

Title: Advanced endoscopic technologies for colorectal cancer screening

Authors: Obstein KL¹ and Valdastri P².

Running title: Advanced endoscopic technologies for CRC screening

(1) Keith L Obstein, Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN, 37232, USA

(2) Pietro Valdastri, STORM Lab, Department of Mechanical Engineering, Vanderbilt University, Nashville, TN, 37235, USA

Author contributions: Obstein KL, Valdastri P contributed to the concept and design, acquisition of data, analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and provided final approval of the version to be published; contributed to the concept and design, acquisition of data, analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and provided final approval of the version to be published.

Supported by the National Center for Research Resources, Grant UL1 RR024975-01, and is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Correspondence to: Pietro Valdastri, PhD, Assistant Professor, Department of Mechanical Engineering, Director of the STORM Lab, Vanderbilt University, 2301 Vanderbilt Place PMB 351592, Nashville, TN, 37235, USA. p.valdastri@vanderbilt.edu

Telephone: +1-615-875-6955 **Fax:** +1-615-343-6687

Received: Revised: Accepted: Published online:

Abstract

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide. Diagnosing colorectal has been increasingly successful due to advances in technology. Flexible endoscopy is considered to be an effective method for early diagnosis and treatment of gastrointestinal cancer; making it a popular choice for screening programs. However, millions of people who may benefit from endoscopic colorectal cancer screening fail to have the procedure performed. Main reasons include psychological barriers due to the indignity of the procedure, fear of procedure related pain, bowel preparation discomfort, and potential need for sedation. Therefore, an urgent need for new technologies addressing these issues clearly exists.

In this review, we discuss a set of advanced endoscopic technologies for colorectal cancer screening that are either already available or close to clinical trial. In particular, we focus on visual-inspection-only advanced flexible colonoscopes, interventional colonoscopes with alternative propulsion mechanisms, wireless capsule colonoscopy, and technologies for intraprocedural bowel cleansing. Many of these devices have the potential to reduce exam related patient discomfort, obviate the need for sedation, increase diagnostic yield, reduce learning curves, improve access to screening, and possibly avert the need for a bowel preparation.

© 2012 Baishideng. All rights reserved.

Key words: Endoscopy; Technology; Capsule colonoscopy; Colorectal cancer; Screening

Obstein KL, Valdastrì P. Advanced endoscopic technologies for colorectal cancer screening. *World J Gastroenterol* 2012;

Available from:

DOI:

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide with approximately 608,000 people dying each year^[1]. In the United States alone there are approximately 1.14 million people alive who have a history of CRC and 1 in 20 will be diagnosed with cancer of the colon or rectum in their lifetime.^[2] Unfortunately, this number is projected to increase by 62% by the year 2030^[3].

Diagnosing CRC has been increasingly successful due to numerous advances in technology. One of the paramount technological advances has been the ability to directly visualize the gastrointestinal (GI) tract (and provide therapy) with the flexible endoscope. The earliest flexible endoscope, completely based on optical fibers, was presented at the American Gastroscopy Society annual meeting in May 1957 by Hirschowitz^[4]. This achievement was inspired by a paper published in 1954, entitled "A flexible fiberscope using static scanning", by Hopkins and Kapani at the Imperial College of Science and Technology in London^[5]. Building on this history of technological innovation, and driven by breakthroughs in electronics, material science, computational capabilities, sensing, and actuation strategies, many novel GI devices and diagnostic techniques have emerged. In this review, we will discuss a set of advanced endoscopic technologies for CRC screening that are either already available or close to clinical trial; and have the potential to reduce procedure related patient discomfort and increase diagnostic yield.

LIMITATION OF STANDARD GI ENOSCOPY

Flexible endoscopy is considered to be an effective method for early diagnosis and treatment of GI cancer, thus is a primary choice for screening programs. Few complications are associated with this technique, with cardiorespiratory problems related to sedation and analgesia being the most common (0.03% to 20% incidence^[6]). Less frequent complications include, infection (0.2%

incidence^[7]), bleeding (0.2%-2.1% incidence) or perforation (0.1% incidence^[8]), which potentially require subsequent medications, transfusions, or endoscopic/surgical intervention to correct.

Based on the efficacy and low complication rate of flexible endoscopy, it is clear that the main clinical challenge facing GI endoscopy is one of distribution. Millions of people who may benefit from endoscopic CRC screening fail to have the procedure performed. The reasons cited include psychological barriers due to the indignity of the procedure, fear of procedure related pain, bowel preparation discomfort, and potential need for sedation^[9].

How rational are these fears? From a mechanical perspective, the endoscope consists of a long and fairly stiff (compared to the compliant colon) tube with a steerable head. The colonoscope must easily navigate the colon curves and traverse the intestinal environment efficiently--meaning that a colonoscope must be simultaneously stiff and compliant. If the colonoscope is too stiff, it will deform the colon wall significantly at turns; yet, if it is too compliant there will be undesired buckling^[10]. Since the colonoscope must be pushed from the back, while the tip is aimed along the lumen center, when the intestine bends, the shaft pushes against the colon wall until the lumen and its surroundings provide sufficient counter pressure to force the endoscope shaft to bend. This stretches the colon and often leads to "loop" formation, thus potentially causing substantial discomfort. In particular, looping occurs when the colonoscope continues to be advanced into the colon without a corresponding progression of the tip. This displaces the colon from its native configuration and stretches mesentery muscles. Looping of the endoscope has been shown to be responsible for 90% of the pain episodes in colonoscopy and increases the chance of tissue damage and perforation^[11]. Special maneuvers can be performed to minimize this effect, making colonoscopy a procedure that requires a great degree of training, technical skill, and experience to safely perform^[12, 13]. Despite these techniques, even expert endoscopists can not always prevent all challenges or complications;

partially because the flexible endoscope design is one of compromise and is not perfect for its intended purpose^[10]. Additionally, the need for a bowel preparation acts as a potential deterrent due to the unpleasantness of ingesting powerful medications to clean the intestine. A detailed discussion on bowel preparation is beyond the scope of this review and will only be discussed briefly.

TOWARD MECHANISMS ENABLING PAINLESS COLONOSCOPY

Several colonoscope modifications have recently been presented with the common goal of preventing excessive force application to the colon wall and consequent looping. These devices can be categorized into two groups: those designed purely for visual inspection (visual inspection devices), and those that contain internal channels through which interventional devices (i.e. biopsy, snare, needle, etc.) can be passed (interventional devices). In addition to flexible colonoscope modifications, wireless capsule colonoscopy is emerging as a “patient-friendly” alternative technique for visual inspection of the colon. In this section we will provide an overview of recent advancements in these three device categories.

Figure 1 The CathCam system, reprinted from [15], with permission from Elsevier.

Visual-inspection-only advanced flexible colonoscopes

An example diagnostic-only device is the CathCam, whose development has been supported by Ethicon Endo Surgery, Inc., represented in Figure 1. 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. The catheter is designed for single use, while 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 enable the system to provide suction, irrigation, and visualization. An accessory channel (2.8 mm in diameter) is provided for a looped guide wire (0.024-inch hinged lumen-seeking guide wire) that is advanced through the channel and into the lumen of the colon. The guide wire then serves to guide the catheter forward when the catheter is pushed^[14]. This device has demonstrated 30% to 40% peak force reduction in benchtop experiments and in live pigs, in comparison to standard colonoscopes^[15].

Figure 2 The Aer-O-Scope™ system, reprinted from [18], with permission from Elsevier.

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^[16], represented in Figure 2. 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 silicon 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. CO₂ is insufflated between the two inflated balloons, and gas pressure advances the vehicle balloon, endoscope, and a trailing supply cable. The supply cable on the endoscope/scanning balloon is a flexible polyurethane multi-lumen catheter, 5.5 mm in diameter, coated with a hydrophilic material, which supplies the electro-optical capsule (the scope) and its vehicle balloon with electricity, air, water, and suction. The volume of the vehicle/scanning balloon is pressure-regulated. The balloon is designed to adapt to the shape of the colon as it travels forward. The balloon has a large

predetermined maximal volume and thin wall (8 μm) that help it adapt to the shape of the colon in response to pressure exerted by the colonic walls. These features allow the balloon to maintain the seal with the colon wall, so that gas introduced on one side of the balloon does not escape to the other side. This allows a pressure gradient to develop from behind the balloon to in front of it during forward propulsion, and vice versa during withdrawal. Since the tip has no steering capabilities, an omnidirectional colonoscopic viewing system has been installed on the tip of the latest prototype^[17]. The Aer-O-Scope™ is intended to be used for diagnostic purposes and therefore does not have a working channel for therapeutic instruments. In a preliminary pilot feasibility study^[18], the Aer-O-Scope™ effectively intubated the cecum in 10 out of 12 subjects (83%) with an average time to cecum of 14 ± 7 minutes.

Figure 3 The Endotics™ system, image courtesy of Era Endoscopy.

Another approach, inspired by Geometer moths, is inchworm locomotion^[19]. Inchworm locomotion is similar to the motion utilized in double balloon endoscopy where there is lengthening and shortening along two anchor points (distal anchor and proximal anchor). The Endotics™ system (Era Endoscopy s.r.l., Pisa, Italy) effectively utilized inchworm locomotion and consists of a disposable robotic probe as 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 electro-pneumatic connector. The Endotics™ endoscopic device is represented in Figure 3. The head hosts both a vision system, including camera, Light Emitting Diode (LED) light source and channels for a water jet and air insufflation/suction. The operator can steer the head of the robotic colonoscope 180° in every direction, elongate the body of the probe in order to move it forward along the intestine, and can control rinsing, insufflation, and suction. A semiautomatic sequence of actions is implemented to move the probe like an inchworm, wherein two vacuum anchors located in the

proximal and distal ends of the probe are sequentially actuated between extensions and retractions of the central body. Experiments in a phantom model with embedded force sensors demonstrated 90% lower force application than conventional colonoscopy^[20]. A human study^[21] with 71 unsedated patients demonstrated that this system has a comparable diagnostic accuracy to colonoscopy, and does not require sedation. The frequency of successful procedures (i.e. reaching the cecum), the total procedure time, and the need for sedation were recorded in this study. In 13 cases (18%), the device was unable to reach the cecum and the average procedure time was 45.1 min \pm 18.5 min for the Endotics™ system compared to 23.7 min \pm 7.2 min for traditional colonoscopy ($P < 0.0001$).

Currently, the lack of tissue interaction makes it improbable that diagnostic-only devices will completely replace traditional colonoscopes. Only prospective comparative outcome trials will be able to conclusively determine whether a diagnostic-only device (followed by conventional colonoscopy for potential therapeutic intervention) will be preferable to conventional colonoscopy with both diagnostic and therapeutic capabilities.

Interventional colonoscopes with alternative propulsion mechanisms

A first subset of this class of colonoscopes consists of shape retention devices, which are essentially tubes that are initially flexible and can be stiffened when desired. While several examples of devices utilizing this principle are described in literature^[10], only one has reached the clinical trial stage. This is the NeoGuide™ from NeoGuide Systems Inc. (a company based in San Jose, California, USA that was acquired in 2009 by Intuitive Surgical of Sunnyvale, California, USA). The NeoGuide™, represented in Figure 4, consists of a 173 cm-long endoscope composed of sixteen 8cm-long independent vertebrae. Each segment can be directed to assume a right, left, up, down, circular curve, or a combination of these motions. During manual insertion of the device, the position and angle of the scope tip are encoded into a computer algorithm. As

the colonoscope is advanced, the computer directs each successive vertebra to take the same shape that the tip had at a given insertion depth. The insertion tube thus changes its shape at different insertion depths in a "follow-the-leader" manner. By controlling the shape of the insertion tube, the NeoGuide™ does not rely on conventional pushing against the colon wall to maneuver. The cross-sectional diameter of the NeoGuide™ insertion tube is approximately 14 mm at the tip, increasing to approximately 20 mm at the proximal shaft of the scope (the working channel is 3.2 mm). The mechanical valves that control insufflation, suction, or water irrigation are the same as in conventional endoscopes. Biopsies and therapeutic maneuvers are conducted with the scope in passive mode; where the shape and stiffness of the endoscope is the same as that of a standard colonoscope. In vitro evaluation of the NeoGuide™ system^[22] showed significantly less looping and lateral force required for advancement than procedures with a standard colonoscope. An initial clinical trial of 10 sedated patients demonstrated a looping rate of 40%. Although looping was defined as extensive in three of four cases, it was successfully straightened under computerized 3D imaging and the cecum was reached in all patients^[11]. The 3D map images generated by the NeoGuide™ endoscopy system provide information regarding tip position, insertion tube position, and colonic looping^[23]. These additional pieces of information may contribute to a safer and more comfortable procedure for the patient.

Figure 4 The NeoGuide™ system, reprinted by permission from Macmillan Publisher Ltd: The American Journal of Gastroenterology [11], copyright 2007.

Another computer-aided colonoscope is the disposable Invendoscope™ (Invendo Medical GmbH, Kissing, Germany). The colonoscope, represented in Figure 5, has a working length of 210 cm and the internal functional endoscope is covered by several layers, starting 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 it to move forward. The “inverted sleeve” mechanism causes the colonoscope to “grow” at a position 10 cm below the distal end. Similarly, when the colonoscope is being retracted, the drive wheels rotate in the opposite direction and the endoscope “shrinks.” This technology, combined with a small bending radius, was designed to reduce the forces exerted on the walls of the colon, with the goal of minimizing patient discomfort—even without sedation. Other than these mechanisms, the Invendoscope™ functions in a manner similar to conventional endoscopes, allowing for insufflation, rinsing, and suction. It also has a 3.2-mm working channel, allowing for therapeutic procedures to be performed.

Figure 5 The Invendoscope™ system, reprinted from [24] with permission from Elsevier.

A pilot study of 34 healthy volunteers (19 men, mean age 49.7 years) demonstrated that the Invendoscope was able to reach the cecum without any sedation in 80% to 90% of cases^[22]. This result was supported by a prospective single-arm study of 61 healthy volunteers (34 men and 27 women; mean age 57.5 years) undergoing screening colonoscopy, with a cecal intubation rate of 98.4% with less than 5% of patients requiring sedation^[25].

The ColonoSight™, a disposable, self-propelling device based on IntraPull and ProtectiScope technologies by Stryker, Inc., 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 (Figure 6). 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

controlled by depressing a foot pedal. The material of the sleeve does not allow expansion, and therefore the increased pressure inside the sleeve creates a force directed toward the tip of the colonoscope, thus pushing the tip forward as the folded part of the sleeve is deployed. The maximum force generated is 4.9 N (0.5 kgf) whereby the maximum force generated with a standard colonoscope is approximately 44 N (4.5 kgf). Once the endoscopist releases the foot pedal, the sleeve is deflated and the applied force is removed. A pilot prospective study of 178 participants (48 women and 130 men, mean \pm SD age 51.8 ± 10.7 years) reported a success rate of 90% in reaching the cecum without complication of bleeding or perforation. All patients in the study were sedated using midazolam, mepiridine, or propofol; therefore, no data on patient discomfort was reported^[26].

Figure 6 The ColonoSight™ system, reprinted from [26] with permission from Elsevier.

With the exception of the Endotics™ system, tip deflection of the above devices are accomplished by wires travelling the length of the device -- effectively creating a minimum outer endoscope diameter (lower boundary) of approximately 10 mm. If however, one could “pull” rather than “push” the endoscope, the outer diameter lower boundary may be reduced further; limited by the space needed for the therapeutic channel and the electrical connections to the vision module^[21]. Magnetic steering and control was 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 multi-lumen soft tether^[27]. This connection was used for insufflation, passage of a therapeutic instrument, activation of a lens cleaning mechanism, and for operating the vision module. The external magnet was held by a 7 degree-of-freedom (DoF) robotic arm that was controlled in real-time by the endoscopist. The external magnet driving the endoscopic

device is represented in Figure 7.

Figure 7 Magnetic endoscopic device described in [27].

A magnetic field sensor was also embedded in the device head to enable localization and closed loop control. The magnet capsule system allowed for “pulling” of the device throughout the colon thus eliminating the need for structural cables traveling the length of the device and the need for pushing the endoscope at the base in order to forward advance the scope. This approach would appear to prevent looping and reduce stretching of the colon wall. These advantageous characteristics are enhanced by dramatic reduction in both the bending stiffness of the shaft and in the mass of the proposed device (from 1240 grams for a standard colonoscope to 34 grams, including the soft tether), while retaining the therapeutic capabilities provided by a conventional colonoscope. The device has been tested in ex-vivo colon models and animal trials with encouraging results. Human trials are planned, but have not yet been conducted.

Another noteworthy mechanism for locomotion, designed to improve cecal intubation rate when standard colonoscopy fails, is the Spirus Endo-Ease™ system^[28]. The Endo-Ease™ system, represented in Figure 8, 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 host 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. Bowel pleating is accomplished without apparent twisting of the lumen because the mesentery attachment resists the rotation. In a preliminarily clinical trial^[29] of 22 patients (the median age 68 years, 58% men) with incomplete colonoscopy secondary to redundancy of their colon, the cecal intubation rate was reported in 22 patients (92%) with a median time to cecum of 14.2 min (range 6 min - 30 min). No complications were reported.

Figure 8 The Endo-Ease™ overtube over a pediatric colonoscope, reprinted from [28], with permission from Elsevier.

The same principle was used in a computer-aided colonoscope^[30] where two sections with a spiral thread rotate to achieve forward motion. While preliminary qualitative data about in vivo experience shows the feasibility of this approach (forward speed of 11mm/min), clinical trials have not been reported to date.

A common theme in reducing discomfort associated with standard colonoscopy appears to be shifting the location of the propulsive force from the base of the device outside of the patient (i.e. “pushing”, typical force profile available in literature^[31]) to the tip of the colonoscope inside the patient (i.e. “pulling”). The latter can result in improved alignment of the direction of the applied force with the desired direction of forward tip motion. Several devices have demonstrated that this technique can reduce forces applied to the colon wall during insertion, which is believed to correlate with a reduction in patient discomfort and the risk of colon perforation. Diverse methods for reducing tip forces have been proposed, ranging from pneumatic pressure^[22, 25, 26] to robotic locomotion^[21] to magnetic fields^[27]. While it remains to be seen which of these technologies will achieve market penetration and widespread clinical use; the thin tether of the last two devices described previously appears advantageous.

An alternative approach to minimize looping of the endoscope may lie in the endoscopists ability to “visualize” the shape of the endoscope as she or he advances it throughout the colon. A commercially available endoscopic system from Olympus, the ScopeGuide™ (CF-H180DL), integrates electromagnetic tracking into a standard colonoscope and provides a real-time rendering of the endoscope shape in free space on a display. A recent study^[32] comparing this platform with standard colonoscopy reported

reduced cecal intubation time (181 s *vs.* 216 s; $P < 0.05$) and reduced patient discomfort on a 10-point visual analog scale (2.44 *vs.* 1.85; $P < 0.05$). Unfortunately, other studies^[33] of expert endoscopists utilizing this device have not reproduced these results; leading one to believe that the application of the system may be limited to novices.

In regard to reducing the learning curve, computer-aided devices or image guided techniques^[23, 16, 21, 25, 27, 30] have the potential to make colonoscopy less technically challenging for novices. Haptics has also been explored with promising results to facilitate colonoscopy^[34]. In particular, lumen detection by real-time image analysis was used to provide a feedback force at the user interface that should aid the physician to steer the endoscope tip toward the lumen. Given the increasing role of technology in healthcare, one day it may be possible for examinations to be carried out remotely (i.e. patient and provider are not in the same physical location) by health care professionals in the community in order to meet the increased demand for screening colonoscopy.

Table 1. Main characteristics of advanced flexible colonoscopes.

Wireless Capsule Colonoscopy

Trends in consumer electronics such as miniaturization, low power operation, and wireless technologies have paved the way to the introduction of wireless capsule endoscopy (WCE) in 2000^[35]. This technology has now become essential for small bowel inspection^[36] and it is trying to expand its reach for use in the large intestine with purposely developed capsule devices, such as the PillCamTM Colon by Given Imaging (Yokneam, Israel). The effectiveness of the second generation of PillCamTM Colon^[37] as an alternative to colonoscopy for CRC screening has been analyzed in a recent editorial^[38] that appeared in this journal on the basis of recent clinical trials. Although the sensitivity for polyp detection for the PillCamTM Colon is close to 90%,

specificity remains disappointingly low due to a substantial rate of false-positive results^[39]. Therefore, despite clear patient comfort benefits provided by WCE, colonoscopy is still the gold-standard for CRC screening^[40].

A main research stream for WCE toward the final goal of replacing flexible endoscopy consists in providing the capsule with the possibility to be remotely controlled and manipulated. Magnetic coupling is one of the few physical phenomena capable of transmitting actuation forces across a physical barrier. Remote magnetic manipulation has been adopted to steer capsule endoscopes by several research groups worldwide. 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^[41]. This demonstrated the feasibility of magnetic steering, but revealed that more research was required to increase the reliability and accuracy of magnetic control^[42]. An alternative technique for generating the external magnetic field, jointly developed by Olympus and Siemens, involved use of a magnetic resonance imaging scanner to create the field and field gradients^[43]. In a recent nonrandomized blinded pilot study comparing a capsule device to traditional endoscopy for evaluation of the stomach, the overall diagnostic yield was similar for both methods ^[44].

A robotic navigation system -- commonly used for cardiovascular clinical procedures (Niobe™, Stereotaxis, Inc, USA) -- was used to control the orientation of a wireless capsule endoscope throughout the entire GI tract in several ex-vivo and in-vivo animal trials^[45, 46, 47]. This technique was validated by equipping a PillCam™ with a custom-made coaxial magnetic shell^[48] glued to its external surface. In vivo tests performed with 3D fluoroscopic localization demonstrated an accuracy of 1° in orientation^[47]; however, the Niobe™ does not allow for field-gradient control, thus controlled translations of the capsule are not possible -- this is an important limitation for this approach.

Magnetic control over position and orientation of a capsule inside the colon was demonstrated by coupling permanent magnets – one embedded inside the endoscopic capsule and the other connected as the end effector of a 6 DoF industrial robotic arm in an animal pilot study^[49]. The same kind of magnetic coupling was used by the first ever reported wireless therapeutic endoscopic capsule^[50]. This pilot study in a porcine model demonstrated the feasibility of wireless controlled deployment of a surgical clip to close an iatrogenic bleed in the colon. In a different study^[51], the combined use of external static magnetic fields and internal actuation to move small embedded permanent magnets allowed for wirelessly controlled precise camera steering. This approach was used to obtain a full 360° view in the gastric cavity and a 45° span inside the colon.

Overall, this body of literature indicates that precise capsule manipulation can be achieved by means of magnetic coupling and that, if relevant clinical evidence will further support this approach, the next generation of wireless capsule endoscopes may eventually have a concrete potential to replace traditional colonoscopy, at least for CRC screening.

TOWARD MECHANISMS ENABLING UNPREPARED COLONOSCOPY

A significant common disadvantage of both conventional and novel colonoscopes is the need for bowel preparation. An innovative device addressing this challenge is the ClearPath™ system^[52] that 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 multi-lumen, custom-made, extruded tube. The tube has two channels: one that supplies water for irrigation and one that provides suction. When attached to the standard colonoscope, the ClearPath™ system adds an additional 6mm to the outer diameter of the standard colonoscope. Water for irrigation flows through four 0.6-mm nozzles in the distal head and debris is evacuated through a single 18-mm²

cross-sectional aperture. Preliminary animal trials on partially prepared domestic swine demonstrated effective intraprocedural colon cleaning with no immediate mucosal damage, acute complication (i.e. perforation), or delayed adverse consequence.

An alternative approach^[53] for cleaning the colon during colonoscopy 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 standard colonoscope and into fecal matter. When the water jet is activated the solid stool can be broken apart for removal by suction. The water jet catheter tip has 4 radial nozzles through which the water is pumped. Feasibility studies in the unprepared colons of anesthetized pigs demonstrated effectiveness; however, mucosal trauma, bleeding, perforation, clogging of the colonoscope suction channel, and electrolyte imbalances may limit the overall impact.

A similar approach^[54] for intraprocedural bowel cleansing, still based on a disposable catheter, has been developed by Medjet Ltd., Tel Aviv, Israel. The MedJet digestive tract lumen cleaning device provides controlled delivery of a supersonic two-phase jet of micro-droplets consisting of minimal amounts of saline solution and CO₂. The solution is accelerated through the catheter, and enhances visibility by clearing away stool, secretions, or blood; and by disintegrating small particles for suctioning through the working channel of the endoscope during colonoscopy. In a recent clinical study^[54], the MedJet was reported to be effective -- offering significant improvement in bowel cleansing in 32 patients with no device-related adverse events.

CONCLUSION

In summary, there have been promising advances in the development of devices utilized for CRC screening with the devices designed to achieve a common goal – to improve the way we directly view the colon (and possible intervene on any pathology present). The main principle that must be kept in mind with any new device is patient safety. Secondary principles that

continue to be addressed include ease of use, reduction of the learning curve, improvement in colonic visualization, improvement in patient procedural comfort, better access to endoscopic screening, and possibly obviation of the need for a bowel preparation. With technology improving at a rapid pace, it may not be long before a disruptive innovation takes hold and we see the conventional colonoscope as an item on the shelf in a medical museum.

REFERENCES

- 1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127(12):2893-917. DOI: 10.1002/ijc.25516. PMID: 21351269
- 2 **Howlander N**, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site 2012.
- 3 **O'Callaghan T**. Introduction: The prevention agenda. *Nature* 2011; 471(7339):S2-4. DOI: 10.1038/471S2a. PMID: 21430716
- 4 **Classen M**, Tytgat GNJ, Lightdale CJ. *Gastroenterological Endoscopy*. 2002. Stuttgart, Ger.: George Thieme Verlag.
- 5 **Hopkins HH**, Kapany NS. A flexible fiberscope, using static scanning. *Nature* 1954; 173:39–41. DOI: 10.1038/173039b0.
- 6 **Nelson DB**, McQuaid KR, Bond JH, Lieberman DA, Weiss DG, Johnston TK. Procedural success and complications of large-scale screening colonoscopy. *Gastrointest. Endosc.* 2002; 55(3):307–14. DOI: 10.1067/mge.2002.121883. PMID: 11868001
- 7 **Dafnis G**, Ekbohm A, Pahlman L, Blomqvist P. Complication of diagnostic and therapeutic colonoscopy within a defined population in Sweden. *Gastrointest. Endosc.* 2001; 54:302–9. DOI: 10.1067/mge.2001.117545. PMID: 11522969
- 8 **Varadarajulu S**, Banerjee S, Barth BA, Desilets DJ, Kaul V, Kethu SR, Pedrosa MC, Pfau PR, Tokar JL, Wang A, Wong Kee Song LM, Rodriguez SA. GI endoscopes. *Gastrointest. Endosc.* 2011; 74:1–6. DOI: 10.1016/j.gie.2011.01.061. PMID: 21704803
- 9 **Bujanda L**, Sarasqueta C, Zubiaurre L, Cosme A, Muñoz C, Sánchez A, Martín C, Tito L, Piñol V, Castells A, Llor X, Xicola RM, Pons E, Clofent J,

- de Castro ML, Cuquerella J, Medina E, Gutierrez A, Arenas JI, Jover R. Low adherence to colonoscopy in the screening of first-degree relatives of patients with colorectal cancer. *Gut* 2007; 56(12):1648-50. DOI: 10.1136/gut.2007.120709. PMID: 17400596.
- 10 **Loeve A**, Breedveld P, Dankelman J. Scopes too flexible... and too stiff. *IEEE Pulse* 2010; 1(3):26–41. DOI: 10.1109/MPUL.2010.939176. PMID: 21097368
 - 11 **Eickhoff A**, van Dam J, Jakobs R, Kudis V, Hartmann D, Damian U, Weickert U, Schilling D, Riemann JF. Computer-assisted colonoscopy (the NeoGuide Endoscopy System): results of the first human clinical trial (“PACE study”). *Am. J. Gastroenterol.* 2007; 102(2):261–66. DOI: 10.1111/j.1572-0241.2006.01002.x. PMID: 17156149
 - 12 **Lee SH**, Chung IK, Kim SJ, Kim JO, Ko BM, Hwangbo Y, Kim WH, Park DH, Lee SK, Park CH, Baek IH, Park DI, Park SJ, Ji JS, Jang BI, Jeon YT, Shin JE, Byeon JS, Eun CS, Han DS. An adequate level of training for technical competence in screening and diagnostic colonoscopy: a prospective multicenter evaluation of the learning curve. *Gastrointest. Endosc.* 2008; 67(4):683–89. DOI: 10.1016/j.gie.2007.10.018. PMID: 18279862
 - 13 **Obstein KL**, Patil VD, Jayender J, San José Estépar R, Spofford IS, Lengyel BI, Vosburgh KG, Thompson CC. Evaluation of colonoscopy technical skill levels by use of an objective kinematic-based system. *Gastrointest Endosc.* 2011; 73(2):315-21. DOI:10.1016/j.gie.2010.09.005. PMID: 21111413
 - 14 **Fritscher-Ravens A**, Fox S, Swain CP, Milla P, Long G. CathCam guide wire-directed colonoscopy: first pilot study in patients with a previous incomplete colonoscopy. *Endoscopy* 2006; 38(3):209-13. DOI: 10.1055/s-2006-925138. PMID: 16528644
 - 15 **Long G**, Fritscher-Ravens A, Mosse CA, Mills T, Swain P. The Cath-Cam: a new concept in colonoscopy. *Gastrointest. Endosc.* 2006; 64(6):997–1001. DOI: 10.1016/j.gie.2006.06.033. PMID: 17140912

- 16 **Pfeffer J**, Grinshpon R, Rex D, Levin B, Rösch T, Arber N, Halpern Z. The Aer-O-Scope: proof of the concept of a pneumatic, skill-independent, self-propelling, self-navigating colonoscope in a pig model. *Endoscopy* 2006; 38(2):144-8. DOI: 10.1055/s-2006-925089. PMID: 16479421
- 17 **Arber N**, Grinshpon R, Pfeffer J, Maor L, Bar-Meir S, Rex D. Proof-of-concept study of the Aer-O-Scope omnidirectional colonoscopic viewing system in ex vivo and in vivo porcine models. *Endoscopy* 2007; 39(5):412-7. DOI: 10.1055/s-2007-966452 . PMID: 17516347
- 18 **Vucelic B**, Rex D, Pulanic R, Pfefer J, Hrstic I, Levin B, Halpern Z, Arber N. The Aer-O-Scope: proof of concept of a pneumatic, skill-independent, self-propelling, self-navigating colonoscope. *Gastroenterology* 2006; 130(3):672–77. DOI: 10.1053/j.gastro.2005.12.018. PMID: 16530508
- 19 **Phee L**, Accoto D, Menciassi A, Stefanini C, Carrozza MC, Dario P. Analysis and development of locomotion devices for the gastrointestinal tract. *IEEE Trans. Biomed. Eng.* 2002; 49(6):613–16. DOI: 10.1109/TBME.2002.1001976. PMID: 12046707
- 20 **Cosentino F**, Tumino E, Passoni GR, Morandi E, Capria A. Functional evaluation of the Endotics system, a new disposable self-propelled robotic colonoscope: in vitro tests and clinical trial. *Int J Artif Organs* 2009; 32(8):517-27. DOI: N/A. PMID: 19844894
- 21 **Tumino E**, Sacco R, Bertini M, Bertoni M, Parisi G, Capria A. Endotics system vs. colonoscopy for the detection of polyps. *World J. Gastroenterol.* 2010; 16(43):5452–56. DOI:10.3748/wjg.v16.i43.5452. PMID: 21086563
- 22 **Eickhoff A**, Jakobs R, Kamal A, Mermash S, Riemann JF, van Dam J. In vitro evaluation of forces exerted by a new computer-assisted colonoscope (the NeoGuide Endoscopy System). *Endoscopy* 2006; 38(12):1224-9. DOI: 10.1055/s-2006-945014. PMID: 17163323
- 23 **Striegel J**, Jakobs R, Van Dam J, Weickert U, Riemann JF, Eickhoff A. Determining scope position during colonoscopy without use of ionizing radiation or magnetic imaging: the enhanced mapping ability of the

- NeoGuide Endoscopy System. *Surg Endosc.* 2011; 25(2):636-40. DOI 10.1007/s00464-010-1245-1 . PMID: 20730449
- 24 **Rösch T**, Adler A, Pohl H, Wettschureck E, Koch M, Wiedenmann B, Hoepffner N. A motor-driven single-use colonoscope controlled with a hand-held device: a feasibility study in volunteers. *Gastrointest. Endosc.* 2008; 67(7):1139–46. DOI: 10.1016/j.gie.2007.10.065. PMID: 18355823
- 25 **Groth S**, Rex DK, Rösch T, Hoepffner N. High cecal intubation rates with a new computer-assisted colonoscope: a feasibility study. *Am J Gastroenterol.* 2011; 106(6):1075-80. DOI: 10.1038/ajg.2011.52 . PMID: 21386833
- 26 **Shike M**, Fireman Z, Eliakim R, Segol O, Sloyer A, Cohen LB, Goldfarb-Albak S, Repici A. Sightline ColonoSight system for a disposable, power-assisted, non-fiber-optic colonoscopy (with video). *Gastrointest. Endosc.* 2008; 68(4):701–10. DOI: 10.1016/j.gie.2007.12.062. PMID: 18501356
- 27 **Valdastri P**, Ciuti G, Verbeni A, Menciaci A, Dario P, Arezzo A, Morino M. Magnetic air capsule robotic system: proof of concept of a novel approach for painless colonoscopy. *Surg. Endosc.* 2012; 26(5):1238–46. DOI: 10.1007/s00464-011-2054-x. PMID: 22179445
- 28 **Akerman PA**, Agrawal D, Chen W, Cantero D, Avila J, Pangtay J. Spiral enteroscopy: a novel method of enteroscopy by using the Endo-Ease Discovery SB overtube and a pediatric colonoscope. *Gastrointest Endosc.* 2009; 69(2):327-32. DOI: 10.1016/j.gie.2008.07.042. PMID: 19100974
- 29 **Schembre DB**, Ross AS, Gluck MN, Brandabur JJ, McCormick SE, Lin OS. Spiral overtube-assisted colonoscopy after incomplete colonoscopy in the redundant colon. *Gastrointest. Endosc.* 2011; 73(3):515–19. DOI: 10.1016/j.gie.2010.11.047. PMID: 21353848
- 30 **Trovato G**, Shikanai M, Ukawa G, Kinoshita J, Murai N, Lee JW, Ishii H, Takanishi A, Tanoue K, Ieiri S, Konishi K, Hashizume M. Development of a colon endoscope robot that adjusts its locomotion through the use of

- reinforcement learning. *Int J Comput Assist Radiol Surg.* 2010; 5(4):317-25. DOI: 10.1007/s11548-010-0481-0. PMID: 20480247
- 31 **Dogramadzi S**, Virk GS, Bell GD, Rowland RS, Hancock J. Recording forces exerted on the bowel wall during colonoscopy: in vitro evaluation. *Int J Med Robot* 2005; 1(4):89-97. DOI: 10.1002/rcs.61. PMID: 17518409
- 32 **Szura M**, Bucki K, Matyja A, Kulig J. Evaluation of magnetic scope navigation in screening endoscopic examination of colorectal cancer. *Surg. Endosc.* 2012; 26:632–38. DOI: 10.1007/s00464-011-1930-8. PMID: 21959687
- 33 **Shah SG**, Thomas-Gibson S, Brooker JC, Suzuki N, Williams CB, Thapar C, Saunders BP. Use of video and magnetic endoscope imaging for rating competence at colonoscopy: validation of a measurement tool. *Gastrointest Endosc.* 2002; 56(4):568-73. DOI: 10.1016/S0016-5107(02)70449-5. PMID: 12297780
- 34 **Reilink R**, Stramigioli S, Kappers AM, Misra S. Evaluation of flexible endoscope steering using haptic guidance. *Int J Med Robot* 2011; 7(2):178-86. doi: 10.1002/rcs.386. PMID: 21462290
- 35 **Iddan G**, Meron G, Glukhovskiy A, Swain P. Wireless capsule endoscopy. *Nature* 2000; 405(6785):417. DOI: 10.1038/35013140. PMID: 10839527
- 36 **Ladas SD**, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, Delvaux M, de Franchis R, Costamagna G. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy* 2010; 42(3):220-7. DOI: 10.1055/s-0029-1243968. PMID: 20195992
- 37 **Eliakim R**, Yassin K, Niv Y, Metzger Y, Lachter J, Gal E, Sapoznikov B, Konikoff F, Leichtmann G, Fireman Z, Kopelman Y, Adler SN. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009; 41(12):1026-31. DOI: 10.1055/s-0029-1215360. PMID: 19967618

- 38 **Riccioni ME**, Urgesi R, Cianci R, Bizzotto A, Spada C, Costamagna G. Colon capsule endoscopy: Advantages, limitations and expectations. Which novelties? *World J Gastrointest Endosc* 2012; 16;4(4):99-107. DOI: 10.4253/wjge.v4.i4.99. PMID: 22523610
- 39 **Spada C**, De Vincentis F, Cesaro P, Hassan C, Riccioni ME, Minelli Grazioli L, Bolivar S, Zurita A, Costamagna G. Accuracy and safety of second-generation PillCam COLON capsule for colorectal polyp detection. *Therap Adv Gastroenterol* 2012; 5(3):173-8. DOI: 10.1177/1756283X12438054. PMID: 22570677
- 40 **Spada C**, Hassan C, Galniche JP, Neuhaus H, Dumonceau JM, Adler S, Epstein O, Gay G, Pennazio M, Rex DK, Benamouzig R, de Franchis R, Delvaux M, Devière J, Eliakim R, Fraser C, Hagenmuller F, Herrerias JM, Keuchel M, Macrae F, Munoz-Navas M, Ponchon T, Quintero E, Riccioni ME, Rondonotti E, Marmo R, Sung JJ, Tajiri H, Toth E, Triantafyllou K, Van Gossum A, Costamagna G. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2012; 44(5):527-36. DOI: 10.1055/s-0031-1291717. PMID: 22389230
- 41 **Keller J**, Fibbe C, Volke F, Gerber J, Mosse AC, Reimann-Zawadzki M, Rabinovitz E, Layer P, Swain P. Remote magnetic control of a wireless capsule endoscope in the esophagus is safe and feasible: results of a randomized, clinical trial in healthy volunteers. *Gastrointest Endosc* 2010; 72(5):941-6. DOI: 10.1016/j.gie.2010.06.053. PMID: 20855064
- 42 **Keller J**, Fibbe C, Volke F, Gerber J, Mosse AC, Reimann-Zawadzki M, Rabinovitz E, Layer P, Schmitt D, Andresen V, Rosien U, Swain P. Inspection of the human stomach using remote-controlled capsule endoscopy: a feasibility study in healthy volunteers (with videos). *Gastrointest Endosc* 2011; 73(1):22-8. DOI: 10.1016/j.gie.2010.08.053. PMID: 21067740
- 43 **Rey JF**, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, Aihara H, Pangtay I, Hibi T, Kudo S, Tajiri H. Feasibility of stomach exploration with

- a guided capsule endoscope. *Endoscopy* 2010; 42(7):541-5. DOI: 10.1055/s-0030-1255521. PMID: 20593331
- 44 **Rey JF**, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, Aihara H, Pangtay I, Hibi T, Kudo SE, Tajiri H. Blinded nonrandomized comparative study of gastric examination with a magnetically guided capsule endoscope and standard videoendoscope. *Gastrointest Endosc* 2012; 75(2):373-81. DOI: 10.1016/j.gie.2011.09.030. PMID: 22154417
- 45 **Carpi F**, Galbiati S, Carpi A. Controlled navigation of endoscopic capsules: concept and preliminary experimental investigations. *IEEE Trans Biomed Eng* 2007; 54(11):2028-36. DOI: 10.1109/TBME.2007.894729. PMID: 18018698
- 46 **Carpi F**, Pappone C. Magnetic maneuvering of endoscopic capsules by means of a robotic navigation system. *IEEE Trans Biomed Eng* 2009; 56(5):1482-90. DOI: 10.1109/TBME.2009.2013336. PMID: 19174328
- 47 **Carpi F**, Kastelein N, Talcott M, Pappone C. Magnetically controllable gastrointestinal steering of video capsules. *IEEE Trans Biomed Eng* 2011; 58(2):231-4. DOI: 10.1109/TBME.2010.2087332. PMID: 20952324
- 48 **Carpi F**, Galbiati S, Carpi A. Magnetic shells for gastrointestinal endoscopic capsules as a means to control their motion. *Biomed Pharmacother* 2006; 60(8):370-4. DOI: 10.1016/j.biopha.2006.07.001. PMID: 16935464
- 49 **Ciuti G**, Donlin R, Valdastrì P, Arezzo A, Menciassi A, Morino M, Dario P. Robotic versus manual control in magnetic steering of an endoscopic capsule. *Endoscopy* 2010; 42(2):148-52. DOI: 10.1055/s-0029-1243808. PMID: 20017088
- 50 **Valdastrì P**, Quaglia C, Susilo E, Menciassi A, Dario P, Ho CN, Anhoeck G, Schurr MO. Wireless therapeutic endoscopic capsule: in vivo experiment. *Endoscopy* 2008; 40(12):979-82. DOI: 10.1055/s-0028-1103424. PMID: 19065478
- 51 **Valdastrì P**, Quaglia C, Buselli E, Arezzo A, Di Lorenzo N, Morino M,

Menciassi A, Dario P. A magnetic internal mechanism for precise orientation of the camera in wireless endoluminal applications. *Endoscopy* 2010; 42(6):481-6. DOI: 10.1055/s-0029-1244170. PMID: 20506065

52 **Moshkowitz M**, Hirsch Y, Carmel I, Duvdevany T, Fabian I, Willenz EP, Cohen J. A novel device for rapid cleaning of poorly prepared colons. *Endoscopy* 2010; 42(10):834–36. DOI: 10.1055/s-0030-1255777. PMID: 20886401

53 **Fritscher-Ravens A**, Mosse CA, Mills T, Ikeda K, Swain P. Colon cleaning during colonoscopy: a new mechanical cleaning device tested in a porcine model. *Gastrointest. Endosc* 2006; 63:141–43. DOI: 10.1016/j.gie.2005.05.023. PMID: 16377331

54 **Kiesslich R**, Schuster N, Hoffman A, Goetz M, Galle PR, Santo E, Halpern Z. MedJet - a new CO₂-based disposable cleaning device allows safe and effective bowel cleansing during colonoscopy: a pilot study. *Endoscopy* 2012; 44(8):767-71. DOI: 10.1055/s-0031-1291703. PMID: 22438188

S- Editor Lv S **L- Editor** **E- Editor**

FIGURES AND TABLES.



Figure 9 The CathCam system, reprinted from [15], with permission from Elsevier.

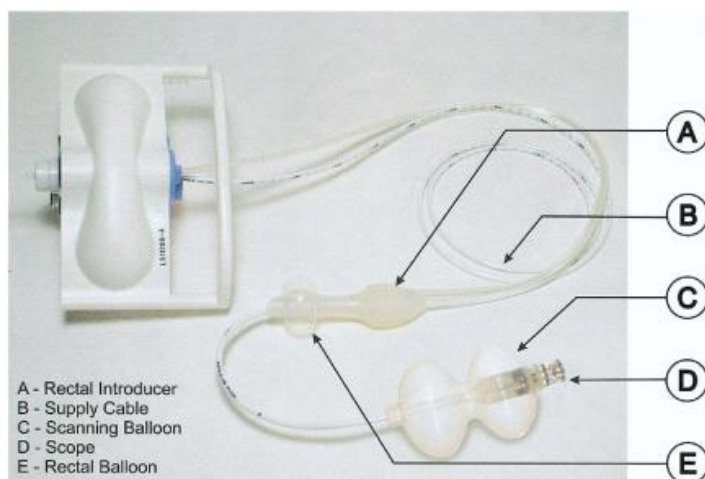


Figure 10 The Aer-O-Scope™ system, reprinted from [18], with permission from Elsevier.



Figure 11 The Endotics™ system, image courtesy of Era Endoscopy.



Figure 12 The NeoGuide™ system, reprinted by permission from Macmillan Publisher Ltd: The American Journal of Gastroenterology [11], copyright 2007.



Figure 13 The Invendoscope™ system, reprinted from [24] with permission from Elsevier.

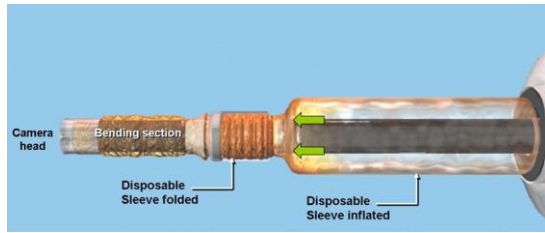


Figure 14 The ColonoSight™ system, reprinted from [26] with permission from Elsevier.

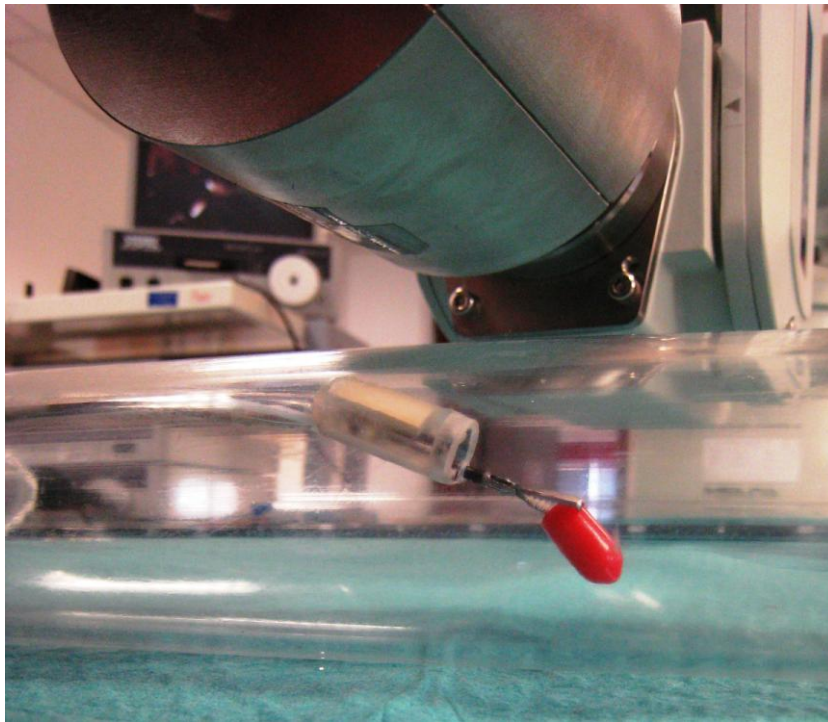


Figure 15 Magnetic endoscopic device described in [27].



Figure 16 The Endo-Ease™ overtube over a pediatric colonoscope, reprinted from [28], with permission from Elsevier.

Technology	Advantages	Disadvantages	Human studies
CathCam	Disposable; peak force reduction with respect to standard colonoscope	No instrument channel; No steering	No
Aer-O-Scope™	Disposable; “tip pulling” locomotion; computer-aided control	No instrument channel; No steering	Yes ^[18]
Endotics™	Disposable; Steerable head; “tip pulling” locomotion; computer-aided control; thin tail	No instrument channel; average procedure time longer than colonoscopy	Yes ^[20, 21]
NeoGuide™	Instrument channel; shape retention; 3D map of the device; computer-aided control	Reusable (need for cleaning); large diameter	Yes ^[11]
Invendoscope™	Disposable; instrument channel; “tip pulling” locomotion; computer-aided control	Diameter similar to a colonoscope	Yes ^[24, 25]
ColonoSight™	Disposable; instrument channel; “tip pulling” locomotion	Diameter similar to a colonoscope	Yes ^[26]
Magnetic Endoscopic Device	Instrument channel; “tip pulling” locomotion; computer-aided control; thin tail	Complexities related to magnetic control	No
Endo-Ease™	Facilitates cecal intubation	Large diameter	Yes ^[29]
ScopeGuide™	3D real-time visualization of the device	Standard colonoscope	Yes ^[32, 33]

Table 1. Main characteristics of advanced flexible colonoscopes.