approach, although mucosal trauma, bleeding, perforation, clogging of the colonoscope channels, and electrolyte imbalance may limit its impact.

2.2. Image-Enhanced Endoscopy

As mentioned in Section 1.2, standard GI endoscopy is based on visible white-light image acquisition. However, this approach can fail to reveal important information (41). Studies have shown that even experienced endoscopists can miss up to 6% of advanced adenomas and up to 30% of all adenomas when using standard white-light colonoscopy (42). Other disorders, including Barrett's esophagus and dysplastic and early neoplastic changes that occur in specialized intestinal metaplasia, may not be readily identifiable using standard endoscopy. In addition, biopsy specimens obtained using standard endoscopy are prone to sampling error. Furthermore, because of patchy involvement of the mucosa in inflammatory bowel disease, pathology may be missed by standard white-light endoscopy even with the procurement of multiple random biopsy specimens. There

is clearly a need for newer endoscopic imaging techniques that easily differentiate normal from abnormal mucosa to guide biopsy collection, and, in some cases, perhaps even to eliminate the need to obtain biopsy specimens. The following subsections review several emerging enhanced imaging techniques, and the interested reader is also directed to the informative review by Sauk & Itzkowitz (43).

2.2.1. Chromoendoscopy. Chromoendoscopy is based on the application of various dye solutions to the mucosa of the GI tract, which enhance subtle mucosal changes that are difficult to perceive in standard endoscopy and which may assist in obtaining targeted biopsy specimens. This procedure is indicated for both lesion detection and lesion characterization, and its demonstrated efficacy has resulted in its incorporation into guidelines for surveillance in patients with long-standing ulcerative colitis (41). However, staining of the entire colonic mucosa remains a time-consuming process and may lead to operator-dependent results. New methods described in the following subsections aim to produce similar results without the need for staining.

2.2.2. Narrow band imaging. Narrow band imaging (NBI) uses filters to narrow projected light to blue (415-nm) and green (540-nm) wavelengths in order to generate a colored image. Blue-green light enhances superficial mucosal capillaries and mucosal surface patterns; greater absorption of illuminating bands by hemoglobin causes the blood vessels to look darker. Because the shape and density of microvessels change in neoplastic lesions, it has been theorized that NBI might improve the assessment of these lesions. From a technological perspective, this technique can easily be implemented with standard video endoscopy through the use of groups of red-green-blue LEDs (instead of white-light) in conjunction with a CCD and CMOS sensor—both of which are sensitive to a wide spectrum of light. If all LEDs are activated at the same time, they would provide white light. If all LEDs except those of one single color are switched off, the vision sensor can acquire a picture with information similar to that obtained via chromoendoscopy. As with chromoendoscopy, NBI is indicated for both lesion detection and lesion characterization. The results of initial studies on the detectability of colorectal neoplastic lesions using NBI have reported controversial opinions and conclusions; however, a recent meta-analysis of randomized trials comparing NBI and white-light endoscopy in patients undergoing screening or surveillance colonoscopy demonstrated that NBI does not increase the yield of colon polyps, adenomas, or flat adenomas, nor does it decrease the miss rate of colon polyps or adenomas (44).

2.2.3. High-definition gastrointestinal endoscopy. With the increased availability of miniaturized high-definition vision sensors for consumer products and the widespread use of high-definition and 3D endoscopes in laparoscopic surgery, the development of high-definition GI endoscopy was a natural step. High-resolution endoscopes with high-density CCD sensors (600,000–1,000,000 pixels) produce high-magnification images for the detection of microscopic abnormalities in tissue. They provide image enlargement up to 100 times compared with 30 times of standard endoscopes (41). In spite of this, a recent study (45) concluded that the differences between high-definition and standard colonoscopy for the detection of colonic polyps/adenomas was marginal, and that high-definition colonoscopy did not improve the detection of high-risk adenomas. In light of this, high-definition colonoscopy does not seem to be a game-changing technology. However, as costs are reduced, endoscopists will likely migrate to high-definition technology for the more visually appealing images it provides.

2.2.4. Autofluorescence imaging. With autofluorescence imaging, short wavelengths of light illuminate tissue, and this energy radiation excites endogenous fluorophores to emit light at longer

wavelengths. In the GI tract, autofluorescence imaging detects subtle changes in the concentrations of specific chemicals in tissue that have the ability to fluoresce when activated by specific wavelengths of light. Malignant tissue is associated with emission of relatively longer wavelengths of light (a shift from the green end of the spectrum toward the red). Thin-film optical filters and silicon photodiodes can be used to achieve miniaturized devices for selection and detection of different spectral bands (46). This technique, still in the early stages of development, appears to hold promise for lesion detection, although multicenter trials are still required to confirm its efficacy.

2.2.5. Confocal laser endomicroscopy. Whereas the aforementioned technologies assist in the macroscopic view of the lumen, confocal laser endomicroscopy (CLE) provides histologic views of targeted areas within the mucosa. CLE is available in two forms: eCLE (endoscope-based CLE), in which the measurement system is integrated inside a flexible endoscope (e.g., Pentax Medical Company, Montvale, New Jersey), and pCLE (probe-based CLE), in which the measurement system can be introduced though the operative channel of a standard flexible endoscope (e.g., Mauna Kea Technologies, Paris). The Pentax confocal endomicroscope provides microscopic sections of 475 μm × 475 μm, consisting of slices that each have a cross-sectional thickness of 7 μm and an imaging depth of up to 250 μm (47). The Mauna Kea probe-based confocal microendoscope has slightly lower resolution but faster image acquisition than the endoscope-mounted version. Whereas several studies (e.g., 43) have demonstrated that a smaller number of optical, rather than traditional, biopsies is required to achieve the same diagnostic result, the difficulty in obtaining good images via this technique, and thus its learning curve, has thus far prevented its wide adoption.

3. WIRELESS CAPSULE ENDOSCOPY

3.1. Commercially Available Capsule Endoscopes

The introduction of wireless capsule endoscopy (WCE) in 2000 (48) was a natural consequence of advances in miniaturization and efficiency of semiconductor technology. WCE entails the ingestion of a miniature pill-sized camera that moves passively through the digestive system and enables visualization of the GI tract without discomforts such as intubation, insufflation, or sedation, thus offering an appealing alternative to traditional flexible scope–based endoscopy. Once the patient has swallowed the capsule, he/she can go back to normal activities without needing to stay confined in a hospital room.

Over the past 10 years, owing to advancements in capsule-related research (publication rates have continuously increased) and widespread clinical use (more than 1 million capsules have been deployed clinically), WCE established itself as the gold standard for diagnosis of suspected diseases of the small intestine. These include obscure GI bleeding, angiodysplasia, Crohn's disease, celiac disease, polyposis, and tumors. Furthermore, whereas wireless capsule endoscopes have been developed for the esophagus and colon, they have not yet become the gold standard for those areas.

A wireless capsule endoscope consists of an external biocompatible shell, typically the size of a large antibiotic pill (11 mm in diameter, 26 mm in length), that contains a vision module, a control and communication unit, and an energy source. The vision module usually consists of an imager with LED-based illumination and an optical lens defining the field of view. A set of antennas is placed on the body of the patient to receive wireless data and, in some cases, to localize the capsule. The image stream is stored on a portable device outside the patient and downloaded

by the endoscopist at the end of the procedure. Software is provided to support the doctor in identifying suspicious lesions in the large number of pictures recorded (equivalent to 8 h of video).

Once swallowed, capsules are pushed through the GI tract via peristalsis and move at a rate of 1–2 cm min^{-1}. The time of passage through the entire GI tract is approximately 8–10 h, with approximately 1 h spent in the stomach, 4 h in the small intestine, and 5 h in the colon. The bowel preparation procedure is similar to that for traditional endoscopy, requiring ingestion of a strong laxative to ensure adequate bowel cleanness and facilitate progression of the capsule through the GI tract.

Since Given Imaging (Yokneam, Israel) released PillCam™ Small Bowel (SB) in 2001, several commercial capsules for the small intestine have become available. An example is the company's second-generation capsule, PillCam SB2. It has the same dimensions (26 mm long, 11 mm wide) as does the SB, with a wider angle of view (156° versus 140°) and an enhanced vision system that can produce 2 frames per second (fps) with uniform light exposure. Compared with images acquired by the SB, images from the SB2 have enhanced depth of view, sharpness, and resolution (49). An additional feature introduced in the SB2 is the ability to view images transmitted by the capsule in real time.

Another commercial capsule is the EndoCapsule (Olympus, Tokyo), which uses a high-definition CCD sensor instead of a CMOS sensor. It has a magnification capacity of 1:8, which enables physicians to identify villous atrophy with a sensitivity of 70%. Eight antennas (combined into one) provide high-quality radio frequency (RF) transmission, and the antenna receiving the strongest signal is used to localize the capsule position in the GI tract. As in PillCam SB2, an external monitor provides real-time image view capability while image-analysis software detects the color red, helping doctors identify bleeding in the small intestine. The diagnostic yield reaches 92.3%, 44.2%, and 12.9% for patients with ongoing-overt bleeding, obscure-occult bleeding, and past bleeding, respectively (50).

The commercial capsule with perhaps the most innovative wireless communication method is the MiRo capsule (IntroMedic, Seoul, Korea), which uses a proprietary electric field propagation technique whereby the human body is used as a conductive medium for data transmission. This method reduces power consumption compared with traditional RF technology, enabling longer battery life (11 h compared with 8–9 h for other capsules) and more images to be transmitted (3 fps versus 2 fps for other capsules). Another advantage of this data transmission method is that image compression is no longer required, enabling visualization of fine structural details of the intestine surface including villi and vasculature (51).

The most recently introduced commercial device is the OMOM capsule (Jinshan Science and Technology Group Co., China), which has been widely tested in China. It has features similar to those of PillCam SB but is slightly larger in size (27.9 mm long, 13 mm in diameter). The main advantages are that it offers an adjustable image format, variable image capture sampling frequency and light intensity, and the option of automatic or manual exposure and white balance control (52).

With respect to diagnostic capabilities in the small intestine, one can compare WCE with the alternative of balloon enteroscopy. WCE demonstrates a higher sensitivity (90.6% versus 65.6%) and diagnostic yield (71.9% versus 65.9%), the latter of which is defined as the likelihood that a test or procedure will provide the information needed to establish a diagnosis (53). The primary advantage of enteroscopy in comparison with WCE is that it is able to collect biopsy samples and deliver treatments.

The main potential complication of WCE is the risk of capsule retention, which is usually caused by an intestinal stenosis. Patients with Crohn's disease or those who use nonsteroidal anti-inflammatory drugs are at higher risk of capsule retention. A capsule designed to address this is Given Imaging's Agile capsule, which is equipped with a small RF tag (2 mm × 12 mm)

contained within a radio-opaque lactose and barium biodegradable (after 30 h) casing that matches the dimensions of a standard capsule. This device enables the physician to verify adequate capsule passage before introducing the standard, nonbiodegradable capsule in patients with known or suspected strictures (54).

The reach of WCE has also been extended beyond the small intestine to the esophagus and colon. The most recent dedicated esophageal capsule, Given Imaging's PillCam ESO2, was introduced in 2007. It is equipped with two cameras (one at either end) and is capable of acquiring 18 fps for 30 min with a view angle of 169°. The high frame rate and dual-camera approach enable the capsule to cope with fast transit in the esophagus (10 s in a standard patient). This device yielded higher detection rates than esophagogastroduodenoscopy did for suspected Barrett's esophagus, with a sensitivity of 100% and a specificity of 74% (55). However, WCE has not yet replaced esophagogastroduodenoscopy for the diagnosis and management of Barrett's esophagus in part because histological confirmation is not possible. Also, recent studies provide reason to question whether WCE will be sufficiently cost effective in this application (56).

The most advanced capsule developed specifically for the colon is Given Imaging's PillCam Colon 2. Like the ESO2, it has two cameras and a wide angle of view (172°). To enhance colon coverage, conserve battery energy, and optimize video length, the capsule captures images at an adaptive frame rate, between 4 fps when it is (approximately) stationary and 35 fps while it is in motion. Until small bowel images are detected and the adaptive frame rate mode activated, the capsule works at a low rate of only 14 images per min. A preliminary Europe-wide study (57) enrolling 100 patients obtained a sensitivity of 84% and specificity of 64% in polyps ≥6 mm, and a sensitivity of 88% and specificity of 95% for polyps ≥10 mm. Despite these encouraging results, both sensitivity and specificity must rise to well above 90% to be comparable with the sensitivity and specificity traditional colonoscopy. Thus PillCam Colon 2 cannot yet be considered a replacement for screening colonoscopy. A table comparing all the commercial wireless capsule endoscopes discussed in this section is shown in **Figure 4**.

	PillCam SB2	EndoCapsule	MiroCam	OMOM	PillCam Colon 2	PillCam ESO2
Photo						
Diameter	11 mm	11 mm	11 mm	13 mm	11.6 mm	11 mm
Length	26 mm	26 mm	24 mm	27.9 mm	31.5 mm	26 mm
Weight	3.4 g	3.8 g	3.4 g	6 g	2.9 g	3.4 g
Frame rate	2 fps	2 fps	3 fps	0.5–2 fps	4–35 fps	18 fps
Image sensor	CMOS	CCD	CCD	CCD	CMOS	CMOS
Field of view	156°	145°	150°	140°	2 × 172°	2 × 169°
Illumination	6 white LEDs	6 white LEDs	6 white LEDs	6 white LEDs	2 × 6 white LEDs	2 × 6 white LEDs
Antennas	8	8	9	14	8	8
Real-time view	RT viewer	VE-1 viewer	Microviewer	RT monitoring	No	No
Recording time	8 h	9 h	11 h	7–9 h	10 h	30 min
FDA approval	Yes (2005)	Yes (2007)	No	No	No	Yes (2007)

Figure 4

Comparative table for the commercially available wireless capsule endoscopes. Abbreviations: CCD, charge-coupled device; CMOS, complementary metal-oxide semiconductor; fps, frames per second; LED, light-emitting diode; RT, real-time.

In view of the existing commercially available WCE technologies, one can conclude that the only region of the GI tract where WCE has succeeded in becoming the gold standard is the small intestine. The primary reason for this is that the small intestine is so long and so deep inside the body that flexible endoscopy cannot be accomplished with standard colon or esophageal/stomach scopes. Despite clear patient comfort benefits provided by esophageal and colon capsules, the fact that they are easy for the physician to use, and the fact that they provide reasonable visualization, they have not yet replaced traditional endoscopy because (*a*) their diagnostic accuracy is not yet equivalent to conventional techniques; (*b*) they are currently more costly than traditional endoscopes, which can be reused many times; and (*c*) they are not yet able to interact with tissue to collect biopsy samples or deliver therapy.

In summary, these are the main limitations of the commercially available capsule endoscopes:

- **Passive locomotion.** It is desirable for the endoscopist to be able to move the camera view arbitrarily as desired rather than relying on peristalsis to drive the capsule. Often the endoscopist wants to obtain multiple view angles and move forward and backward in the vicinity of a suspicious lesion.
- **No means of lumen diameter adaptation.** The need for swallowability requires the capsule to be small. Although a swallowable size matches the diameter of the small intestine well, it is usually not possible to ensure visualization of the entire surface area when the capsule reaches the stomach or the large intestine. Without a mechanism to create space (i.e., the purpose of the insufflation used in conventional colonoscopy), polyps may remain hidden within the folds of the deflated lumen, resulting in false-negative diagnoses.
- **Lack of tissue interaction.** Polyp clipping and biopsy collection are key advantages of conventional endoscopy versus WCE.

To address these limitations and endow wireless capsule endoscopes with advanced capabilities, researchers are pursuing numerous novel designs and innovative strategies, which are the subjects of Sections 3.2–3.4.

3.2. Advanced Sensing Methods

Advanced sensing methods for WCE are progressing along three distinct lines of inquiry. One is advanced image-based approaches, which seek to enhance visualization of the GI tract. Another is non-image-based sensing, i.e., the ability to sense physiological parameters. Lastly, the capsule position must be known, so that sensor measurements can be associated with specific GI tract locations.

3.2.1. Image-based sensing and processing. It is challenging for capsule endoscopes to provide the same imaging performance (in terms of, e.g., color resolution, spatial resolution, and frame rate) as a flexible endoscope. Although lateral size and packaging constraints may be comparable, power and data transmission bandwidth currently limit the performance of WCE-based imaging. In flexible endoscopy, wire-based transmission of images can easily reach hundreds of megabits per second (58), and power can be supplied through the scope. For WCE, the power available is determined by onboard battery capacity, and the wireless data transmission rate is on the order of a few megabits per second (59). Therefore, in all capsule endoscopes, image quality must be sacrificed to some extent to satisfy bandwidth constraints and to limit power consumption to a level at which the capsule can continue to function for the duration of its passage through the region of interest.

These considerations affect all components of the video signal chain, from the pill-based camera to the display. Assuming $N \times M$ is the image resolution in pixels and each pixel is P bits, a

single-color image has a payload of $PL = 3 \times N \times M \times P$ bits, where the factor 3 takes into account the red-green-blue pixel triplet. Depending on the desired frame rate *FR*, the required data rate for a single image becomes $DR_I = PL \times FR = 3 \times N \times M \times P \times FR$. This data rate must match the available telemetry bandwidth DR_T. To meet this goal, a compressor can be used to reduce DR_I by a factor *CR*. In the end, the equation that must be satisfied reads as follows:

$$DR_T = \frac{3 \times N \times M \times P \times FR}{CR}. \quad (1)$$

A flexible endoscope usually has a *FR* of 25 fps and a resolution of at least 500 × 582 pixels. Compression algorithms purposely developed for WCE, thus optimized in terms of power consumption [typically on the order of a few milliwatts (60)], can reach a *CR* ranging from 16 [in the case of colon images, which are richer in small features (61)] to 25 [in the case of gastric images (62)]. Concerning DR_T, 20 Mbps are claimed by Lee et al. (63) for a novel telemetry system purposely designed for WCE. As for the imaging chip, off-the-shelf chips optimizing the trade-off between image quality and power consumption are not available. This is mainly because current chips are designed for the consumer electronics market, where power consumption and data rate are not the primary considerations. A possible approach to minimizing the data payload involves lowering the image resolution while widening the dynamic range. A 320 × 240 10-bit pixel array with a 60-dB dynamic range, consuming less than 40 mW, was presented by Vatteroni et al. (64). The dynamic range can even be increased up to 112 dB through the use of a linear-logarithmic CMOS pixel, as suggested by the same authors in a subsequent study (65).

Taken altogether, these technologies allow clinicians to achieve imaging performances comparable with those offered by a flexible endoscope, even if power consumption and battery lifetime may still be a relevant downside for WCE, as better detailed in Section 3.4. A detailed description of the complete signal chain typical for a wireless capsule endoscope and the required electronic backbone was provided by Cavallotti et al. (66), who demonstrated a real-time 19-fps video capsule.

It is generally agreed that 25 fps, i.e., providing a fluent image stream on the display, is a desirable target for WCE if the physician is to actively control capsule motion (see Section 3.3) in real time. Furthermore, it appears possible to integrate most of the image-enhanced techniques described in Section 2.2 into a WCE platform, despite the fact that examples of doing so have appeared only recently in the literature (67). It may even be possible in the future to provide imaging capabilities in a capsule that exceed those of standard clinical endoscopes by adding, for example, stereoscopy (68), controllable focusing (69), or panoramic viewing capabilities (70).

Lastly, a highly useful adjunct to advancements in imaging technology consists of image analysis and postprocessing. Because a typical small intestine capsule captures approximately 55,000 images per procedure (71), it is useful to provide automatic ways to identify images to which a physician should devote particular attention. Automatic detection of Crohn's disease was reported by Bejakovic et al. (72), whereas the motion-descriptive characteristics were used by Szczypinski et al. (73) to indicate video fragments that exhibit segmentary contractions, peristalsis, and areas of capsule retention. Also, a 3D reconstruction of the colon from capsule images was proposed by Fan et al. (74), whereas an algorithm for lumen detection intended for active locomotion control was proposed by Zabulis et al. (75).

3.2.2. Physiological parameter sensing. Given that the complexity of integrating cameras into capsules far exceeds the complexity of integrating other sensors, it is surprising that there has not been more research activity in this area. The only relevant commercial product available with a sensor other than an imager is the Bravo pH Monitoring System (76) for diagnosing GERD; initially commercialized by Medtronic, Inc., it was recently acquired by Given Imaging. In terms

of research prototypes, the first telemetric capsule to measure intragastric pH dates back to 1965 (77). This device, also known as the Heidelberg capsule (8 mm × 18 mm), consisted of a discrete-component Hartley oscillator in which the carrier frequency was modulated by a pH-sensitive capacitor. More recently, an innovative impedance-pH wireless capsule capable of discriminating between acidic and nonacidic reflux in GERD was reported by Gonzalez-Guillaumin et al. (78), whereas wireless pressure monitoring from the gastric cavity was demonstrated by Valdastri et al. (79). An infrared-based capsule to identify and localize GI bleeding was reported by Liu et al. (80). Several systems are able to acquire and manage multiple parameters (81); perhaps the most complex of these is an electronic "tongue" for the characterization of GI fluids (82).

3.2.3. Capsule position sensing. Identifying the physical location of each capsule image is important in both diagnostic and therapeutic applications of WCE. However, it is challenging because the GI tract is a long tubular structure that folds upon itself many times and is free to move within the abdominal cavity. Two kinds of localization are possible: (*a*) obtaining the absolute position of the capsule in space, and (*b*) determining the capsule position relative to the GI tract structure in which the capsule resides.

The first kind of localization (absolute position and possibly orientation in Cartesian space) is the most straightforward from a technical perspective. One method of obtaining it is by RF triangulation, whereby an external sensor array measures signal strength of capsule transmissions at multiple points. This system is implemented in the Given Imaging platforms (83) and can produce an average experimental error of 37.7 mm (84). Another approach is magnetic tracking of a small permanent magnet mounted in the capsule using an external magnetoresistive sensor array. A system based on this approach, known as 3D-MAGMA (Matesy GmbH, Jena, Germany), collects individual measurements at 50 Hz, before filtering and processing, to provide position information with an accuracy of 5 mm and 2° at a rate of 2 Hz (85). Similar results were also obtained with a wearable Hall effect sensor-based system (86). Another possible localization approach involves the use of ultrasonic pulses emitted from outside the body and echoed by the capsule (87). Information about orientation of the capsule can be obtained by placing an inertial sensor on board, as proposed by Ciuti et al. (88).

With respect to the second kind of localization mentioned above (i.e., localization relative to specific GI structures), recent computer vision approaches have been employed. Feature tracking across images, vector quantization, component analysis, and neural networks have been used to classify images as belonging to the upper or lower GI tract with an accuracy of 95% (89). An energy-based event boundary detection algorithm has been used to identify different digestive organs on the basis of their unique patterns of muscular contraction, with an accuracy of 76% (90). An advantage of image-based techniques is that they can provide estimates of capsule position without any additional hardware onboard the capsule, although there is still clearly much work to be done to enhance their accuracy in making specific position measurements.

3.3. Actuation for Capsule Locomotion and Therapy Delivery

A great deal of attention has been paid in the research community to active locomotion of wireless capsule endoscopes, with the motivation of returning active control of camera position to the endoscopist. In Sections 3.3.1–3.3.4, we describe both onboard locomotion techniques (whereby all components enabling locomotion reside within the capsule) and external locomotion techniques (whereby forces and torques are transmitted to the capsule from outside the body, generally via magnetic fields). Also, because the actuation methods for biopsy sampling and therapy delivery share similarities with locomotion actuation, we include these as well.

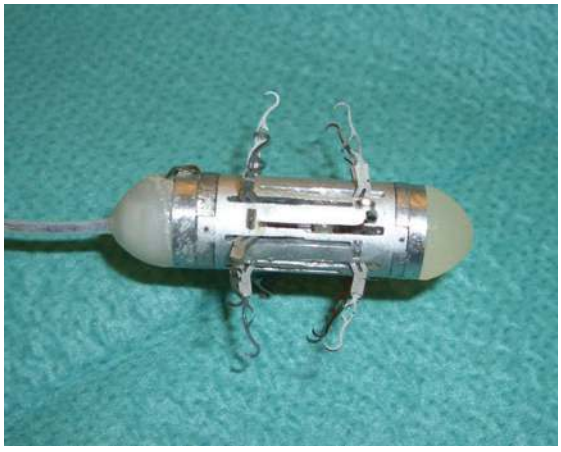

Figure 5

A prototype of a 12-leg capsule for active locomotion and tissue distension in the colon (98).

3.3.1. Onboard locomotion. Perhaps the simplest mechanism for onboard locomotion is vibratory actuation, obtained by a motor with an asymmetric mass on the rotor, which aids forward progression of the capsule along the GI tract by reducing friction (91). Other mechanisms inspired by biology have also been employed. These include earthworm-like (92), cilia-like (93), and legged (94) locomotion systems actuated by cyclic compression/extension of shape memory alloy (SMA) spring actuators.

Drawbacks of SMA actuation include high power consumption, low efficiency, low speed (due to required heating and cooling cycles), short functional lifetimes, and poor controllability. To address this, alternative actuators were developed. One design uses magnetic attraction/repulsion and consists of a fixed permanent magnet and a linearly movable solenoid (95). A variation on this basic idea uses a motorized rotating magnet coupled with a linearly movable magnet that can provide propulsive force to move a capsule forward owing to directional friction of the polymeric outer shell of the capsule (96). Another approach is to use a miniature direct-current (DC) brushless motor linked to a linear mechanism that is attached to fins moving relative to the capsule body. This "paddling" technique, whereby the leg-like fins travel the length of the capsule, provides high reliability and velocity (8–20 cm min^{-1}) but does not provide bidirectional motion (97).

Fully bidirectional legged locomotion has been developed over the past 10 years at Scuola Superiore Sant'Anna through a series of increasingly sophisticated legged robot prototypes. The latest design (11 mm in diameter and 25 mm long, represented in **Figure 5**) (98) is able to distend tissue in a uniform manner with six points of contact at each end of the capsule (enhancing camera visibility); these points are made by 12 optimized bioinspired legs (99, 100). The capsule has the ability to travel the length of the colon at 5 cm min^{-1}, passing fully through it without insufflation in a length of time comparable with that in traditional colonoscopy. The total pulling force that enabled the capsule to withstand peristalsis and expand the surrounding tissue was 3.6 N.

All the aforementioned locomotion mechanisms were specifically developed for the colon, i.e., a collapsed tubular environment. A similar tubular environment is present in the esophagus, but there the main concern is slowing down the capsule rather than actively propelling it forward. A capsule that incorporates bioinspired gecko-like microfeatures at the ends of three legs has been developed specifically for this district (101). In contrast to the intestine and esophagus, the stomach is a large, collapsed cavity that requires 3D locomotion. This requirement prompted the development of a submarine-like capsule that is ingested by the patient after he/she drinks 1 liter

of water (which stays in the stomach for 30 min). This capsule uses four independent propellers actuated by embedded DC brushed motors, and its speed and direction can be controlled with a joystick. Other possible methods of swimming in the water-filled cavity include flagellar or flap-based swimming mechanisms (102, 103).

As the number of onboard actuators increases, wireless drivers that can receive instructions from the operator and drive the motors accordingly in real time play an important role in capsule design. An example of a flexible platform composed of off-the-shelf electronic components and a real-time operating system was described by Susilo et al. (104). This platform was used to drive some of the robotic capsules discussed in Sections 3.2–3.4 (70, 98, 103, 105–107). A different approach is to develop a specific silicon integrated circuit to drive onboard actuators, as done by Alonso et al. (108), thus optimizing size and power consumption.

Although many innovative mechanisms for onboard capsule locomotion have been reported, there remain numerous challenges in moving them from research laboratories to the clinical setting. Some prototypes have not yet been reduced to swallowable dimensions, and others face power supply challenges due to actuator selection. All will require reliability testing and sterilization procedures to be defined. Although these challenges are significant, all seem to be in principle surmountable, and it is reasonable to expect that capsules with onboard locomotion systems will eventually make their way into clinical use.

3.3.2. External locomotion. An approach that may have a somewhat quicker path to clinical implementation, because it does not require the construction of miniature actuators and mechanisms, is the use of external locomotion strategies. The main external locomotion approach developed thus far is the use of magnetic fields to impart forces and torques to the capsule. The idea is that a large magnetic field is created near (but outside) the patient, either by electromagnet(s) or permanent magnet(s). Then onboard the capsule, a much smaller magnetic field is created. The net result of the interaction between this small field and the large externally created field is that the capsule experiences forces and torques. This approach can remove the need for onboard actuators, mechanisms, and batteries, in favor of a small onboard magnetic field generator, e.g., a permanent magnet. Magnetic actuation has also been developed for other medical devices, ranging from catheters (e.g., the Niobe™ Magnetic Navigation System from Stereotaxis) (109) to microscale robots (110).

Generating the small magnetic field onboard the capsule has been accomplished by three orthogonal internal coils (111), a magnetic shell (112), and simply via permanent magnets (88). Given Imaging has investigated the use of a handheld external magnet to translate and orient a capsule in the upper GI tract using a modified version of PillCam Colon, which was half-filled with magnets. This demonstrated the feasibility of magnetic steering but revealed that more research was required to increase the reliability and accuracy of magnetic control (113). An alternative technique for generating the external magnetic field, jointly developed by Olympus and Siemens, involved use of an MRI scanner to create the field and field gradients (114). An approach that lies somewhere between the simplicity of a handheld magnet and the complexity of an MRI scanner is the use of a 6-DoF industrial robotic arm to hold and manipulate a large permanent magnet outside the patient (88), as represented in **Figure 6*a***. This method provides finer control and higher diagnostic reliability than manual operation (115).

The Stereotaxis system has also recently been successfully applied to magnetic capsule steering. In vivo tests performed with 3D fluoroscopic localization showed that it demonstrated an accuracy of 1° in orientation but had limited translational capabilities (112). Furthermore, recent studies show that use of a dedicated levitation system, combined with the use of diamagnetic material

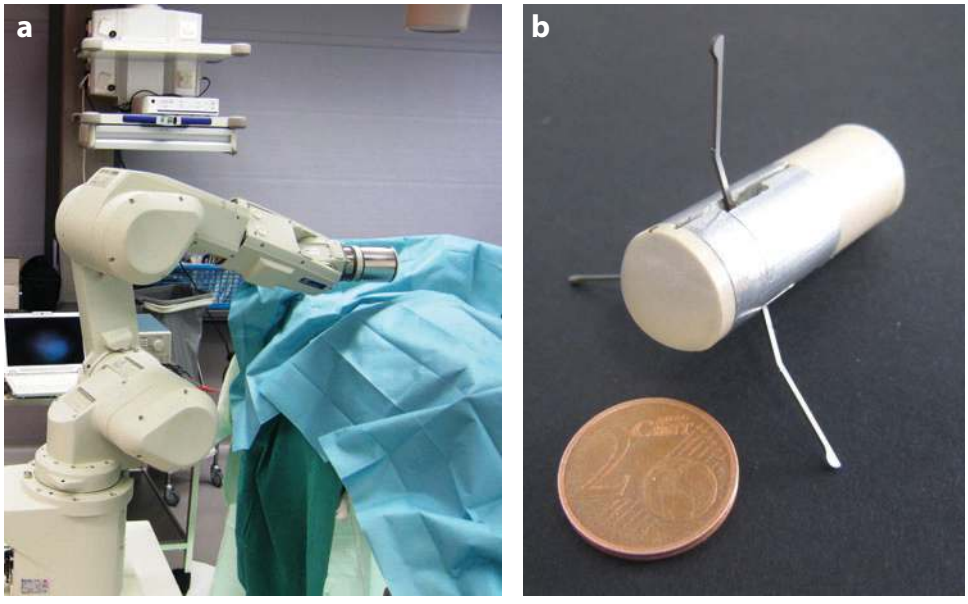

Figure 6

(*a*) The 6-DoF robotic arm described in Reference 115, holding a permanent magnet for controlled locomotion of an endoscopic capsule. (*b*) The hybrid locomotion capsule described in Reference 107. The three legs can span 180° from front to back and vice versa.

(such as bismuth) in the capsule shell, can enhance motion stability and withstand peristaltic force (1.5 N) (116).

A promising new approach for magnetic locomotion in a liquid-filled environment (particularly the stomach) consists of exploiting the vibration of a permanent magnet surrounded by an alternating-current magnetic field. Placing a fin with an embedded magnet at the bottom of a capsule can control the direction and speed of this swimming robot by modifying the alternating current that generates the external magnetic field (117).

The main downside of external locomotion is the lack of ability to distend tissue away from the capsule, in order to enable the capsule to move, or to improve visualization of the entire intestine surface. To address this, a hybrid internal/external system was developed whereby the capsule had internal actuated legs along with simultaneous external magnetic locomotion (107) (**Figure 6*b***). Limiting the use of the onboard mechanism to situations in which external locomotion is not effective reduces the power consumed by the capsule, extending battery life.

3.3.3. Biopsy sampling. Collecting biopsy samples is a fundamental procedure in GI diagnosis. Standard biopsy currently requires approximately 1 mm^3 of tissue samples to be analyzed within 1–2 h of extraction. This is a challenging requirement for a wireless capsule because of the volume of material required, the need to collect this material from a specific location, and the need to retrieve it from the body rapidly. Attaching a tether to the capsule assists with both biopsy collection and retrieval but also blurs the line between capsule and colonoscope. The Crosby capsule, developed in 1957, was the first tethered device for GI tract biopsy collection. Today, it is used mainly in children owing to its small size. Suction applied to the tube triggers an onboard mechanism that causes a spring-loaded knife to sweep across an aperture in the capsule, cutting away any mucosa protruding into the aperture and collecting the sample in a chamber (118).

The first example of a wireless biopsy capsule consists of a rotational tissue-cutting razor attached to a torsional spring and constrained by a paraffin block. When the paraffin block melts by heating, the razor is released, collecting a tissue sample (119). Another compact solution, designed to be integrated into the MiRo commercial capsule, consists of a microbiopsy spike with protruding barbs, a spring, and a micromechanism actuated by SMA (120). The device is designed to operate sequentially so that the tissue sampling, sealing, and fixing are achieved in one operation. However, it is not yet clear whether such a mechanism will be able to collect a sufficient number or volume of samples for accurate external histological analysis. In all the proposed solutions, system stabilization during sampling remains one of the main problems.

A recent design, presented by Simi et al. (121), takes advantage of magnetic fields both to stabilize the capsule during sampling and to operate the mechanism. Two couples of cylindrical, diametrically magnetized permanent magnets onboard the capsule act as magnetic torsional springs. For each couple, one magnet is integrated into the chassis and cannot move, whereas the other is fixed on a shaft with a razor blade and is free to rotate under the effect of magnetic torque. The coupling between the fixed and rotating magnets forces the blade to close the lateral hole (**Figure 7*a***). When a strong external magnetic field is provided (i.e., when a permanent magnet is placed close to the patient's abdomen), the magnet mounted on the shaft rotates together with the blade, exposing the cavity (**Figure 7*b***). At the same time, the device is stabilized against the mucosa, promoting tissue penetration inside the chamber. When the external magnet is gradually taken away from the capsule, the rotating magnet-blade assembly moves back to its original position, cutting the tissue. Thanks to such an innovative magnetic mechanism, battery and actuators are not required onboard, thus allowing a compact size (9.5 mm in diameter and 17 mm in length; **Figure 7*c***) and potentially extending the reach of this technology to pediatric patients.

3.3.4. Therapy delivery. A main limitation of current capsule endoscopes is that they cannot treat the lesion as they discover it. Treatment delivery requires a subsequent flexible endoscopic procedure. Providing clinical capsules with interventional and therapeutic capabilities has the potential to make WCE a much more powerful weapon with which physicians can combat disease. It is theorized that the ability to deliver drugs directly at the source of the problem (e.g., colitis, Crohn's disease, cancer) will lower dosage levels and thus reduce unwanted side effects (122).

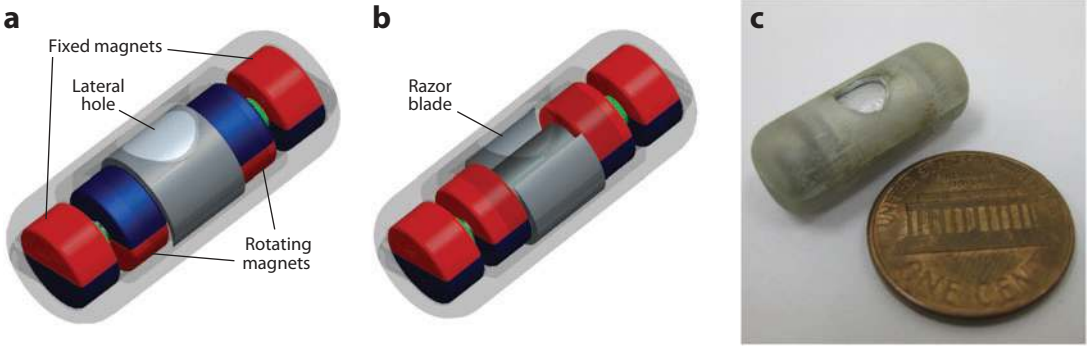

Figure 7

The magnetomechanic biopsy capsule described in Reference 121. (*a*) The coupling of the fixed and rotating magnets forces the razor blade to close the lateral hole. (*b*) An external magnetic field may trigger the complete rotation of the rotating magnets and the razor blade, thus opening the lateral hole. (*c*) A picture of the biopsy capsule prototype.

Modern drug delivery capsules include the InteliSite™ capsule (Innovative Devices, LLC, Raleigh, North Carolina), which uses SMA wires to align perforated inner and outer sleeves to disperse a drug through the holes (123); the Enterion™ capsule (Phaeton Research and Pharmaceutical Profiles, Nottingham, United Kingdom), which can deliver a treatment agent using a piston/spring actuation system (124); the blind multisensorized iPill capsule (Philips Research); and the MAARS (Magnetic Active Agent Release System; Matesy GmbH, Jena, Germany) capsule, which can be magnetically localized and also disassembled to release a drug contained within it (125). Another device that is actuated magnetically for drug release is a soft capsule for the stomach with an axial extra degree of freedom, which can perform drug injection or biopsy sampling (126). In a study by Pi et al. (127), a combustion process controlled by a microfabricated thruster produces a sufficient amount of gas to force medication out of the drug reservoir. Localized drug delivery was achieved by magnetic retention under biplane fluoroscopy in a study by Laulicht et al. (122), in which a drug-loaded magnetic capsule was held in a specific position of the GI tract. A future prospect for drug delivery over time is the use of mucoadhesives to stably attach the capsule to a desired point in the GI tract without the need for magnetic fields, as suggested by Pensabene et al. (128). This adhesive technology is reversible, and detachment occurs after a certain time that can be trimmed by adjusting the polymer formulation.

In bariatric procedures, a volume-adjustable pill, capable of inflation and deflation of a balloon, can be used as a noninvasive therapeutic device to reduce hunger in obese patients. A wireless system is used to control the gas generated as the product of a chemical endothermic reaction (129).

The only example of a wireless surgical capsule reported in the literature was developed for a controlled release of a surgical clip designed to stop localized bleeding in the colon. This device uses embedded permanent magnets, enabling external locomotion via magnetic fields, and a preloaded SMA clip, which can be fired by the action of a miniature integrated DC brushless motor on the basis of a wireless command (106). The capsule during an in vivo experiment in a porcine model is represented in **Figure 8**.

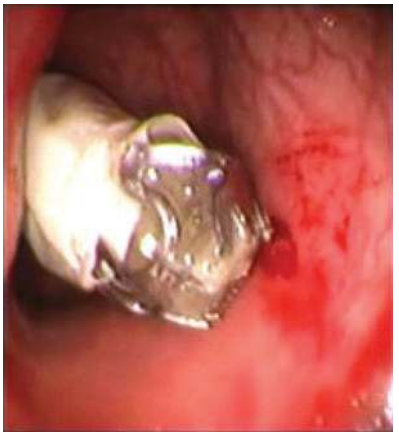

Figure 8

The surgical clip–releasing capsule during an in vivo experiment on a porcine model. Bleeding was induced on the inner colon wall, and a clip-releasing capsule was manipulated by magnetic fields to face the bleeding with clip jaws. Once the capsule reached the desired position, a clip-releasing command was sent by wireless communication, and the clip was released to stop the bleeding (106).

3.4. Advancement in Powering

Nearly all the aforementioned capsules require power. Actuators, cameras, sensors, and many other subsystems require electrical power. Commercial endoscopic capsules rely on silver-oxide coin cell batteries, which are the only batteries approved for clinical use in WCE. These batteries provide 3 V at 55 mAh for approximately 8 h, which implies an average power delivery of approximately 20 mW. For actuators requiring higher peak currents, lithium-ion polymer batteries are often used in prototypes. They have the highest energy density (approximately 200 Wh kg^{-1}) available in off-the-shelf batteries and are capable of supplying peak currents up to 20 times their nominal current. Often, actuation requirements call for larger batteries than capsule designers would prefer—particularly when robotic mechanisms are used (98). One potential way to improve this situation is to incorporate custom-shaped lithium-ion polymer batteries, which enable the battery to be designed to fill whatever space is available. However, advancements in battery technology are clearly needed. Experimental studies show that the addition of polymeric compounds [poly(ethylene glycol) dimethyl ether and polyethylene oxide] to the electrolytes significantly improves the structure and electrochemical behavior of electrodeposited molybdenum sulfide cathode materials, increasing microbattery capacity by a factor of 2.0–3.5 (130). Thus, there is reason to believe that increasingly powerful batteries will be developed in the near future.

Inductive coupling provides a means of wirelessly transferring power to a remote device and is becoming increasingly common in consumer electronics, as demonstrated by the success of companies such as Witricity Corp. (131). This technique was applied to WCE utilizing three internal coils with a ferromagnetic core, which derive power from a magnetic field established by an external solenoid coil. This solution is capable of providing 400 mW of power in a small size (1 cm^3), enabling integration into a wireless capsule endoscope (132). A similar solution was able to achieve 490 mW by keeping the compound vector of the energizing magnetic field orthogonal to the cross section of the power-receiving coil (133). The main advantage of the inductive coupling approach involves providing an unlimited amount of energy to the capsule, whereas the main drawback is the need of external coils that may interfere with patients' movements. Another potential future power source, which promises dramatic improvement in energy density, is the use of chemofluidic phase transition to generate pneumatic pressure from a liquid. This approach has been applied in the context of endoscopic capsules and has the additional advantage that waste gas can be expelled to the environment to provide insufflation (134).

In conclusion, enhanced batteries or alternative sources of power (e.g., inductive coupling or fluid power) are required to enable clinically applicable robotic capsules. A future potential solution to this problem may be to use the same kind of power the human body uses. This might one day be achieved by the integration of muscular tissues or cells fed by glucose and the dissociation of adenosine triphosphate, as suggested by Akiyama et al. (135). As with inductive coupling, this approach would theoretically provide a never-ending supply of energy.

4. CONCLUSIONS

A major objective for bioengineers working in the field of GI technologies is to find a practical method for mass screening of colorectal cancer that will be well tolerated by patients; such a method would dramatically reduce the mortality of the disease by early diagnosis. A new generation of flexible instruments appears poised to meet this challenge, owing to computer-aided painless locomotion techniques and enhanced diagnostic capabilities. An example is WCE, which, despite becoming a gold standard in the small intestine, has yet to achieve similar success in the colon. To become an effective replacement technology for flexible endoscopy, WCE still requires

advancements in several features. Although streaming images and controlled locomotion seem to be achievable with solutions already published in the scientific literature, tissue sampling and therapeutic capabilities have yet to reach maturity. Also, advancements in power are required for effective deployment of the current generation of wireless capsule robots. However, dramatic and unforeseen technological breakthroughs can happen. In particular, a promising alternative approach that may substantially replace traditional GI diagnostic techniques is represented by genetics (136). Genetic testing to help diagnose heritable GI cancer syndromes is already available, but its sensitivity still needs to be significantly improved. However, until such a paradigm-shifting technology becomes available, physicians will require methods to see inside the GI tract and to collect samples and deliver therapies to the correct locations. Advanced flexible scopes and wireless capsules have the potential to improve the way this is done and thus help physicians save lives.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Volume 14, 2012

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