Review Article

Review: capsule colonoscopy—a concise clinical overview of current status

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Abstract: The colon capsule endoscopy (CCE) was first introduced in 2007. Currently, the main clinical indications for CCE are completion of incomplete colonoscopy, polyp detection and investigation of inflammatory bowel disease (IBD). Although conventional colonoscopy is the gold standard in bowel cancer screening, incomplete colonoscopy remains a problem as lesions are missed. CCE compares favourably to computer tomography colonography (CTC) in adenoma detection and has therefore been proposed as a method for completing colonoscopy. However the data on CCE remains sparse and current evidence does not show its superiority over CTC or conventional colonoscopy in bowel cancer screening. CCE also seems to show good correlation with conventional colonoscopy when used to evaluate IBD, but there are not many published studies at present. Other significant limitations include the need for aggressive bowel preparation and the labour-intensiveness of CCE reading. Therefore, much further software and hardware development is required to enable CCE to fulfill its potential as a minimally-invasive and reliable method of colonoscopy.

Keywords: Colon capsule endoscopy (CCE); colonoscopy; computer tomography colonography (CTC); colorectal cancer screening; adenomas; polyps; inflammatory bowel disease (IBD); review

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Colon capsule specifications

The first-generation colon capsule endoscopy (CCE) was introduced in 2007 (1). The main difference between the CCE and conventional small bowel capsule endoscopes was the introduction of two optical domes at either end of the capsule to enable fuller visualisation of the relatively wider lumen structure in the colon. The currently available second-generation CCE (CCE-2) (Medtronic, Minneapolis, USA) (*Figure 1*) consists of a swallowable video capsule (11.6 mm × 31.5 mm, weight 2.9 g), which has an improved optical system allowing for nearly 360° coverage via two 172° angle cameras. The battery life is about 10 hours. It is equipped with the adaptive frame rate function, which modulates the frame rate according to capsule progression speed in order to save battery and optimise video length. The frame rate alternates between 4–35 images per second depending on the motion of the capsule. The RAPID® reviewing system allows dual communication between the CE and data recorder. In addition, the new data recorder is able to actively elaborate information received from the capsule and to alert the patient at planned intervals to drive the laxative booster ingestion (2,3). At present the main clinical indications for CCE are: (I) completion of incomplete colonoscopy (*Figure 2*); (II) polyp detection

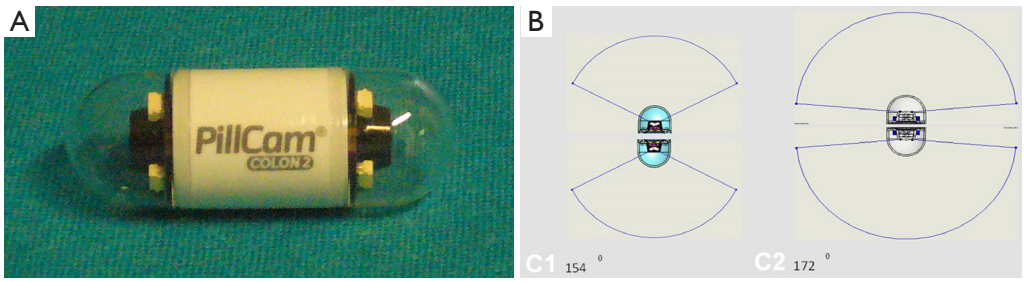

Figure 1 Colon capsule endoscopy hardware. (A) Figure of PillCam Colon 2; (B) comparison of the fields of view of first (left) and second (right)-generation CCEs. CCE, colon capsule endoscopy. [*Figure 1B*© 2013 Adler SN, Hassan C. Published in (Adler SN, Hassan C. Colon Capsule Endoscopy: Quo Vadis? INTECH Open Access Publisher; 2013) under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/53055].

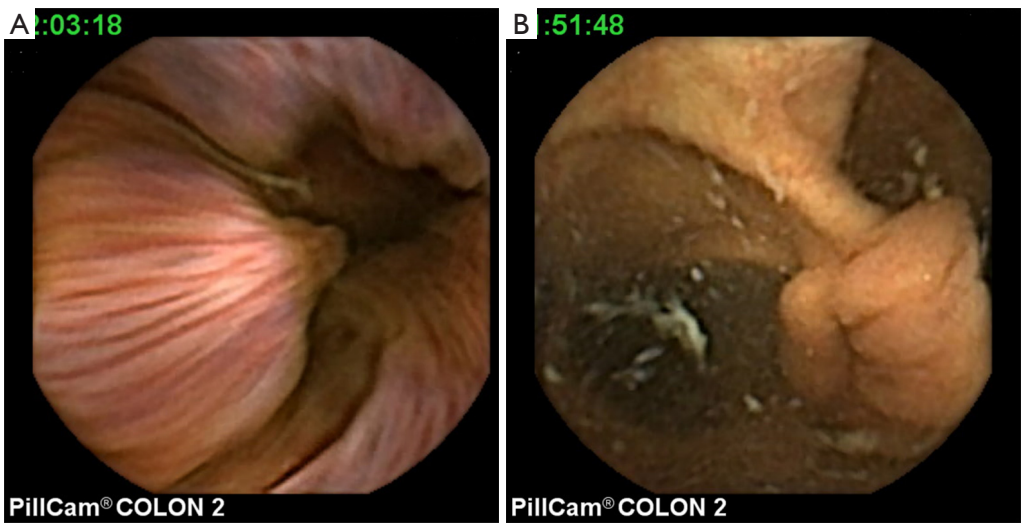

Figure 2 Anatomical landmarks (A) anal verge and (B) ileocaecal valve seen on CCE-2. CCE-2, second-generation CCE.

(*Figure 3*); and (III) investigation of inflammatory bowel disease (IBD) (*Figure 4*).

The need for complete colonoscopy

Conventional colonoscopy is the gold standard in bowel cancer screening, but remains an uncomfortable experience for many patients, and clinical performance varies widely between endoscopists and centres (4-6). As the incidence of bowel cancer increases, there is extra demand for high quality colonoscopy services. Therefore, a working group was formed in 2013 from the Joint Advisory Group on Gastrointestinal Endoscopy (JAG), the British Society of Gastroenterology (BSG), and the Association of Coloproctology of Great Britain and Ireland (ACPGBI), to review existing and define new quality assurance measures and key performance indicators in colonoscopy (7).

The major key quality indicators are caecal intubation rate and adenoma detection rate. Nowadays, caecal intubation rate is a well-recognized measure of colonoscopy quality and the working group has defined a target rate of 95%. While large scale screening colonoscopy studies have reported a completion rate above this recommended threshold (8-10), population-based studies report that the caecal intubation rate in clinical practice is far less (approximately 80–85%) (11-13).

Incomplete colonoscopy is associated with missed lesions (14). Imperiale *et al.* (15) calculated that up to 50% of clinically significant lesions would be missed by failing to visualise the entire colon. Consistently, a study by Brenner

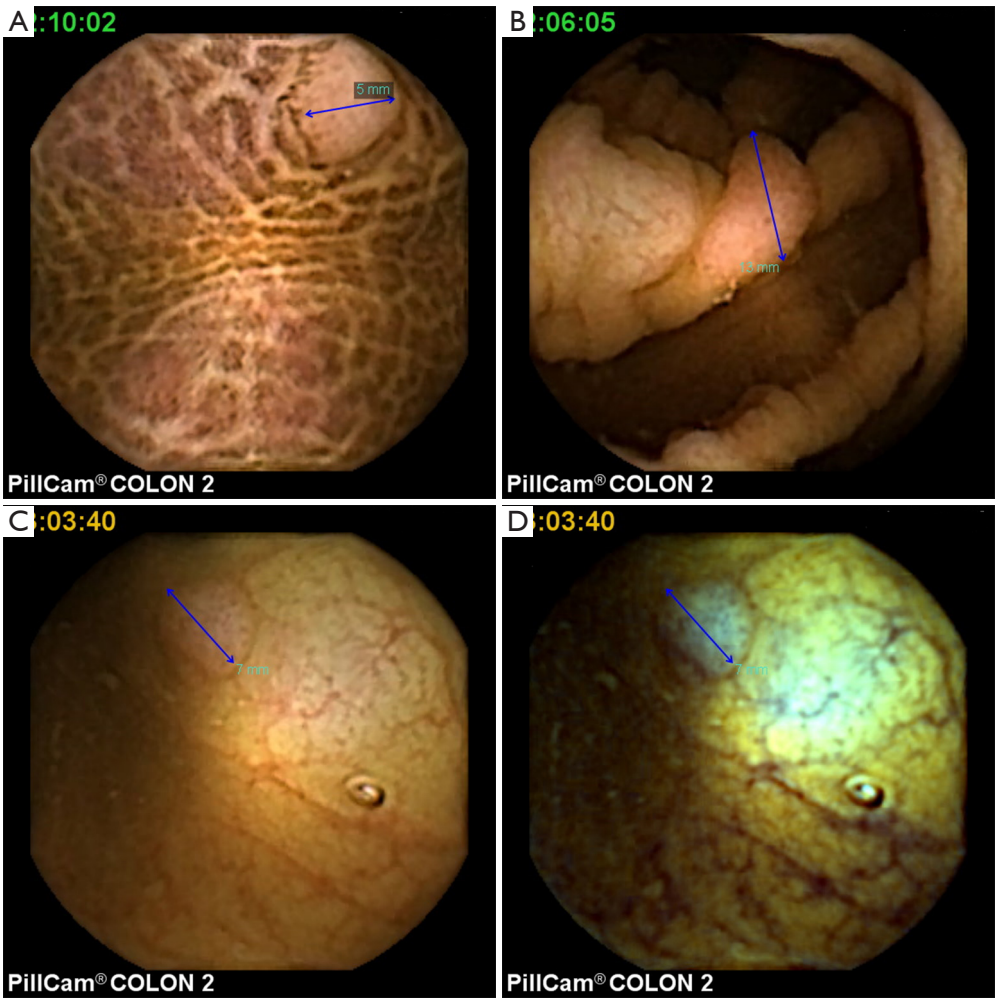

Figure 3 Colonic polyps identified on CCE examinations. (A) Melanosis coli and polyp; (B) pedunculated 13 mm polyp; (C) sessile polyp; (D) polyp as in 2c viewed under FICE 1. CCE, colon capsule endoscopy.

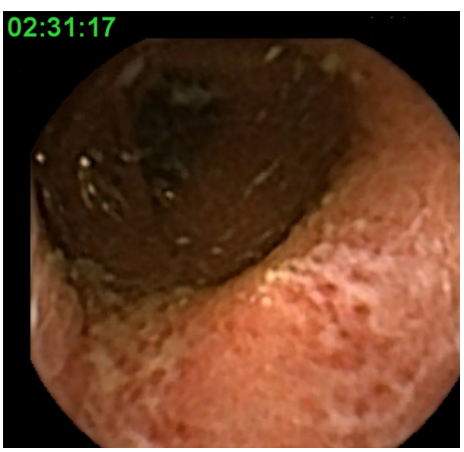

Figure 4 Proctitis as seen on CCE-2. CCE-2, second-generation CCE.

et al. (16) showed a 2-fold increased risk in proximal cancer after incomplete colonoscopy. Recently, Ridolfi *et al*. (17) reported 171 patients with initial incomplete colonoscopy. In 21 patients (12%) undergoing follow-up examinations, significant lesions were discovered by either repeating colonoscopy (80 patients) or radiological imaging tests (91 patients). Stoffel *et al*. (18) conducted a study on post-colonoscopy colorectal cancer (CRC). They found that in patients diagnosed with CRC within a year after colonoscopy, 38% had had incomplete colonoscopies compared to 16% of those who were diagnosed 1–10 years after colonoscopy. The same study reported that tumours found in patients who had had colonoscopies were more likely to be proximal; this could have been

Table 1 Cohort studies evaluating the role of CCE in completing previous incomplete conventional colonoscopy

Author	No. of patients	Colon capsule generation	Complementation of conventional colonoscopy (%)
Pioche *et al*., 2012 (30)*	107	First	83
Alarcón-Fernández *et al*., 2013 (32)	34	First	85
Nogales *et al*., 2013 (31)	96	Second	93
Baltes *et al*., 2014 (34)	74	Second	95
Triantafyllou *et al*., 2014 (33)	75	First	91
Spada *et al*., 2015 (35)	100	Second	98

*, patients with either incomplete or contraindicated colonoscopy were enrolled in this study; results are not reported separately for the patients (n=77) with incomplete standard colonoscopy. CCE, colon capsule endoscopy. Modified from Spada *et al.* (3) and from Triantafyllou *et al.* (36).

why these tumours had been missed initially. le Clercq *et al*. (19) reported on a cohort of patients diagnosed with metachronous colorectal cancer diagnosed more than 6 months after initial diagnosis of a primary CRC. They found that 43% of metachronous CRC were attributable to non-compliance with surveillance, 43% to missed lesions and 3.2% to inadequate examination.

Factors associated with incomplete colonoscopy include poor bowel preparation, severe diverticulosis or stenosis, tortuous and redundant colon, low body mass index, previous abdominal surgery, female sex, young age, patient intolerance and ineffective sedation (11-13,20-24). Therefore, several technical and technological solutions have been suggested in recent years to achieve complete colonoscopy in these situations. These include the use of optimized bowel prep schedules or imaging techniques (i.e., magnetic scope guidance or fluoroscopy) to monitor the scope progression, use of deeper sedation protocols, of water immersion technique or carbon dioxide insufflation, or the use of specific endoscopes (i.e., stiffer or thinner endoscopes, device-assisted endoscopes). Moreover, the endoscopist's manual dexterity and expertise significantly affect the caecal intubation rate (25,26). Therefore, the large majority of patients with initial incomplete colonoscopy can undergo a successful repeated colonoscopy at tertiary referral centers (22,23,25,26), where expert endoscopists and dedicated endoscopes are both available. Nevertheless, in case of initial incomplete colonoscopy, several techniques alternative to conventional colonoscopy, such as computer tomography colonography (CTC) or CCE are also recommended. There appears to be a low to minimal risk of CCE retention (2,3,27).

Use of CCE to complete colonoscopy

In 2008 Spada *et al*. (1) reported the first case where CCE managed complete colon inspection where conventional colonoscopy had been stopped at the sigmoid by inflammatory stenosis. In this patient the capsule showed a 10 mm polyp not reached on conventional colonoscopy. Thereafter, other case-reports (28) and small case-series (29) have reported successful complete colon inspection by CCE in patients with previous incomplete conventional colonoscopy. To the best of our knowledge, six cohort studies (30-34) have been published so far on the use of CCE to complete colon examination (*Table 1*). These studies have collected more than 450 patients overall, with a completion rate of approximately 90% of cases (range, 72–98%). Significant findings were identified in more than one third of patients (range, 23–49%). Based on these data, in 2012 the ESGE issued a guideline (37) recognising CCE as a feasible and safe tool for visualization of the colonic mucosa in patients with incomplete colonoscopy without stenosis. In the same paper the authors recommended further randomized trials comparing CCE with radiological imaging and/or conventional colonoscopy in order to confirm the efficacy of CCE in this setting and define the patients in whom CCE is most suitable.

To the best of our knowledge, there has been only one prospective head-to-head study comparing CTC and CCE in patients with incomplete colonoscopy (38). In this study, 100 patients with previous incomplete colonoscopy underwent both CCE and CTC; conventional colonoscopy was eventually performed if one of the two techniques

identified significant findings (mass lesion or at least one polyp ≥6 mm). CCE was able to achieve complete colonic evaluation in the vast majority of patients (98%), identifying significant polyps in a quarter of them. Compared to CTC, CCE identified more polyps with size thresholds of 6 and 10 mm [colon capsule relative sensitivity: 2.0, 95% confidence interval (CI): 1.34–2.98 and 1.67, 95% CI: 0.69–4.00 respectively]. No adverse events related to CCE or CTC were reported in this study. Interestingly, the study confirms the limitations of CTC in identifying flat/sessile lesions; all the 12 cases of discrepancies between CTC and CCE were non-polypoid lesions (2 of them ≥10 mm). Based on these findings, the authors concluded that both procedures are very effective in completing previous incomplete conventional colonoscopy, however, CCE seems to have a higher diagnostic yield. Nevertheless, since patients with negative CCE and CTC did not undergo repeat conventional colonoscopy, the false negative rate has not been assessed. Furthermore, despite employing a novel bowel preparation regimen, the rate of CCE examinations with adequate bowel preparation was only 83%. When CCE failed to visualize the entire colon (in 7% of patients in the study), it is not always possible to determine the length of colon examined based on results of previous conventional colonoscopy. Of note, even in the study from Spada *et al*. (38), a second conventional colonoscopy attempt, performed in patients with positive CCE or CTC, was always successful.

Taking into account the aforementioned limitations, as well as colon transit time (which ranges in the majority of studies between 75 and 200 min) (39-41), CCE does not show major advantages over conventional colonoscopy or CTC and may therefore not increase uptake for CRC screening, as hoped. At present conventional colonoscopy remains the reference standard for polyp detection, whereas CCE-2, similarly to CTC, may represent a valid alternative in average-risk patients refusing to undergo conventional colonoscopy or in those in which conventional colonoscopy did not allow a complete colon exploration (37). In a cost-benefit analysis by Health Quality Ontario, the cost-effectiveness of CCE compared to CTC is $26,750 per life-year, assuming an increased sensitivity of CCE. They estimated that the replacement of CTC with CCE would have moderate costs to the health care system (42).

Use of CCE for polyp detection

CTC has been proven to be more effective than barium enema (43,44) and as effective as conventional colonoscopy in the detection of colonic masses and large (i.e., ≥1 cm) polyps (45-47). Therefore, the US Preventive Services Task Force recently included CTC as a viable screening strategy for average risk asymptomatic 50–75 years subjects (48). Moreover, it has been also recommended by Scientific Societies as the imaging modality of choice in case of incomplete colonoscopy (49,50). Nevertheless, CTC requires X-ray exposure, and its accuracy in detecting colonic polyps significantly decreases when dealing with polyps smaller than 10 mm (46,47) or flat lesions (i.e., right sided sessile serrated lesions) (51,52). Furthermore, it can result in unnecessary diagnostic testing or treatment of incidental extra-colonic findings, which are identified in about 40% to 70% of CTC screening examinations (48).

A recently published comprehensive meta-analysis (27) pooled data from 14 studies: 7 of them (involving 1,128 patients) tested the accuracy of CCE-1 (first-generation of colon capsule), while the remaining 7 series (1,292 patients) tested that of CCE-2. This analysis has confirmed that the sensitivity values achieved by CCE-2, (i.e., 86% and 87% for ≥6 and ≥10 mm polyps, respectively) represent a clinically relevant improvement, compared to the corresponding values shown by CCE-1, (i.e., 58% and 54% for ≥6 and ≥10 mm polyps, respectively) (*Table 2*). In addition, the accuracy of CCE-2 reported in this paper favourably compares to that of CTC.

Non-CRC indications for CCE

The ESGE has proposed potential future applications for CCE, although there is currently scarce data on these further indications. Areas where CCE could be applied include colon examination where optical conventional colonoscopy (OC) is contraindicated or refused, as well as the diagnosis and evaluation of IBD (37). In a prospective study (53) of 40 patients with Crohn's disease (CD) undergoing both conventional colonoscopy and CCE, there was good agreement between the Crohn's Disease Endoscopic Index of Severity (CDEIS) score using both modalities. However, CCE appeared to underestimate disease severity and there was poorer agreement in the distal colon with low specificity for colonic ulceration. Furthermore, the potential of the capsule to be a pantenteric examination tool could make it useful in assessing the entire gastrointestinal (GI) tract in CD patients. In a small study, the capsule was able to achieve complete GI tract visualization in 10/12 CD patients (54). There have

Table 2 Results of a recently-published meta-analysis pooling studies exploring the accuracy of CCE in detecting polyps

Colon capsule generation	No. of studies	No. of patients	Polyp ≥6 mm		Polyp ≥10 mm		Rate of capsule excretion (95% CI) (%)	Proportion of patients with adequate preparation (%)
			Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)		
First	7	1,128	58.0 (44.0–70.0)	85.7 (80.2–90.0)	54.0 (29.0–77.0)	97.4 (96.0–98.3)	86.7 (79.3–91.7)	78
Second	7	1,292	86.0 (82.0–89.0)	88.1 (74.2–95.0)	87.2 (81.0–91.0)	95.3 (91.5–97.5)	90.5 (88.3–92.4)	81

CI, confidence interval; CCE, colon capsule endoscopy.

been more studies on the use of CCE in ulcerative colitis (UC), showing good sensitivity and specificity for colonic inflammation. Studies detailing the use of CCE in IBD are summarized in *Table 3*.

Limitations faced by CCE

The aforementioned meta-analysis by Spada *et al.* (27) highlights some of the limitations of CCE in polyp detection compared to conventional colonoscopy. In the studies where CCE-2 was used, the completion rate was 90.5%. On the other hand, even after using preparation regimens with large volumes of polyethyleneglycol (PEG) solution and boosters, the rate of patients with adequate colon preparation remained around 80%. Unfortunately, both these parameters do not meet the thresholds established for conventional colonoscopy in quality improvement programs (66). In addition, although newly-developed polyp sizing software is now included in the RAPID® reading platform, it has never been validated. Therefore, polyp sizing using such software has been given a wider margin of error in recently published studies, potentially affecting the reliability of accuracy parameters calculation (39): the margin of error allowed for measurements made using CCE was 50% over or less than measurements made by conventional colonoscopy. Furthermore, the lack of insufflation and the underwater capsule navigation can affect the endoscopic appearance of certain lesions, e.g., flat lesions, making recognition and sizing difficult. Overall, the performance of CCE does not stack up favourably compared to increasingly sophisticated conventional colonoscopy techniques, which offer high definition imaging and are able to provide therapeutic intervention and biopsies.

Another important limitation of CCE is the need for bowel preparation to ensure adequate visualisation. Under current guidelines, a total of 4 L of PEG must be ingested prior to and during CCE (37). Furthermore, the use of sodium phosphate (NaP) as a booster precludes the use of CCE in patients at risk of NaP toxicity. Although a split-dosage regimen is advocated in order to improve the tolerability and efficacy of bowel preparation, it remains a highly unpleasant part of examination, negating the benefits of its noninvasive nature. Other booster preparations have been investigated but there is currently no conclusive evidence on their use (67).

Notably, CCE-2 reading is a time-consuming task, requiring intense and focused attention (68). This time and labour-intensiveness can significantly impact on everyday clinical activities. For instance, due to its patient acceptability, CCE-2 has been proposed as a possible "filter" or screening test for the selection of patients for conventional colonoscopy (39,41). Nevertheless, the amount of resources and manpower required for the provision of such service may place further strain on already-overstretched healthcare services. At present, there are no guidelines or formal training requirements for granting credentials to CCE readers. A recent meta-analysis from our group (unpublished data; under review) showed that properly trained physician extenders and/or specialist nurses could replace physicians in the reading of small-bowel capsule endoscopy videos. There is in fact no reason to suggest that the same should apply in CCE.

Future capsule colonoscopy hardware

Although the PillCam colon remains the only commercial model for capsule colonoscopy, several experimental attempts have been made by other companies. Filip *et al.* (69) have presented a self-stabilizing capsule endoscope and tested it in a live canine model (*Figure 5*). The proposed modified capsule delivered a significant improvement in

Table 3 Summary of studies investigating the use of CCE in inflammatory bowel disease (IBD)

Authors	Colon capsule generation	No. of patients	Type of IBD	CCE role examined	Performance of CCE
Sung *et al*., 2012 (55)	First	100	UC	Evaluation of colonic inflammation in (known & suspected) UC	Sens & spec of CCE for colonic inflammation 89% & 75%, respectively
Hosoe *et al*., 2013 (56)	Second	40	UC	Evaluation of severity of mucosal inflammation in patients with known UC	Strong correlation between Matts endoscopic scores as determined by CCE & OC
Kobayashi *et al*., 2013 (57)	Second	49	UC	Evaluation of disease activity in patients with UC	Strong correlation of Matts' endoscopic scores between OC & CCE
Manes *et al*., 2013 (58)	First	20	UC	Evaluation of colonic inflammation in patients with known UC	Complete agreement between CCE & OC in activity assessment in 10/20 patients. Agreement in assessment of extent of UC in 11/18 patients
Meister *et al*., 2013 (59)	First	13	UC	Assessment of mucosal disease activity & localisation of areas of inflammation in patients with known UC	Higher Rachmilewitz scores in OC compared to CCE, more detection of mucosal disease activity on OC. Disease extension underestimated by CCE compared to OC
Shavrov *et al*., 2014 (60)	Second	5	CD	Evaluation of CCE role in paediatric case series with GI symptoms	CCE able to diagnose CD in small bowel and colon
Singeap *et al*., 2013 (61)	Second	15	Both	Assessment of colonic CD, known UC or unclassified colitis	CCE consistent with OC in 6/10 patients, generally good agreement with OC
Ye *et al*., 2013 (62)	First	25	UC	Evaluation of extent of mucosal damage & inflammatory lesions in patients with known UC	Significant correlation of severity & extent of UC between CCE & OC
Negreanu *et al*., 2014 (63)	Second	6	CD	Assessment of disease in CD patients refusing OC or with previous incomplete OC	Both small bowel & colonic involvement detected in 4/6 patients
Oliva *et al*., 2014 (64)	Second	30	UC	Paediatric UC patients, evaluation of disease activity	Sensitivity & specificity of CCE: 96% & 100%, respectively
San Juan-Acosta *et al*., 2014 (65)	Both	42	UC	Evaluation of extent of activity in patients with known UC	Good correlation between CCE and OC in assessing disease severity & extent of inflammation
Boal Carvalho *et al*., 2015 (54)	Second	12	CD	Evaluation of mucosal healing in both small bowel and colon in patients with steroid-free clinical remission	Entire GI tract observed in 10/12 patients. Significant inflammatory activity seen in 9/12, good visualisation achieved in both small bowel and colon
D'Haens *et al*., 2015 (53)	Second	40	CD	Evaluation of severity of CD	Good agreement between CCE and CDEIS; however CCE tended to underestimate severity. Sensitivity of CCE to colonic ulcerations 86%, specificity 40%

CCE, colon capsule endoscopy; CD, Crohn's disease; UC, ulcerative colitis; CDEIS, Crohn's Disease Endoscopic Index of Severity; OC, optical (conventional) colonoscopy.

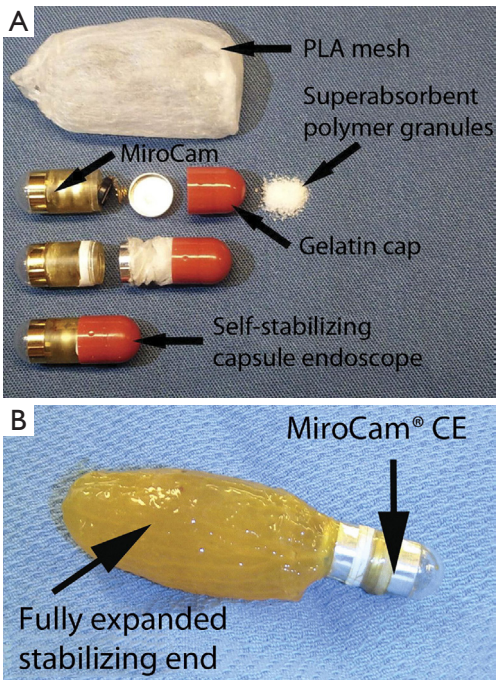

Figure 5 Self-stabilising capsule from Filip *et al.* (A) Components of the self-stabilising capsule. The gelatin cap dissolves in aqueous medium at body temperature to release the expandable stabilising component (PLA mesh); (B) fully expanded self-stabilising capsule. (Images used with permission from Elsevier, originally published in: Filip D, Yadid-Pecht O, Muench G, *et al.* Suture marker lesion detection in the colon by self-stabilizing and unmodified capsule endoscopes: Pilot study in acute canine models. Gastrointest Endosc 2013;77:272-9).

detection rates of colon suture markings when compared with an unmodified conventional capsule endoscope (MiroCam, IntroMedic, Seoul, Korea). However, since this presentation there has been no further information on further phase I studies and no market release date for this product has been officially announced.

More recently, a magnetically-controlled capsule endoscopy (MCCE) system has been developed (70). A pilot study to assess its maneuverability and safety among volunteers undergoing CRC screening is under way. Another project funded by the European Union, the Endoscopic Versatile robotic guidancE, diagnoSis and theraPy of magnetic-driven soft-tethered endoluminAl robots (EndoVESPA) project, is in the process of developing a capsule-based colonoscopy device which is inserted similarly to a conventional colonoscope via the anus and moved through the colon to the caecum by external magnets. It retains a soft tether which allows air insufflation and instrumentation where necessary (*Figure 6*). A study assessing the feasibility of a magnetic robotically-driven capsule endoscopy has been detailed by Arezzo *et al.* (71).

The recently developed Check-Cap® (Check-cap; Mount Carmel, Israel) is a capsule device that images the colon using low-dose radiation (total dose equivalent to a plain abdominal radiograph) and does not require bowel preparation (14,72,73) (*Figure 7*). The patient swallows the capsule with a small amount of a radio-opaque contrast agent, and can continue their everyday activities while data are transmitted to an external hand-held receiver for storage. The clinical performance of Check-Cap is under investigation and the device is still not commercially available.

Software developments

Current capsule endoscopy reading aids take the form of software which (I) improves the visibility of lesions; (II) selects frames for review in order to speed up reading times. Recent software developments are moving towards computer-aided diagnostic systems, aiming to increase diagnostic yield, reduce inter-observer variability and ultimately make the process of capsule endoscopy reading more efficient (74). Some of these have been trialled in other forms of endoscopy, including upper GI tract endoscopy for Barrett's oesophagus (75), and small-bowel capsule endoscopy (76-79). A small number of studies have been published detailing the feasibility of automated polyp detection software in CCE (80,81), but much further development is required.

Conclusions

In 2009, we commented that conventional colonoscopy remains the cornerstone of a successful bowel screening programme either as a primary investigation or following a stool sample positive for faecal occult blood, not only as a diagnostic but also as a therapeutic tool (82). Of note, the bowel preparation regimen requires much adjustment to improve both the accuracy and patient acceptability of CCE. The addition of high definition imaging and further software image enhancement should allow further improvement of CCE validity. CCE has not as yet reached its full potential, and continuous further leaps are

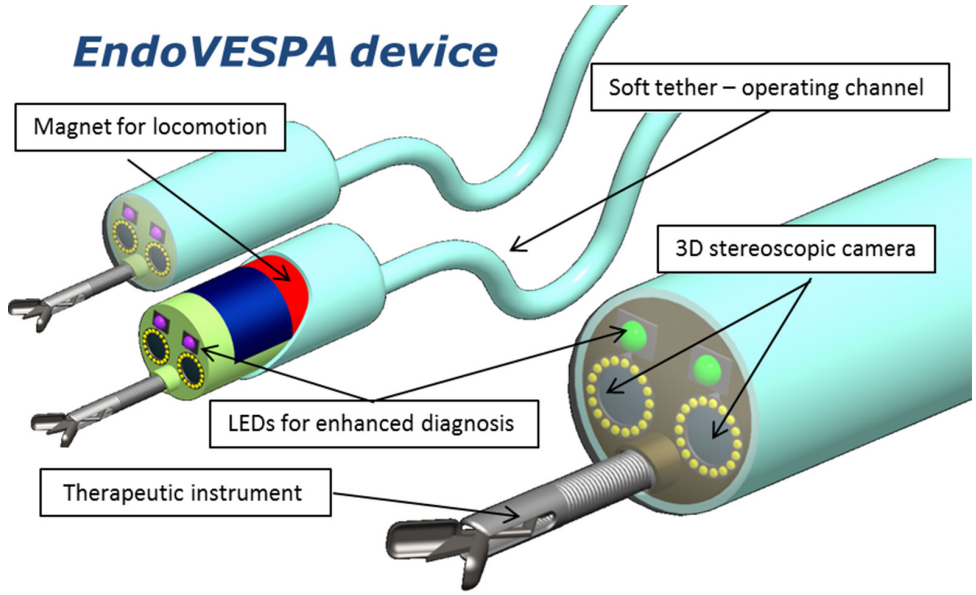

Figure 6 The proposed EndoVESPA platform which is currently under development. EndoVESPA, Endoscopic Versatile robotic guidancE, diagnoSis and theraPy of magnetic-driven soft-tethered endoluminAl robots. (Image used with permission of creator Dr. Gastone Ciuti).

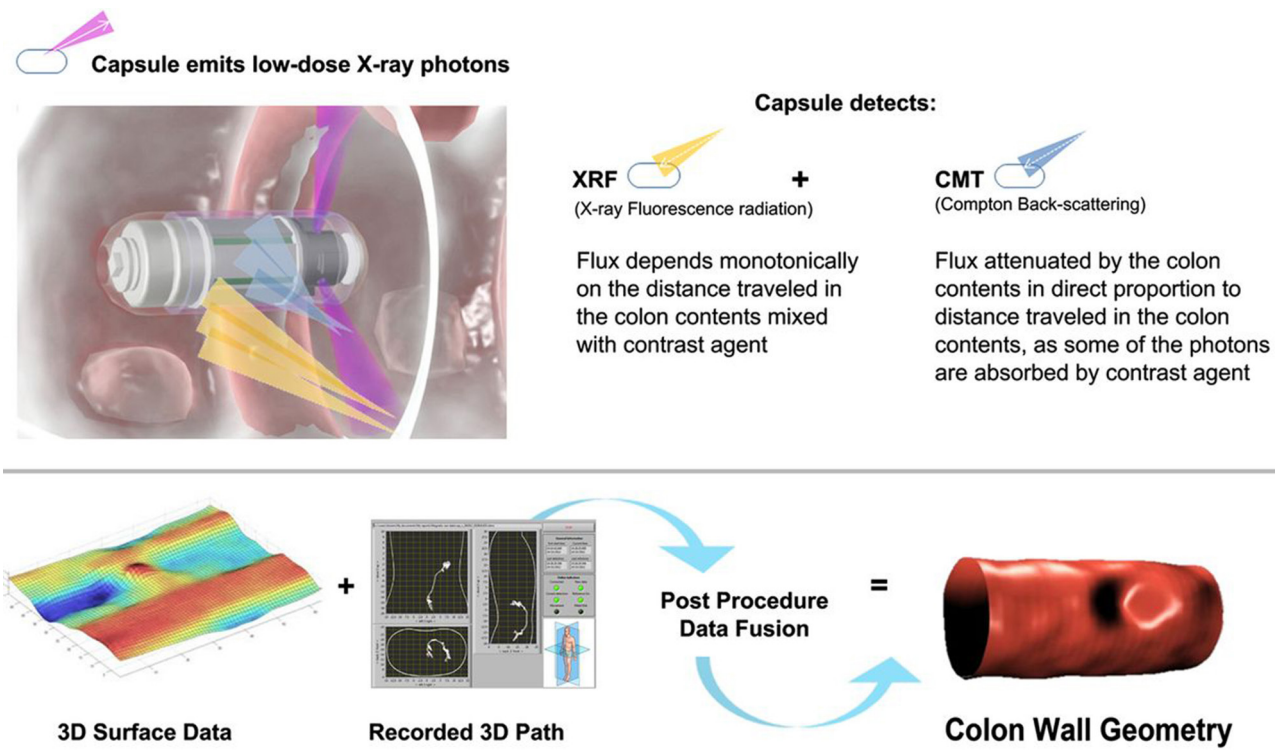

Figure 7 Image acquisition and reconstruction by the Check-Cap®. (Image used with permission from BMJ Publishing Group Ltd., originally published in: Gluck N, Shpak B, Brun R, *et al*. A novel prepless X-ray imaging capsule for colon cancer screening. Gut 2016;65:371-3).

necessary to bring this technology to the point of offering accurate and sustainable panenteroscopy. The show must go on!

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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