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REVIEW

Capsule endoscopy – Recent developments and future directions

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ABSTRACT

Introduction: Capsule endoscopy (CE) is an established modality in the diagnostic algorithm of small bowel (SB) pathology. Its use has expanded for investigation of upper and lower gastrointestinal diseases with similar prototypes.

Areas covered: This review covers the role and recent advances of CE, as a non-invasive investigative tool.

Expert opinion: The use of upper gastrointestinal CE is useful in patients who require surveillance for varices particularly in the current era of the COVID-19 pandemic. It has also shown high accuracy in the detection of upper gastrointestinal hemorrhage in patients presenting with a suspicion of hemorrhage. Findings on CE help to guide further management by device-assisted enteroscopy. The data on colon CE suggest comparable diagnostic accuracy to colonoscopy for polyp detection; however, more evidence is required in the high-risk group. Crohn's CE has become an integral part of the management of patients with Crohn's disease offering a comparative assessment tool post escalation of therapy. Artificial intelligence within CE has demonstrated similar if not better diagnostic yield compared to the human with a significantly shorter reading time. Artificial intelligence is likely to be in-built within CE reading platforms over the next few years minimizing reporting time and human error.

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Small-bowel capsule endoscopy; Crohn's capsule endoscopy; artificial intelligence; magnetically controlled upper gastrointestinal capsule; colon capsule endoscopy

1. Introduction

The diagnosis and management of small bowel (SB) pathology have been revolutionized with the advent of capsule endoscopy (CE). The SB is the longest organ within the gastrointestinal tract and thus it has been the most challenging domain to examine. The invention of the wireless CE has allowed gastroenterologist to investigate the whole of the SB in a noninvasive manner [1]. CE is accepted as the first-line modality to investigate patients with suspected SB gastrointestinal bleeding and is complementary to radiology for investigations of patients with refractory celiac disease and inflammatory bowel disease [2]. Studies have also demonstrated that allied health-care professionals have comparable pick up rate to physicians for a range of pathologies [3,4]. In comparison to radiology, one of the drawbacks of CE, is the length of time to read and report a video in its entity with an average of 30–60 minutes reporting time depending on the SB transit and pathology seen [5–7]. Another challenge faced in CE is the risk of missing pathologies because of the subtle nature of lesions and also because of the fatigability of the human reviewer combined with the low pre-reading experience some reviewers have.

Over the years new features in the capsule reading software have been introduced to minimize human error and to help free up the gastroenterologist for alternative roles such as performing therapeutic endoscopies. SB capsule technology has also been adapted for use in the upper gastrointestinal tract and in the colon. Technology has had to be adapted to suit the different shape of organs and to delineate different pathologies. In inflammatory bowel disease, a single capsule has been developed to identify disease in both the small and large bowel. This is a very attractive alternative for patients who would otherwise require repeated invasive endoscopies at regular intervals.

This review encompasses developments in SB capsule endoscopy, recent advances in upper gastrointestinal endoscopy, colon CE, and the recently introduced PillCam Crohn's capsule. It also highlights the use of artificial intelligence in CE and areas where more evidence is needed to optimize the use of CE in clinical practice.

2. Upper gastrointestinal capsule endoscopy

CE technology has been adapted to provide a noninvasive modality of investigating the upper gastrointestinal tract. Some patients refrain from seeking medical advice because of their concerns of undergoing invasive procedures that they would struggle to tolerate and that involve risks. This also follows a series of studies that have shown the better tolerance of CEs when compared to endoscopic procedures [8–11]. The noninvasive approach to investigating the upper gastrointestinal tract has never been so important to recognize as in the current COVID-19 situation where there has been continuous effort to minimize aerosol-generating procedures and where the demand for endoscopies is greater than the available endoscopic capacity.

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Article highlights

- Magnetically controlled upper gastrointestinal endoscopy provides optimum views of the lower esophagus and the stomach in those with suspected pathology.
- Early small-bowel capsule endoscopy has the added advantage of higher diagnostic yield and reduced hospital stay.
- A repeat capsule endoscopy in patients with refractory coeliac disease can detect mucosal healing demonstrating an additional benefit compared to repeat histology and coeliac antibodies.
- Colon capsule endoscopy is useful in patients with lower risk of colonic pathologies.
- Crohn's capsule endoscopy offers a single investigative modality to patients with inflammatory bowel disease to assess mucosal healing;
- The use of artificial intelligence in capsule endoscopy can help improve reading time, the delineation of subtle changes and eliminate errors associated with human fatigability.

Upper gastrointestinal CE has been investigated as an alternative to gastroscopy as screening or surveillance for gastric and esophageal varices in patients with liver cirrhosis [12,13]. It has been studied for use in patients presenting with upper gastrointestinal bleeding prior to a gastroscopy within the emergency setting. Currently, the standard practice is for patients with suspected upper gastrointestinal bleeding to be triaged according to the Glasgow-Blatchford score. Depending on their score, patients are then admitted to hospital for a gastroduodenoscopy. A recent meta-analysis (five studies; 193 patients) has shown upper gastrointestinal CE to have a high diagnostic accuracy in the detection of upper gastrointestinal hemorrhage (diagnostic odds ratio of 12.62) within the emergency department [14]. CE in the emergency department has also been shown to be more accurate than the Glasgow-Blatchford score in triaging patients who require a hospital admission and cost-effective as it minimizes hospital admissions and the need for gastroduodenoscopy (standard cost for CE including interpretation: 1000 USD vs standard practice of hospital admission with an average length of 4 days hospital stay: 23,549 USD) [15,16]. A CE can increase the likelihood of identifying a cause for bleeding if it is administered at the early stages following hospital admission with anemia or overt gastrointestinal bleeding [17]. Although feasibility of CE in the emergency department may be challenging, it has shown to be beneficial in the low-medium risk groups and warrants further study.

Development of upper gastrointestinal CE has been flawed with challenges. The rapid transit with which the capsule travels down the esophagus and the duodenum has meant that it has been a struggle to obtain adequate views of these two regions [18,19]. Advancement in the technology of upper gastrointestinal endoscopy over the years has reflected the need to overcome these hurdles. A meta-analysis on the use of upper gastrointestinal CE revealed only an 80% sensitivity in detecting Barrett's esophagus [19]. This was based on the use of a dual-headed esophageal capsule that captured images at 18 frames per second for 20 minutes. A more recent study, utilizing a dual-headed capsule that captures images at 35 frames per second for 10 minutes followed by 18 frames per second for a further 80 minutes showed more promising results [20].

The capacious nature of the stomach, the lack of insufflation during CE and the contracted nature of the stomach when an individual fasts have provided additional challenges in upper gastrointestinal CE. The administration of water and simethicone and repetitive position change can help distend the stomach and obtain good views during upper gastrointestinal endoscopy [21,22]. Magnetically assisted upper gastrointestinal capsule endoscopies (MACE) have been developed to overcome some of these challenges. MiroCam Navi (Intromedic, Seoul, South Korea) which is a capsule that can be controlled by an external, handheld magnet was more likely to identify pathology than gastroscopy in patients with refractory iron deficiency anemia. Additionally, 34.7% of patients had significant pathology beyond the second part of the duodenum providing an additional yield compared to gastroscopy [11]. Another study reported a sensitivity for MACE of 73.3% and 100% [23]for the diagnosis of esophageal varices and Barrett's esophagus respectively.

The weight of the external magnet and potential operator fatigue led to the development of the Navicam system (AnX Robotica, Shanghai, China). This consists of a robot-controlled magnet and a capsule that can be moved using joysticks and equipped with pre-programmed, automated, and computer-generated maneuvers. It has been utilized for the detection of gastric cancer in high prevalence populations with a sensitivity of 90% [24]. The reading time can be as short as 14 minutes [24]. This is comparable to the duration of a gastroscopy including the time spent to prepare the instrument prior to the procedure. This makes MACE more attractive to be used in routine clinical care.

MACE can provide good views of the stomach and is well tolerated by patients [25,26]. Some studies have demonstrated that MACE can have a similar diagnostic yield to that of gastroscopy even for superficial gastric lesions [27–29]. It has been approved by the Chinese food and drug administration as an alternative to gastroscopy [30].

A second-generation robotically controlled MACE (Ankon Technologies Co Ltd, Shanghai, China) with a higher adaptive frame rate of 8 frames per second, better image resolution of 720 × 720 pixels, wider field of view of 150 degrees, extended battery life of more than 12 hours has been developed. In a study comparing the first and second-generation MACE, the second-generation MACE showed better mucosal visualization, examination duration, and maneuverability of the capsule. These technological advancements help to optimize the clinical application of upper gastrointestinal CE [31].

Although MACE is promising for the diagnosis of several upper gastrointestinal pathologies including as a screening tool in populations with a high prevalence of certain diseases, for example, gastric cancer in Asian populations and esophageal varices in patients with liver cirrhosis, several limitations remain including the significant cost of hardware and software installation and the acquisition of tissue samples and the application of therapeutics which mean that some patients will require an additional gastroduodenoscopy that can increase the costs further.

2.1. Small-bowel capsule endoscopy

SBCE was first introduced in 2000 [1]. Since then, its technology has been refined to obtain improved images of the SB and to increase its diagnostic yield.

The first generation SBCE (PillCam SB1) provided an 8-h battery life and captured 2 images per second. The angle of view was 140 degrees and it had an eightfold magnification. The second-generation SBCE (PillCam SB2) provided a wider angle of view (156 degrees) and better optics with automatic light control. The third generation SBCE (PillCam SB3) differs from the second generation of SBCE mainly as it has better optics and in the adaptive frame rate allowing up to six frames per second varying according to the speed of movement of the capsule in the SB. This is an important feature that allows for battery life to be conserved when the capsule is moving slowly along the SB. It also increases the chances of the capsule exiting the SB before it runs out of battery life. This can be important in patients with conditions or on medications that can cause a slow SB transit. Even though there are considerable differences between the second and third generation SBCE, there have been studies that have shown that there is no significant difference in completion rate and diagnostic yield between the two forms of SBCE [32,33]. Another important improvement over the years has been the development of a sensory belt that patients can put on. This replaces the leads that are attached to the chest and abdomen that enable data transmission to the recorder.

Other platforms of CE that are available for use in patients with suspected SB conditions have a longer battery life of up to 11 to 12 hours (MiroCam, CapsoCam) [34]. The angle of view can also be wider (170 degrees in MiroCam). This helps to improve the visualization of the SB mucosa.

Panoramic SBCE was introduced in 2013 [35]. It differs considerably from the standard axial SBCE in that it provides panoramic views as opposed to axial views because it has four cameras (two at either end) as opposed to two cameras [36]. It has a longer battery life of 12 hours and the capsule itself has a data storage system. This means that a recorder, leads, or a sensory belt are not required for data acquisition. It also encompasses the added advantage that SBCE can be posted to patients and does not require a hospital visit, an important aspect to consider in the current situation of the COVID-19 pandemic. However, it also has the added disadvantages that patients have to retrieve the capsule. It can also take longer for physicians to review the SCBE as this type of capsule does not have an adaptive frame rate and has a longer battery life [37]. Interpretation of panoramic images requires considerable experience in the field of SBCE. It has been studied in patients undergoing SBCE for several indications including Crohn's disease and suspected SB bleeding [38]. Panoramic SBCE has been compared to axial SBCE with some studies suggesting a higher diagnostic yield [34] whilst other studies showed a comparable ability to detect lesions [39,40].

The roles of SBCE have expanded over the years to include assessment of disease activity in patients with suspected SB Crohn's disease and to assess mucosal healing in those who have undergone escalation of therapy. SBCE lands a helping hand to device-assisted enteroscopy (DAE), which allows for histology to be obtained and for therapeutic procedures to be performed. As it is invasive and can be associated with complications related to anesthesia, perforation, and bleeding, SBCE should be the first diagnostic investigation of choice in patients with suspected SB pathology. SBCE is also important in determining the route of insertion in DAE [41,42]. If the pathology is within the first 2/3 of the SB, an antegrade DAE is advocated. A repeat SBCE is also useful following DAE where the suspected pathology has not been reached and where the most distal point of SB examined has been tattooed. It will help determine whether there is pathology distal the SB tattoo that has not been reached during DAE [43,44]. SBCE is useful in patients with Crohn's disease and refractory celiac disease (RCD), who undergo repeat SBCE to assess for ongoing active disease and to rule out complications [45–54] In our recent study on the use of CE in the management of patients with RCD, we showed that patients with RCD had an improvement in the extent of affected SB mucosa (42.4±34.1% vs 26.4 ±28.9% $p = 0.012$) after administering steroids and/or immunosuppressants. This contrasted with the lack of variation in celiac disease antibodies and histological changes [51]. In patients with hereditary hemorrhagic telangiectasia, it is useful to carry out an SBCE prior to considering DAE for argon plasma coagulation (APC) of angioectasias to assess number and location of these lesions [55]. Patients with Peutz Jeghers syndrome undergo SBCEs at regular intervals to monitor the size of polyps [56,57]. Larger polyps can be associated with complications such as intussusception and therefore should be considered for removal by DAE. SBCE is non-invasive and therefore the preferred modality to monitor these conditions. It is deemed complementary to MR enterography.

Over the past few years, more literature has emerged on the timing of SBCE in suspected SB bleeding. Repeating endoscopic procedures before considering SBCE has not been shown to be cost-effective in some studies [58,59]. Other studies have also explored the use of early SBCE close to the time of admission to hospital with gastrointestinal bleeding. In a study by Marya et al, a bleeding source was localized in 64.3% of patients receiving an early SBCE and in 31.1% of the patients receiving standard care ($p < 0.01$) [17]. Another group of authors assessed the diagnostic yield of SBCE in patients with overt SB bleeding depending on the timing of SBCE from the time of presentation. They showed that a higher diagnostic yield was achieved if the SBCE was carried out earlier [60]. Similar findings were demonstrated by Singh where patients who had a SBCE within 3 days of presentation had the highest diagnostic yield [61]. Earlier diagnosis of SB pathology can also lead to earlier intervention and a lower rebleeding rate [62]. A higher therapeutic yield is achieved if DAE is carried out closer to the time of bleeding (within 2 days) [63].

The use of biomarkers can help determine who is most likely to benefit from SBCE, improve the diagnostic yield, and make the best use of the resources we have. Fecal immunochemical test (FIT) has been shown to be a useful biomarkers in predicting the likelihood of SB pathology in patients with anemia [64]. It has a high negative predictive value for small-bowel lesions [64,65].

Fecal calprotectin (FC) is a useful screening tool to help select patients with suspected SB inflammation for SBCE and

in patients with established inflammatory bowel disease with a high suspicion of active disease in the SB. FC has a significant diagnostic accuracy for the detection of SB Crohn's disease [66–68]. In patients with suspected CD with an FC less than 50 µg/g, the likelihood of positive diagnosis is very low [69]. FC has a high negative predictive value for inflammation in the SB if levels are low [70,71]. A good correlation has also been demonstrated between FC and Lewis score on CE and Capsule Endoscopy Scoring Index [72,73]. FC is also a good predictor of mucosal healing on CE in patients with established Crohn's disease who have received treatment [73].

The role of virtual chromoendoscopy to improve the delineation of changes on SBCE has been widely studied. This is based on virtual chromoendoscopy (Pentax I scan) and dye spray chromoendoscopy in upper gastrointestinal endoscopy and colonoscopy where indigo carmine is used to improve the delineation of dysplastic changes in patients with inflammatory bowel disease and to help identify the pit pattern of colonic polyps. Flexible spectral color enhancement (FICE) is a mathematical algorithm that processes SB images in conventional white light and enhances light in certain spectra – mainly red, green, and blue. Different FICE settings can be chosen from the reading software whilst reviewing SBCE (FICE 1, 2, 3, or blue light) in an attempt to improve the diagnostic yield of SBCE. In a recent meta-analysis, it has been concluded that virtual chromoendoscopy does not help to improve the delineation of lesions in the SB except for pigmented lesions mainly angioectasias and ulcers [74]. The underlying theory is that FICE can enhance the light that is captured and reflected by hemoglobin in these lesions.

A dual headed SBCE (one camera at either end) [75] has been compared to a standard single camera SBCE [76]. Although it provides wider coverage of the SB (340 degree views), no statistical improvement in diagnostic yield has been reported. Even though more studies are required to assess the utility of this type of SBCE, without the added benefit of improving the diagnostic yield, it can unnecessarily prolong the physician reading time that is required.

Traditionally, bowel preparation has been administered prior to a SBCE. The type of bowel preparation that is administered prior to SBCE has been widely debated. In a recent meta-analysis, administration of bowel preparation prior to SBCE did not improve the diagnostic yield but it improved the visualization of the SB [77]. This contrasts with a previous meta-analysis that showed better visualization of the SB with bowel preparation and a better diagnostic yield [78]. The results on the type of bowel preparation given in both meta-analysis were also contradictory. Yung et al. demonstrated that patients given polyethylene glycol had a lower diagnostic yield than those that received sodium phosphate [77]. Belsey et al. showed that polyethylene glycol-based regimens showed benefit, while sodium phosphate-based regimes yielded no significant difference from fasting alone [78]. A more recent study has shown that patients receiving 4 liters of clear liquid had significantly higher mean image quality scores when compared to the polyethylene glycol group [79]. Bowel preparation closer to the time of SBCE (4 hours or after real-time confirmation of the arrival of the capsule in the SB) can achieve better views than bowel preparation administered 12 hours or the day before SBCE [80,81]. In more recent studies, the addition of simethicone to polyethylene glycol was shown to improve the quality of visualization in the proximal and distal SB [82,83]. SB units are routinely incorporating simethicone in the bowel preparation regime prior to SBCE [80,84].

Overall, the findings indicate that administration of bowel preparation is associated with a similar diagnostic yield to no bowel preparation. The European Society of Gastrointestinal Endoscopy (ESGE) recommends that prior to SBCE patients follow a modified diet and that they ingest a purgative (2 L of polyethylene glycol) for better visualization. Antifoaming agents are also recommended prior to capsule ingestion [85]. More studies are awaited to enable clear guidelines on bowel preparation to be formulated.

Capsule retention occurs when the capsule does not pass two weeks or more following ingestion requiring endoscopic or surgical intervention to retrieve the capsule [86]. The retention rate is estimated to be 1.2–2.1% for patients with suspected SB bleeding, 2.35% and 4.63% for suspected and established SB Crohn's disease, respectively, 2.2% for those presenting with abdominal pain and diarrhea and 2.1% in patients with neoplastic lesions [87–89].

Patients in whom a capsule is thought to be retained should be followed with an abdominal x-ray to ensure passage of the capsule. Capsule retention can occur in patients with benign inflammatory strictures or malignant strictures and usually occurs proximal to a stricture. Very rarely, capsule retention can precipitate SB obstruction requiring emergency management as it gets retained within a strictured segment [90–92]. DAE can allow for SBCE retrieval [93] and can be combined with stricture dilatation [94]. Patients with SB obstruction, overt SB bleeding due to the capsule causing local ulceration and those with perforation run a higher risk of requiring surgery in case of capsule retention [95,96]. In patients with inflammatory strictures such as those with Crohn's disease, medical treatment (e.g. steroids, anti-TNF therapy) is recommended as the initial management by the ESGE. In case of failure, retrieval by DAE should be considered [2,97].

Capsule retention can be minimized by the use of a patency capsule (PillCam™) [2]. It consists of a lactose body and a barium section that enables fluoroscopic visualization. It also has one timer plug at each end to facilitate controlled disintegration of the capsule body in case of a narrowed SB. Retention of the patency capsule 30 hours after ingestion is an indication not to proceed with SBCE. ESGE guidelines recommend the administration of a patency capsule in high-risk groups such as those with abdominal pain, distention, and symptoms suggestive of obstruction and in patients with a higher risk of strictures such as those with a history of non-steroidal anti-inflammatory drug use or those with SB Crohn's disease. This is to minimize the risk of retention [2]. Patency capsule has a pooled sensitivity of 97% and specificity of 83% in confirming SB patency [98]. Retention rates have been

shown to be minimized by 2.88% in patients with underlying Crohn's disease [89]. A limited CT scan is better at localization of a retained patency capsule than an abdominal x-ray [99,100].

2.2. Colon capsule endoscopy

Colonoscopy is considered the gold standard and investigation of choice in patients with lower gastrointestinal symptoms and those suspected of having neoplasia. However, a significant proportion of examinations in the symptomatic population are found to be normal [101]. The use of fecal immunochemical test (FIT) has been found to be helpful in stratifying patient risk [101]. Colon capsule endoscopy (CCE) is an alternative wireless modality for the lower gastrointestinal tract and is now in its second iteration (CCE-2). Whilst it is marginally larger than the SB capsule, it is equipped with an additional camera head (one on either side). It has an adaptive frame rate to acquire images up to 35 frames per second depending on the velocity of the capsule and thus also preserving battery life. The laxative required for the examination is deemed more burdensome than that for a colonoscopy [102]. The data recorders that patients wear have inbuilt software that detects capsule location and releases prompts for patients to take the additional laxative boosters.

CCE-2 has been evaluated mainly for the detection of neoplasia and when compared to computed tomography colonography (CTC) in patients with incomplete colonoscopy, CCE2 had similar if not better yield [102,103]. Meta-analysis suggests that colon capsule endoscopy has a sensitivity and specificity of detecting polyps ≥6 mm of 86–87% and 87–88%, respectively. In the detection of polyps ≥10 mm, CCE had a sensitivity of 87% and specificity of 95% compared to colonoscopy [104,105]. The European Society of Gastrointestinal Endoscopy (ESGE) suggests the use of CCE in low to moderate risk groups [106]. CCE has been studied as a triage tool in a screening population with a positive FIT test to decide on which patients require a colonoscopy [107]. In a Spanish, prospective randomized study of 257 patients with a FIT (≥20 μg of hemoglobin/g of feces), the sensitivity of CCE and CTC in detecting significant lesions (≥6 mm in size at colonoscopy) was 96.1% and 79.3%, respectively. CCE was also better in detecting advanced colorectal neoplasia than CTC (sensitivity 100% and 93.1%) [108].

The recent pandemic of COVID 19 has resulted in the pause of endoscopic activity worldwide. Although endoscopic activity is being resumed, there is a significant reduction in capacity resulting in a delay to patient investigations and treatment [109,110]. Patients with high-risk symptoms or those with FIT level >100 ug/gm are being prioritized for colonoscopy. More recently the National Health Service body for England has recommended CCE as an option in addition to standard CT or CT colonography in patients with lower gastrointestinal symptoms and with a FIT level between 10–100Uug/gm, as there may be a significant delay for colonoscopy [111]. Robust data collection and follow up are recommended in this group. More data particularly within this current time is likely to influence how we investigate patients with increasing use of CCE and steering away from conventional endoscopy [112].

2.3. Pillcam Crohn's

Crohn's disease affects the gut from mouth to anus but has a predilection for the terminal ileum and cecum. Standard investigations include colonoscopy to investigate the large bowel and either magnetic resonance imaging enterography (MRE) or a CE to investigate the SB [113]. The PillCam Crohn's (Medtronic, Dublin, Ireland) is a novel combined panenteric capsule developed to identify inflammatory activity in both domains using a single capsule. The technology is similar to the CCE where it has camera heads at both ends providing a field of view of 344 degrees [114]. The reporting software is equipped with severity scoring over successive examinations for comparisons after modification of treatment. The first comparative study showed the diagnostic yield per subject was 83% for Pillcam Crohn's compared to 69.7% for ileocolonoscopy (incremental yield 13.6%, 95% CI 2.6–24.7) [115].

A 5 center prospective study by Eliakim et al. investigated the feasibility of this new device in 41 patients with Crohn's disease detecting active disease in 53% of the patient cohort. Cleansing was deemed good or excellent. It is imperative that the capsule has complete visualization and in this study the CE reached the toilet in 83% of cases [116]. The BLINK study group compared the use of Crohn's Pillcam versus conventional colonoscopy and MRE in 99 patients recruited from 21 centers [117]. Central readers were trained and blinded. They reported the sensitivity of CE was superior for proximal inflammation whilst the sensitivity for distal SB and colonic inflammation was comparable to the standard arm in 99 patients. However, there was capsule retention behind an ileo-colonic stricture highlighting the importance of the role of a patency capsule. A greater number of patients preferred this combined procedure compared to standard tests.

A simulated 20 year cost analysis comparing panenteric CE versus MRE & colonoscopy calculated a cost of £42,266 with colonoscopy and MRE and £38,043 with panenteric CE [118]. Although costs with panenteric CE were expected to be higher within the first 2 years due to step up of therapy, subsequent surgery was reduced from year 3 onwards suggesting this technique to be cost-effective for the National Health Service in the United Kingdom, with a potential better quality of life from the patients' perspective.

Recent literature suggests that patients may have endoscopic activity seen on CE despite being in clinical remission [119]. The Montreal classification of disease can be upstaged if active disease is detected in the gastrointestinal tract using Pillcam Crohn's in particular if active disease in the proximal SB is detected [120]. This can then guide further treatment escalation. Findings at CE have also shown to predict a clinical relapse [121]. This provides the clinician with motivation for step-up therapy. CE thus provides an important modality for investigation of disease severity and mucosal healing throughout the pathway of the patient from diagnosis, prediction of a clinical flare, post-operative assessment of disease recurrence, and its role in treating to target [122].

2.4. Artificial intelligence in capsule endoscopy

The reading of CE videos can be time-consuming [5–7]. Furthermore, the fatigued human eye may miss subtle

pathology including indiscreet mucosal bulges. In recent years, artificial intelligence has made significant progress in the field of medicine including gastroenterology. Machine Learning has enabled feature extraction and in combination with deep neural networks, image classification has now materialized for routine endoscopy for the clinician.

Artificial intelligence can broadly be broken down into machine learning, artificial and convolutional neural networks, and deep learning. With machine learning, the computer is fed a set of training data by the human so that it can 'machine learn' and generate mathematical algorithms to be used on new data without the help of a human [123]. Artificial neural networks are hidden pathways between a network of multilayer interconnections which have the ability to use the weight of a connection to produce the best result.

Artificial intelligence has been utilized for the detection of early neoplasia in Barrett's esophagus, neoplastic lesions in stomach, and mucosal changes related to Helicobacter pylori [124,125].

Another particular area of machine learning development has been colorectal polyp detection. The detection rate of adenomas has been a quality indicator for standard colonoscopy particularly in screening cohorts as it has shown to reduce interval cancer. Whilst high-quality colonoscopy remains the aspiration of all endoscopists, studies have demonstrated a miss rate for polyps of up to 22% [126]. It is thought that at least 50% of all interval carcinomas arise from missed lesions during colonoscopy [127]. The breakthrough in artificial intelligence has been both in 'real time' and increase in the detection rate of adenomas [128,129].

The SB however has lagged behind until recently. Artificial intelligence has been used for the detection of bleeding lesions, ulcers, and celiac disease [130,131]. In a large study by Ding et al., a deep convolutional neural networks were trained on more than 150,000 images to recognize common SB pathologies. This model was further validated in 5000 patients and identified pathologies with 99.9% sensitivity and specificity, respectively. This was superior to the human reviewer who identified abnormalities with a 74.6% sensitivity. The machine model was also instrumental in decreasing the reading time from 96.6 minutes to 5.9 minutes [131]. In another study, DAISY descriptors were used to project two-dimensional images onto one-dimensional vectors and therefore help identify features of celiac disease on CE. The reported sensitivity and specificity were 94.35% and 83.20%, respectively, in distinguishing celiac disease features from controls on SBCE [132].

In a recent meta-analysis, the reported ulcer detection sensitivity and specificity were 0.95 and 0.94, respectively, and bleeding lesions were detected with 0.98 and 0.99 sensitivity and specificity, respectively, [130]. Although a number of studies have been carried out that demonstrate the potential of artificial intelligence in the detection of SB pathology on SBCE, none of these algorithms have been embedded in the capsule reading software for use in clinical practice.

One of the contentious issues in artificial intelligence has circled around the training set of data that is fed to the machine which begins the human-machine collaboration. If this initial data set is flawed with bias, such as demographics and range of pathology, the output from the computer-aided design model will also be skewed and this is reflected in the final algorithm output.

Table 1 provides a summary of indications and evidence for use of different CE platforms (Table 1).

2.5. Training in small-bowel capsule endoscopy

Although CE has been utilized widely, training in CE has lagged behind other forms of endoscopy. Recently, the ESGE recognized this gap and formulated a working group to devise a curriculum for SB endoscopy, which has been published [133]. Prior experience in bidirectional endoscopies helps in the detection of pathologies on SBCE and is desirable for training in SBCE [134]. The curriculum also describes the importance of structured courses where indications and contraindications of SBCE are covered and where hands-on experience is encouraged [135]. Training in SBCE is ideally carried out in the form of a fellowship program where trainees are exposed to a high volume workload of SBCE and with regular participation in SB multidisciplinary team meetings where SB imaging is discussed as a complementing investigation to SBCE. For quality of training to be ensured, a training center must carry out a minimum number of 75 to 100 SBCEs per year [133]. Competence in SBCE can be assessed ideally in a structured training program using direct observation of procedural skills [136], short test videos, and multiple-choice questions [137]. Achieving competence in SBCE interpretation

Table 1. A summary of indications and evidence for use of different capsule endoscopy platforms.

Upper gastrointestinal capsule endoscopy	It is a noninvasive alternative approach to gastroscopy for esophageal and gastric varices. Magnetically controlled capsule can provide better views of the stomach & minimize reading time.
Small bowel capsule endoscopy	As it is noninvasive, it should be the first diagnostic investigation in patients with suspected small bowel pathology particularly mid gut bleeding. If the pathology is within the first 2/3 of the small bowel, antegrade device assisted enteroscopy can be carried out to assess, biopsy lesions or apply therapeutics. Early capsule endoscopy in relation to presentation, can increase the diagnostic yield in patients with small bowel bleeding. Biomarkers (fecal calprotectin, FIT) help to increase the diagnostic yield of capsule endoscopy. A modified diet, 2 liters of polyethylene glycol with antifoaming agents are recommended prior to capsule endoscopy Capsule retention can occur in up to 1.2% of patients with suspected small bowel bleeding and is higher (up to 4.63%) in patients with established small bowel Crohn's disease. A patency capsule minimizes the risk of retention and is indicated in higher risk groups.
Colon capsule endoscopy	It has a good sensitivity & specificity for the detection of colonic polyps compared to colonoscopy and a better diagnostic yield in the detection of polyps and neoplasia compared to CT colonography.
Pillcam Crohn's	It is an alternative single non-invasive investigation for investigating and monitoring patients with Crohn's disease.

forms a good background for training in DAE [41,138,139]. Formalizing training in SBCE will ensure that training in SBCE is uniform and that the skills required to review SBCEs are similar across centers specializing in the management of patients with SB pathologies.

3. Expert opinion

Magnetically controlled upper gastrointestinal capsule has the potential to become a viable alternative for investigation of the upper gastrointestinal tract. The recent developments have demonstrated maximization of views and minimized reading times. Patients with lower risk of pathology and those who are unlikely to require histological samples will benefit the most from upper gastrointestinal capsules. As the esophageal views continue to improve, upper gastrointestinal capsule will likely replace gastroscopy in the surveillance of esophageal and gastric varices. However, more data are required for other cohorts of patients who require ongoing surveillance such as those with Barrett's esophagus. These patients do not necessarily require histological samples to be taken unless there are suspicious mucosal changes and therefore are ideal candidates for upper gastrointestinal CE as a surveillance tool. To overcome the limitation of not being able to take gastric biopsies, patients with symptoms of dyspepsia and with evidence of gastritis on upper gastrointestinal CE will benefit from combined Helicobacter pylori stool test.

SBCE undoubtedly continues to be useful if carried out early in patients suspected of having SB bleeding, for surveillance in patients with refractory celiac disease, in those with suspected malignancy and patients with SB Crohn's disease. Findings on SBCE help to guide further management by DAE. Chromoendoscopy is not helpful to improve diagnostic yield except in patients with SB ulcers and angioectasias.

Data on bowel preparation prior to SBCE so far are conflicting as some studies suggest that it does not improve diagnostic yield. Studies on bowel preparation closer to the time of SBCE have also shown more promising results. Bowel preparation may potentially impact on the cost-effectiveness of SBCE as it can determine how many patients require a repeat SBCE or alternative dedicated SB imaging. More studies are required to clarify the role of bowel preparation prior to SBCE.

Different SBCE platforms have different battery lives, varying resolutions and not all of them are equipped with an adaptive frame rate. The panoramic SBCE has the added advantage of not requiring a sensory belt or recorder. However, as it lacks an adaptive frame rate, more reading time is required. Optimizing the features of these different platforms may potentially make them more competitive in the SBCE market.

CCE has an important role to play in those patients with a low suspicion of colonic pathologies, in those with incomplete colonoscopies and in patients with ulcerative colitis or colonic Crohn's disease. Further evidence is required for routine use in the higher risk populations such as those with elevated FIT levels. This data will very likely emerge following the COVID-19 pandemic as some centers are adapting their practices to allow patients with a high FIT test to have a CCE and/or a CT colonography whilst they wait for or instead of their colonoscopy which is delayed due to limited endoscopic capacity.

Crohn's CE provides an exciting single pill option for the management of Crohn's disease. It has enabled assessment of disease activity in symptomatic patients prior to escalation of treatment and assessment of mucosal healing following the addition of biologics or combination therapy with immunosuppressants. Patient selection guided by fecal calprotectin may increase the diagnostic yield of Crohn's CE.

AI is likely to be in built with CE reading platforms within the next 2 years. This development will no doubt expand to CE for other parts of the gastrointestinal tract. This wireless and patient-friendly technique combined with rapid reading platforms with the help of artificial intelligence will become an attractive and viable choice to alter how patients are investigated in the future within gastroenterology. One downside to AI is the impact on training as the role of the human reviewer is taken over by the machine. It will be important to continue to recognize the benefits of competence in SBCE reading prior to embarking on training in DAE.

4. Conclusion

This review outlines the utility of CE in the upper gastrointestinal tract, SB, and colon. It provides a non-invasive approach to investigating patients with several gastrointestinal symptoms and also those with established conditions that require ongoing surveillance. Although efforts to improve the visibility of pathologies and to minimize reading time are ongoing, CE has the added advantage of not being associated with risks of sedation/anesthesia and the risks of perforation and bleeding that are established risks in standard endoscopies.

The non-invasive nature of CE means that is an investigation that is greatly sought after in the recovery period following the COVID19 pandemic. This is because it provides an alternative investigative modality without the generation of aerosols and helps offload the pressures from the endoscopic services where currently the demand is greater than the capacity to carry out endoscopic procedures. The use of CE as an alternative to wired endoscopy is also likely to change our practices in the long term. For example, CCE may be utilized more widely to replace colonoscopy in the long term.

We are also learning how to utilize biomarkers such as FC and FIT to maximize the diagnostic yield of CE and to make the best use of CE resources we have.

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• **This is a recent study that compares the sensitivity of panteric capsule endoscopy to MRI of the small bowel and ileocolonosopcy in patients with Crohn's disease**

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