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MINIREVIEWS

Small-bowel capsule endoscopy: A ten-point contemporary review

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Abstract

The introduction of capsule endoscopy (CE) in clinical practice increased the interest for the study of the small-bowel. Consequently, in about 10 years, an impressive quantity of literature on indications, diagnostic yield (DY), safety profile and technical evolution of CE has been published as well as several reviews. At present time, there are 5 small-bowel capsule enteroscopy (SBCE) models in the worldwide market. Head-to-head trials have showed in the great majority of studies comparable results in terms of DY, image quality and completion rate. CE meta-analyses formed the basis of national/international guidelines; these guidelines place CE in a prime position for the diagnostic work-up of patients with obscure gastrointestinal bleeding, known and/or suspected Crohn's disease and possible small-bowel neoplasia. A 2-L polyethylene glycol-based purge, administered the day before the procedure, is the most widely practiced preparation regimen. Whether this regimen can be further improved (*i.e.*, by further decreasing its volume, changing the timing of administration, coupling it with prokinetics and/or other factors) or if it can really affect the DY, is still under discussion. Faecal calprotectin has been used in SBCE studies in two settings: in patients taking non-steroidal anti-inflammatory drugs, to evaluate the type and extent of mucosal damage and, more importantly from a clinical point of view, in patients with known or suspected Crohn's disease for assessment of inflammation activity. Although there is still a lot of debate around the exact reasons of SBCE poor performance in various small-bowel segments, it is worth to remember that the capsule progress is non-steerable, hence more rapid in the proximal than in lower segments of the small-bowel. Capsule aspiration, a relatively unexpected complication, has been reported with increasing frequency. This is probably related with the increase in the mean age of patients undergoing CE. CE video review is a time-consuming procedure. Therefore, several attempts have been made to develop technical software features, in order to make CE video analysis easier and shorter (without jeopardizing its accuracy). Suspected Blood Indicator, QuickView and Fujinon Intelligent Chromo Endoscopy are some of the software tools that have been checked in various clinical studies to date.

Key words: Capsule endoscopy; Calprotectin; Meta-analysis; Review; Preparation; Reading software; Complication; Indications

Core tip: This innovative, concise and "unique" review (structured as Q and A with several tables that make this paper very easy to read and hopefully enjoyable), keeps narrative text to the necessary minimum, in order to guide the reader to consult the wealth of information included in tabulated form. These tables are the outcome of the authors' personal endeavor to compile in a detailed, yet easy to refer way, informa-

tion that has often been overlooked by the plethora of similar reviews and/or info on contentious issues in capsule enteroscopy. We believe that this document can be used as reference for study, in reference lists of future manuscript and as important guide for future clinical research on the field.

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INTRODUCTION

An early conceptual abstract on capsule endoscopy (CE), entitled "an endorobot for flexible endoscopy, a feasibility study", was published in 1994[1]. Then, in 1997 two groups of pioneers, initially working independently in Israel and London, joined forces to achieve wireless endoscope[2]. Three years later, in the Digestive Disease Week meeting of the millennium and almost concurrently in *Nature*[3], Professor Swain presented the world's first wireless capsule endoscope.

Indeed, the brainchild of Iddan[4] has revolutionised the field of gastrointestinal (GI) diagnostics, turning into reality the concept of painless and wireless endoscopy. Furthermore, the introduction of CE in clinical practice increased the interest for the study of the small-bowel. Consequently, in about 10 years, an impressive quantity of literature on indications, diagnostic yield (DY), safety profile and technical evolution of CE has been published as well as several reviews. Therefore, we aim to focus readers' attention on contemporary and contentious issues, often missed from similar reviews on the field. We herein present (in a comprehensive yet user-friendly manner) a systematic review of the current literature in a form of question-and-answer. We expect CE readers, of all experience levels, will find this review useful source of further reading and reference.

WHICH ARE THE DIFFERENCES AMONG THE CURRENT COMMERCIALLY AVAILABLE CAPSULES?

Since 2001, the year of approval by the Food and Drug Administration of the first video capsule with the prophetic, yet slightly unfortunate, brand name mouth-to-anus (M$_2$A®; Given®Imaging, Yoqneam, Israel), a total of more than 2000000 capsules have been ingested worldwide[5]. Furthermore, over the last decade, technology has improved in the field of CE as competition has become quite stiff. At present time, there are 5 small-bowel capsule enteroscopy (SBCE) models in the market worldwide (Table 1)[5,6]. Although similar in size and shape, they differ on several technical aspects. Of the 5 SBCE, four are in widespread use, although most of the published literature studies are with PillCam®. Nevertheless, head-to-head trials have showed in the great majority of studies comparable results in terms of DY, image quality and completion rate (Table 2)[7-11].

DO HIGH-GRADE EVIDENCE SUPPORT THE USE OF CE IN CLINICAL PRACTICE?

In recent years, many authors[12-14] reviewed systematically the validity of SBCE in clinical practice. Out of this evidence base, it clearly emerges that in daily practice the leading indications for CE are: Obscure gastrointestinal bleeding (OGIB accounts for 60%-70% of all SBCE examinations world-wide), and Crohn's disease (CD; known and/or suspected). Other clinical indications, although less common, are coeliac disease, small-bowel polyposis syndromes and clinical suspicion of small-bowel neoplasia[15,16]. Therefore, we decided to summarize (Table 3)[17-32], the results of the more robust - from a methodological point of view - publications which addressed the role of CE in the field of small-bowel coeliac disease. These meta-analyses have formed the basis of national/international guidelines, which place CE in a prime position for the diagnostic work-up of patients with OGIB, known and/or suspected CD and possible small-bowel neoplasia[33-36].

WHICH IS THE BEST PREPARATION REGIMEN FOR SMALL-BOWEL CAPSULE ENDOSCOPY?

This certainly is one of the most contentious issues in CE. Since the introduction of CE in clinical practice, it was clear that small-bowel cleanliness is one of the key factors (as in fact is often the case for endoscopic examinations) to guarantee high diagnostic performance. Thus far, several studies have been performed in order to test whether the administration of different purgatives and/or prokinetics would impact on small-bowel cleanliness. It is noteworthy that these studies are rather heterogeneous in terms of type of laxatives administered, dosages and/or administration schedule (Table 3)[22,25,30]. Furthermore, in some studies laxatives and prokinetics were administered concurrently, which is probably a further source of bias. Essentially, the current evidence base suggests that a preparation regimen based on laxatives [more specifically polyethylene glycol (PEG)] is more effective -than fasting alone- in improving the small-bowel mucosa visualization. Among the PEG-based laxatives, a low volume schedule seems to be at least equally effective than high volume regimens[25,30]. Therefore, a 2-L PEG-based purge, administered the day before the procedure, is the most widely practiced preparation regimen. Whether this regimen can be further improved (*i.e.*, by further decreasing its volume, changing the timing of administration, coupling it with prokinetics and/or other pharmaceutical factors) or if it can really affect the DY, is still under discussion[37].

Table 1 Available types of small-bowel capsule endoscopes and operating characteristics

Capsule device	Company	Country	Field of view (°)	Lens	LEDs	Image sensor	Transmission	Frames per second (fps)	Dimensions (mm)	Weight (g)	Battery life (h)	Real-time imager	FDA approval	Reviewing software	Optical enhancements
PillCam®SB2	Given®Imaging, Yokneam	Israel	156	Multi-element	4	CMOS	Radiofrequency	2-4[1]	11 × 26	3.45	9->11.5[2]	Yes	Yes	Rapid®v7	Blue-mode FICE 1,2,3
MiroCam®v2	IntroMedic® Co., Seoul	South Korea	170	N/A	4	CMOS	EFP	3	ø11 × 24	3.2	12	Yes	Yes	MiroView®v2	ALICE colour-mode
EndoCapsule®	Olympus© Co., Tokyo	Japan	145	N/A	4	CCD	Radiofrequency	2	ø11 × 26	3.45	10	Yes	Yes	OLYMPUS® WS-1	Contrast imaging
OMOM® (SmartCapsule)	Chongding Jinshan Science and Technology Co., Beijing	China	140	N/A	4	CCD	Radiofrequency	2 (variable)	13 × 27.9	6	8	Yes	No	OMOM® workstation	N/A
CapsoCam®SV1	CapsoVision® Inc., Saratoga	United States	360	N/A	16	N/A	On-board EPROM flash memory (USB)	16 (4 per camera)	11 × 31	N/A	15	No	No	CapsoView®	N/A

[1]PillCam®SB2 (L) captures 2 fps - PillCam®SB2-4 captures 4 fps; [2]PillCam®SB2 (L) battery life > 11.5 h - PillCam®SB2-4 battery life 8 h. LED: Light emitting diode; N/A: Not available; CMOS: Complementary metal-oxide-semiconductor; CCD: Charge-coupled device; EFP: Electric field propagation; EPROM: Erasable programmable read-only memory; USB: Universal Serial Bus; FDA: Food and Drug Administration; FICE: Fujinon Intelligent Chromo Endoscopy; ALICE: A Large Ion Collider Experiment.

IS THERE A ROLE FOR FAECAL TESTING (CALPROTECTIN) AS "SELECTION TOOL" FOR CAPSULE ENDOSCOPY

Due to its high DY and its negative predictive value (NPV), CE has shown considerable cost-effectiveness[38]. However, CE still remains less widely available and likely more expensive, when compared to other diagnostic modalities for the small-bowel[39]. Furthermore, although CE is generally considered overall a safe modality, it can lead to severe complications (capsule retention in some patients' subgroups is reported as high as 15%[13-15,40]. Consequently, any tool or methods that allows selection of candidates, hence a more targeted and/or smooth "delivery" of SBCE, is a welcome approach. However, any pre-CE selection tool should be easy to perform, safe, inexpensive and fast[41]. In light of all these issues, faecal inflammation tests [of which, faecal calprotectin (FC) is the more widely available] have been proposed. In fact, FC has been used in SBCE studies in two settings: in patients taking non-steroidal anti-inflammatory drugs, to evaluate the type and extent of mucosal damage (Table 4)[41-44] and, more importantly from a clinical point of view, in patients with known or suspected CD for assessment of inflammation activity (Table 4)[45-48]. In these patients, although there is no clear agreement on a cut-off level, FC seems to be a cost-effective "screening test", able to identify those with higher possibility to present small-bowel lesions.

HAS CE THE SAME DIAGNOSTIC CAPABILITY ALONG THE SMALL BOWEL?

There are several papers, mostly case presentations and/or case series, reporting patients in whom CE failed to identify small-bowel lesions which were subsequently diagnosed by other modalities[49-52]. Such missed lesions (including neoplastic pathology) were occasionally large and often located in the proximal small-bowel[50,51]. Although there is still a lot of debate about the reasons of poor SBCE performance[53], it is worth remembering that for any non-steerable capsule progress is more rapid in the proximal than in lower segments of the small-bowel[53]; furthermore, opaque bile secretions and/or intra-luminal content might consequently hamper/prevent detailed mucosa visualization. Table 5 summarises all studies reporting the number of exams in which one of the few small-bowel landmarks, the ampulla of Vater (AoV), was visible during CE[54-66]. Hence, this evidence base provides an indirect confirmation of the limitations of SBCE in evaluating the proximal small-bowel. Interestingly, even in earlier studies[54] which have not been confirmed since by other investigators, the AoV was missed in > 50% of SBCE examinations. This is obviously an important drawback, especially when SBCE is used as surveillance tool, in patients with small-bowel polyposis syndromes.

Table 2 Head-to-head trials of small-bowel capsule endoscopy systems

Ref.	Country	Centre	Objective(s)	Study type	Design	CE type	Outcome(s)	Conclusion
Hartmann *et al*[7]	Germany	Single centre	Head-to-head evaluation of technical performance and DY of two CE systems (PillCam®SB *vs* EndoCapsule®)	Prospective	►OGIB pts; ►Pts randomized to undergo 2 CEs using different CE in random order	►PillCam®SB (Given®Imaging, Yoqneam, Israel); ►Pts randomized to undergo 2 CEs using different CE in random order	►Pts enrolled: 40; ►CR: PillCam®SB 33/40 (82%); EndoCapsule® 40/40 (100%); P = NS; ►Overall DY: PillCam®SB 26/50 (52%); EndoCapsule® 29/50 (58%); P = NS; ►DY (SB P2): PillCam®SB 22/50 (44%), EndoCapsule® 25/50 (50%), P = NS; ►In all discordant SB P2findings (not detected by the PillCam®SB but detected by EndoCapsule®), PillCam®SB examinations were incomplete	►Statistically non-significant trend for EndoCapsule® to detect more bleeding sources in pts with suspected small-bowel bleeding than PillCam®SB; ►This is (likely) due to the longer recording time with EndoCapsule®
Cave *et al*[8]	United States	Multi-centre (4 centres)	Comparison of performance (DY in pts with OGIB): EndoCapsule® *vs* PillCam®SB	Prospective	►OGIB pts; ►EndoCapsule® and PillCam®SB swallowed by each participant 40 min apart; ►Ingestion of CEs in randomized order; ►Head-to-head comparison of CEs	►EndoCapsule® (Olympus© America, Allentown, PA); ►PillCam®SB (Given®Imaging, Yoqneam, Israel)	►Pts with OGIB (transfused or with haematocrit < 31%) (males) or < 28% (females): 63; ►Available data 51/63; 9 pts excluded for technical reasons + 3 pts for protocol violation; ►24 videos read as normal, 14 as abnormal (from both CEs). Disagreement occurred in 13; ►No adverse events reported for either CE. Overall agreement: 38/51 (74.5%), κ = 0.48, P = 0.008; Limitations: Although ingestion randomized, videos reading not blind (different shape of the image margin)	►Both devices are safe and have comparable DY within the previously reported range; ►Subjective difference in image quality favouring the EndoCapsule®; ►Lack of electromechanical interference between 2 different CE
Kim *et al*[9]	South Korea	Single centre	Head-to-head evaluation of technical performance DY and of two capsule systems (PillCam®SB *vs* MiroCam®)	Prospective	►Pts referred to CE for various indications; ►Each pt was randomly assigned to swallow 1 of 2 CEs, the second CE was swallowed once fluoroscopy indicated that first CE had reached the SB	►MiroCam® (IntroMedic Co. Ltd., Seoul, South Korea); ►PillCam®SB (Given®Imaging, Yoqneam, Israel)	►Pts enrolled: 24; ►Mean operating time: MiroCam® 702 min; PillCam®SB 446 min, P < 0.001; ►CR: MiroCam® 20/24 (83%); PillCam®SB 14/24 (59%), P = 0.031; ►DY: MiroCam® 11/24 (45.8%); PillCam®SB 10/24 (41.7%), P = 1.0; ►DY (additive of both capsules): 12/24 (50%); ►Concordance of findings among the two capsule systems 87.5%, κ = 0.74	►MiroCam shows a longer operating time and a higher CR; ►Nevertheless, the 2 capsule systems showed comparable efficiency; ►Sequential capsule endoscopy with the MiroCam and PillCam SB produced slight (but NS) increase in DY
Pioche *et al*[10]	France	Multi-centre	Head-to-head evaluation of the diagnostic concordance (κ value): PillCam®SB SB2 *vs* MiroCam®	Prospective	►OGIB pts; ►Each pt ingested 2 CEs at a 1 h interval in a random order; ►Videos read in a random order by 2 experienced (> 200 CEs) readers; ►Image-by-image review of cases of disagreement between the readers was performed by 3 expert readers	►MiroCam®; (IntroMedic Co. Ltd., Seoul, South Korea); ►PillCamSB2 (Given®Imaging, Yoqneam, Israel)	►83 pts; drop-outs explained (10 technical issues), 73 pts/videos analysed; ►31 concordant (-) ve cases (42.4%) and 30 concordant (+) ve cases (41.1%); ►Satisfactory diagnostic concordance between the 2 systems (κ = 0.66); ►DY similar among the 2 CE systems(PillCam®SB 2 *vs* MiroCam®: 46.6% *vs* 56.2%, respectively; P = 0.02); ►SBTT longer with MiroCam® *vs* PillCam®SB (mean SBTT: 268 *vs* 234 min, P < 0.05); ►Reading time longer with MiroCam® *vs* PillCam®SB (mean reading time 40 *vs* 23 min, P < 0.05); ►(+) ve diagnosis obtained in 46.6% *vs* 56.2% of pts with PillCam®SB2 *vs* MiroCam®, respectively; ►PillCam®SB2 *vs* MiroCam®CEs identified 78.6% *vs* 95.2% of (+) ve cases, respectively, P = 0.02	►MiroCam® showed a slightly higher DY, difference not statistically significant; ►The 2 CE systems showed comparable efficiency for the diagnosis of OGIB
Dolak *et al*[11]	Austria	Single centre	Head-to-head comparison (MiroCam® *vs* EndoCapsule®) of: CR of SB examinations, DY in SB disease	Prospective	►Pts referred to CE for various indications; ►Each pt was randomly assigned to swallow either MiroCam® first, followed by the EndoCapsule® 2 h later, or vice versa; ►All videos analysed by two investigators independently	►MiroCam® (IntroMedic Co. Ltd., Seoul, South Korea); ►EndoCapsule® (Olympus America, Allentown, PA)	►Pts enrolled: 50; ►CR: MiroCam® 48/50 (96%) *vs* EndoCapsule® 45/50 (90%); P = 0.38; ►DY in SB: MiroCam® 25/50 (50%) *vs* EndoCapsule® 24/50 (48%); P > 0.99; ►Concordance of findings among the two CE systems: 68%; κ = 0.50	►The two capsule endoscopy systems were not statistically different with regards to CR and DY; ►Moderate concordance, mainly caused by missed pathological findings (which affected both devices), needs consideration in clinical practice

DY: Diagnostic yield; CE: Capsule endoscopy; OGIB: Obscure gastrointestinal bleeding; pts: Patients; CR: Completion rate; NS: Not significant (statistically); SB: Small-bowel; P2: Refers to grading of angioectasias; SBTT: Small-bowel transit time.

Table 3 Available meta-analyses and systematic reviews in the field of small-bowel capsule endoscopy

Ref.	Title	Search (start - end date)	Type	Subject	Data extractors	Total titles found	Titles entered meta-analysis	Individuals included	Outcome/conclusion
Liao *et al*[13]	Indications, detection, completion, and retention rates of SBCE: A systematic review	2000 - Jan 2009	Systematic review of evidence base	Indications, DR, CR and RR of SBCE	2	227	227	22753 Pts; 22840 CE	►Most common indications: OGIB (66.0%); investigation of clinical symptoms (10.6%); definite/suspected CD (10.4%); ►Pooled DRs for overall, OGIB, CD, neoplasia: 59.4%, 60.5%, 55.3%, 55.9%, respectively; ►Commonest cause for OGIB: angiodysplasia (50.0%); ►Pooled CRs (overall): 83.5%; breakdown 83.6% (OGIB), 85.4% (clinical symptoms), 84.2% (CD); ►Pooled RRs (overall): 1.4%; breakdown 1.2% (OGIB), 2.6% (clinical symptoms), 2.1% (CD); ►Hence, most common indication for SBCE is OGIB, with high DR and low RR; ►A relatively high RR is associated with definite/suspected CD and neoplasms
Marmo *et al*[17]	Meta-analysis: Capsule enteroscopy *vs* conventional modalities in diagnosis of SB diseases	Jan 1966 - Mar 2005	Meta-analysis of diagnostic test accuracy	DY/safety of SBCE *vs* alternative modalities (PE, SBBaR or enteroclysis) in SB disease	2	187	17	526 pts (289 OGIB and 237 CD)	►17 studies (526 patients) met inclusion criteria; ►Overall, the rate difference for SB disease (*i.e.*, the absolute pooled difference in the rate of positive findings) of SBCE *vs* alternative modalities was 41% (95%CI: 35.6-45.9); ►For OGIB, 37% (95%CI: 29.6-44.1) for Crohn's disease 45% (95%CI: 30.9-58.0); ►Incomplete SBCE occurred in 13%, more often in OGIB (17%) than in pts with CD (8%) ($P < 0.006$); ►Adverse events: 29 pts (6%); ►Capsule retention more frequent in pts with CD (3% *vs* 1%, OR 4.37)
Triester *et al*[18]	A meta-analysis of the yield of CE compared to other diagnostic modalities in patients with OGIB	N/A - April 2005	Meta-analysis of diagnostic test accuracy	IY (yield of CE-yield of comparative modality) and 95%CI of CE over comparative modalities	2	80	14	396 CE-PE; 88 CE-SBBaR	►14 studies ($n = 396$) compared DY CE *vs* PE in OGIB, 63% *vs* 28%, respectively (IY = 35%, $P < 0.00001$, 95%CI: 26%-43%); ►For clinically significant findings ($n = 376$) DY was 56% (CE) *vs* 26% (PE), IY = 30%, $P < 0.00001$, 95%CI: 21%-38%; ►3 studies ($n = 88$) compared DY of CE *vs* SBBaR, 67% *vs* 8%, respectively (IY = 59%, $P < 0.00001$, 95%CI: 48%-70%); ►For clinically significant findings DY was 42% (CE) *vs* 6% (SBBaR); IY = 36%, $P < 0.00001$, 95%CI: 25%-48%; ►NNT to yield one additional clinically significant finding with CE over either modality: 3 (95%CI: 2-4); ►1 study compared DY (significant findings) of CE *vs* intraoperative enteroscopy ($n = 42$, IY = 0%, $P = 1.0$, 95%CI: -16%-16%); ►1 study compared DY (significant findings) of CE *vs* CT enteroclysis ($n = 8$, IY = 38%, $P = 0.08$, 95%CI: -4%-79%); ►1 study compared DY (significant findings) of CE *vs* mesenteric angiogram ($n = 17$, IY = -6%, $P = 0.73$, 95%CI: -39%-28%); ►1 study compared DY (significant findings) of CE *vs* SB MRI ($n = 14$, IY = 36%, $P = 0.007$, 95%CI: 10%-62%); ►CE-DY *vs* PE (vascular lesions): 36% *vs* 20% (IY = 16%, $P < 0.00001$, 95%CI: 9%-23%); ►CE-DY *vs* PE (inflammatory lesions): 11% *vs* 2% (IY = 9%, $P = 0.0001$, 95%CI: 5%-13%); ►CE-DY *vs* PE (tumours or "other" findings): no difference
Leighton *et al*[19]	Capsule endoscopy: A meta-analysis for use with OGIB and CD	N/A - April 2005	Meta-analysis of diagnostic test accuracy	DY and safety of SBCE *vs* alternative modalities (PE, SBBaR or enteroclysis) in SB disease	2	80	20	537 pts	►CE superior to PE/SB radiography for diagnosing SB pathology in pts with OGIB (yield comparable to intraoperative endoscopy); ►Incremental yield of CE over PE/SB radiography is > 30% for clinically significant findings, due to visualization of additional vascular, inflammatory lesions by CE; ►CE was also superior to SB radiography, C + IL, CT enterography, PE for diagnosing non-stricturing SBCD; ►Marked improvement in yield with the use of CE over all other methods in pts who had established CD and were evaluated for SB recurrence; ►Unknown whether these results will translate into improved pt outcomes with the use of CE *vs* alternate methods
Leighton *et al*[19]	Capsule endoscopy: A meta-analysis for use with OGIB and CD	N/A - April 2005	Meta-analysis of diagnostic test accuracy	DY and safety of SBCE *vs* alternative modalities (PE, SBBaR or enteroclysis) in SB disease	2	80	20	537 pts	►CE superior to PE/SB radiography for diagnosing SB pathology in pts with OGIB (yield comparable to intraoperative endoscopy); ►Incremental yield of CE over PE/SB radiography is > 30% for clinically significant findings, due to visualization of additional vascular, inflammatory lesions by CE; ►CE was also superior to SB radiography, C + IL, CT enterography, PE for diagnosing non-stricturing SBCD; ►Marked improvement in yield with the use of CE over all other methods in pts who had established CD and were evaluated for SB recurrence; ►Unknown whether these results will translate into improved pt outcomes with the use of CE *vs* alternate methods
Triester *et al*[20]	A meta-analysis of the yield of CE compared to other diagnostic modalities in patients with non-stricturing SB Crohn's disease	N/A - Aug 2005	Meta-analysis of diagnostic test accuracy		2	82	9	250 pts	►9 studies ($n = 250$) compared DY CE *vs* SBBaR in CD: 63% *vs* 23%, respectively (IY = 40%, $P < 0.001$, 95%CI: 28%-51%); ►4 studies ($n = 114$) compared DY CE *vs* C + IL in CD: 61% *vs* 46%, respectively (IY = 15%, $P = 0.02$, 95%CI: 2%-27%); ►3 studies ($n = 93$) compared DY CE *vs* CT enterography/enteroclysis: 69% *vs* 30%, respectively (IY = 38%, $P = 0.001$, 95%CI: 15%-60%); ►2 studies compared DY CE *vs* PE: (IY = 38%, $P < 0.001$, 95%CI: 26%-50%); ►1 study compared DY CE *vs* SBMRI (IY = 22%, $P = 0.16$, 95%CI: -9%-53%); Sub-analysis (pts with suspected CD): no difference in DY CE *vs* SBBaR ($P = 0.09$), C + IL ($P = 0.48$), CT enterography ($P = 0.07$) or PE ($P = 0.51$); Sub-analysis (pts with established CD): difference in DY CE *vs* SBBaR ($P < 0.001$ C + IL ($P = 0.002$), CT enterography ($P < 0.001$) and PE ($P < 0.001$)

Pasha *et al*[21]	DBE and CE have comparable DY in SB disease: A meta-analysis	N/A - Dec 2006	Meta-analysis of diagnostic test accuracy	Comparison of DY of CE *vs* DBE	2	113	11	397 pts	►Pooled DY CE *vs* DBE: 60% *vs* 57% (IYW = 3%, 95%CI: -4%-10%, P = 0.42, FEM); ►Pooled DY CE *vs* DBE (vascular findings, 10 studies): 24% *vs* 24% (IYW = 0%, 95%CI: -5%-6%, P = 0.88, REM); ►Pooled DY CE *vs* DBE (inflammatory findings, 9 studies): 18% *vs* 16% (IYW = 0%, 95%CI: -5%-6%, P = 0.89, FEM); ►Pooled DY CE *vs* DBE (polyps/tumours, 9 studies): 11% *vs* 11% (IYW = -1%, 95%CI: -5%-4%, P = 0.76, FEM); ►SB disease: CE *vs* DBE have comparable DY, including OGIB, CE should be the initial diagnostic test for determining the insertion route of DBE
Niv[22]	Efficiency of bowel preparation for capsule endoscopy examination: A meta-analysis	N/A - July 2007	Meta-analysis of RCTs and cohort studies	Purgative use *vs* fasting alone for SBCE	1	6	8	130 bowel prep; 107 fasting	►237 pts, 130 with and 107 without preparation; ►Seven out of 8 studies included a comparison of GTT, SBTT and CR; ►SBCE CR: 76% in pts with preparation *vs* 68% without prep (difference did not reach statistical significance); ►No statistically significant difference between CEs performed with or without preparation in GTT (pooled effect size, -0.054; 95%CI: -0.418-0.308) or SBTT (pooled effect size, -0.327; 95%CI: -1.419 - -0.765)
El-Matary *et al*[23]	Diagnostic characteristics of given video capsule endoscopy in diagnosis of celiac disease: A meta-analysis		Meta-analysis of diagnostic test accuracy	Coeliac and CE	2	N/A	3	107 pts	►3 studies (n = 107, 63 pts with CD/44 without) met inclusion criteria; ►Pooled SBCE (overall) Sens and Spec: 83% (95%CI: 71%-90%) and 98% (95%CI: 88%-99.6%), respectively; ►No major complications reported; ►Costs mentioned only in 1 study. Overall, diagnostic characteristics of SBCE, could not justify the routine use of SBCE as alternative to biopsy
Chen *et al*[24]	A meta-analysis of the yield of CE compared to DBE in pts with SB diseases	N/A - Feb 2007	Meta-analysis of diagnostic test accuracy	Comparison of DY of CE *vs* DBE	2	163	8	277 pts	►8 studies (n = 277 pts) prospectively compared the yield of CE and DBE were included; ►No difference between the yield of CE and DBE (170/277 *vs* 156/277, OR 1.21, 95%CI: 0.64-2.29); ►Sub analysis: yield of CE significantly higher than that of DBE without combination of oral+anal insertion approaches (137/219 *vs* 110/219, OR 1.67, 95%CI: 1.14-2.44, P < 0.01), but not superior to the yield of DBE with combination of the two insertion approaches (26/48 *vs* 37/48, OR 0.33, 95%CI: 0.05-2.21, P < 0.05); ►Focused meta-analysis of the fully published articles concerning OGIB showed similar results wherein the yield of CE was significantly higher than that of DBE without combination of oral + anal insertion approaches (118/191 *vs* 96/191, fixed model: OR 1.61, 95%CI: 1.07-2.43, P < 0.05) and the yield of CE was significantly lower than that of DBE by oral+ anal combinatory approaches (11/24 *vs* 21/24, fixed model: OR 0.12, 95%CI: 0.03-0.52, P < 0.01)
Rokkas *et al*[25]	Does purgative preparation influence the diagnostic yield of small bowel video capsule endoscopy? A meta-analysis	N/A - Feb 2008	Meta-analysis of RCTs and cohort studies	Purgative use *vs* fasting alone for SBCE	2	194	12	718 pts purgative; 444 controls	►12 eligible studies (6 prospective/6 retrospective), including 16 sets of data; ►Significant difference in DY between pts prepared with purgatives (n = 263) *vs* pts prepared with clear liquids (n = 213): OR = 1.813 (95%CI: 1.251-2.628, P = 0.002); ►Significant difference in SBVQ between pts prepared with purgatives (n = 404) *vs* pts prepared with clear liquids (n = 249): OR = 2.113 (95%CI: 1.252-3.566, P = 0.005); There was no statistically significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT
Dionisio *et al*[26]	CE has a significantly higher DY in patients with suspected and established small-bowel CD: A meta-analysis	2000 - May 2009	Meta-analysis of diagnostic test accuracy	DY of CE *vs* modalities in patients with suspected/ established CD	2	291	12	428 pts	►8 studies (n = 236 pts) compared CE *vs* C + IL, 4 (n = 119 pts) CE *vs* CTE, 2 (n = 102 pts) *vs* PE, 4 (n = 123 pts) *vs* MRE; ►For suspected CD, several comparisons met statistical significance; Yields in this subgroup were: CE *vs* SBR: 52% *vs* 16% (IYw = 32%, P < 0.0001, 95%CI: 16%-48%), CE *vs* CTE: 68% *vs* 21% (IYw = 47%, P < 0.00001, 95%CI: 31%-63%), CE *vs* C + IL: 47% *vs* 25% (IYw = 22%, P = 0.009, 95%CI: 5%-39%); ►For established CD, statistically significant yields for CE *vs* an alternate diagnostic modality in patients were seen: CE *vs* PE: 66 *vs* 9% (IYw = 57%, P < 0.00001, 95%CI: 43-71%), CE *vs* SBR: 71 *vs* 36% (IYw = 38%, P < 0.00001, 95%CI: 22%-54%), CE *vs* CTE: 71 *vs* 39% (IYw = 32%, $P \leqslant 0.0001$, 95%CI: 16%-47%)
Wu *et al*[27]	Systematic review and meta-analysis of RCTs of Simethicone for GI endoscopic visibility	N/A- Nov 2009	Meta-analysis of RCTs	Simethicone and CE	2	128	4	121 pts	►Adequate or excellent/good SB mucosa visualization in pts receiving Simethicone *vs* those who did not (66.1% *vs* 37.2%); ►Pooled OR = 2.84 (95%CI: 1.74-4.65, P = 0.00); no significant heterogeneity (P = 0.16, I^2 = 38.8%) or publication bias (P = 0.251); ►Sens analysis: studies stratified by factors such as bowel preparation (purgative *vs* fasting): Significant results for bowel preparation + fasting (OR = 4.43, 95%CI: 1.82-10.76, P = 0.00) with P = 0.78, I^2 = 0.0%, No significant results for bowel preparation + purgative (OR = 1.59, 95%CI: 0.78-3.27, P = 0.203) with P = 0.20, I^2 = 38.9%
Rokkas *et al*[25]	Does purgative preparation influence the diagnostic yield of small bowel video capsule endoscopy? A meta-analysis	N/A - Feb 2008	Meta-analysis of RCTs and cohort studies	Purgative use *vs* fasting alone for SBCE	2	194	12	718 pts purgative; 444 controls	►12 eligible studies (6 prospective/6 retrospective), including 16 sets of data; ►Significant difference in DY between pts prepared with purgatives (n = 263) *vs* pts prepared with clear liquids (n = 213): OR = 1.813 (95%CI: 1.251-2.628, P = 0.002); ►Significant difference in SBVQ between pts prepared with purgatives (n = 404) *vs* pts prepared with clear liquids (n = 249): OR = 2.113 (95%CI: 1.252-3.566, P = 0.005); There was no statistically significant difference regarding CR rate. Purgatives did not affect VCE GTT or VCE SBTT

Dionisio *et al*[26]	CE has a significantly higher DY in patients with suspected and established small-bowel CD: A meta-analysis	2000 - May 2009	Meta-analysis of diagnostic test accuracy	DY of CE *vs* modalities in patients with suspected/ established CD	2	291	12	428 pts	►8 studies (n = 236 pts) compared CE *vs* C + IL, 4 (n = 119 pts) CE *vs* CTE, 2 (n = 102 pts) *vs* PE, 4 (n = 123 pts) *vs* MRE; ►For suspected CD, several comparisons met statistical significance; Yields in this subgroup were: CE *vs* SBR: 52% *vs* 16% (IYw = 32%, P < 0.0001, 95%CI: 16%-48%), CE *vs* CTE: 68% *vs* 21% (IYw = 47%, P < 0.00001, 95%CI: 31%-63%), CE *vs* C + IL: 47% *vs* 25% (IYw = 22%, P = 0.009, 95%CI: 5%-39%); ►For established CD, statistically significant yields for CE *vs* an alternate diagnostic modality in patients were seen: CE *vs* PE: 66 *vs* 9% (IYw = 57%, P < 0.00001, 95%CI: 43-71%), CE *vs* SBR: 71 *vs* 36% (IYw = 38%, P < 0.00001, 95%CI: 22%-54%), CE *vs* CTE: 71 *vs* 39% (IYw = 32%, $P \leqslant 0.0001$, 95%CI: 16%-47%)
Wu *et al*[27]	Systematic review and meta-analysis of RCTs of Simethicone for GI endoscopic visibility	N/A - Nov 2009	Meta-analysis of RCTs	Simethicone and CE	2	128	4	121 pts	►Adequate or excellent/ good SB mucosa visualization in pts receiving Simethicone *vs* those who did not (66.1% *vs* 37.2%); ►Pooled OR = 2.84 (95%CI: 1.74-4.65, P = 0.00); no significant heterogeneity (P = 0.16, I^2 = 38.8%) or publication bias (P = 0.251); ►Sens analysis: studies stratified by factors such as bowel preparation (purgative *vs* fasting): Significant results for bowel preparation + fasting (OR = 4.43, 95%CI: 1.82-10.76, P = 0.00) with P = 0.78, I^2 = 0.0%, No significant results for bowel preparation + purgative (OR = 1.59, 95%CI: 0.78-3.27, P = 0.203) with P = 0.20, I^2 = 38.9%
Cohen *et al*[28]	Use of CE in diagnosis and management of pediatric patients, based on meta-analysis	Jan 2001 - May 2010	Systematic review of evidence base	Systematic compilation of data on indications and outcomes of CE in paediatric patients	2	N/A	15	740 examinations; 723 pts	►Most common indication for CE (in pts < 18 yr): suspicion or evaluation of IBD (overall 54%), Breakdown: suspected CD (34%), known CD (16%), UC (1%), indeterminate colitis (3%) ►CR and RR: 86.2% (95%CI: 81.5-90.3%) and 2.6% (95%CI: 1.5-4.0%), respectively; ►CE RR (gastric and SB): 0.5% and 1.9%, respectively, similar to those of adults, by indication; ►CE with positive findings: 65.4% (95%CI: 54.8%-75.2%); ►CE resulting in new diagnosis: 69.4% (95%CI: 46.9%-87.9%); CE leading to change in therapy: 68.3% (95%CI: 43.6%-88.5%)
Teshima *et al*[29]	DBE and CE for OGIB: An updated meta-analysis	N/A - June 2010	Meta-analysis of diagnostic test accuracy	OGIB; CE or DBE	2	147	10	651 CE; 642 DBE	►Pooled DY for CE: 62% (95%CI: 47.3%-76.1%) ►Pooled DY for DBE 56% (95%CI: 48.9%-62.1%); OR for CE *vs* DBE of 1.39 (95%CI: 0.88-2.20; P = 0.16); Subgroup analyses ►DBE-DY after (+)ve CE: 75.0% (95%CI: 60.1%-90.0%) ►DBE-DY after (-)ve CE: 27.5% (95%CI: 16.7%-37.8%) ►DBE-OR (for successful diagnosis after (+)ve CE) compared with DBE: 1.79 (95%CI: 1.09-2.96, P = 0.02) ►In OGIB CE and DBE have similar DY, DBE-DY significantly higher when performed in pts with prior positive CE
Belsey *et al*[30]	Meta-analysis: efficacy of SB preparation for SBCE	Jan 2000 - Dec 2010	Meta-analysis of RCTs	Purgative use *vs* fasting alone for SBCE	2	33	8	291 PEG; 133 NaP; 322 fasting	►8 studies, using PEG or NaP-based bowel cleansing regimens; ►Any form of purgative significantly better visibility than fasting alone (OR = 2.31; 95%CI: 1.46-3.63, P < 0.0001); ►Similar results on DY (OR = 1.88; 95%CI: 1.24-2.84; P = 0.023); Subgroup analyses (per cleansing regimen used): ►PEG-based regimens showed benefit (OR = 3.11; 95%CI: 1.96-4.94, P < 0.0001); ►NaP-based regimens no significant difference from fasting alone (OR = 1.32; 95%CI: 0.59-2.96, P < 0.0001); ►Use of purgatives (alongside fasting) is recommended in SBCE; PEG-based regimens offer a clear advantage over NaP; ►Lower volume PEG regimens as efficacious as higher volumes traditionally used for colonoscopy preparation
Rokkas *et al*[31]	The role of video CE in the diagnosis of coeliac disease: A meta-analysis	N/A - April 2011	Meta-analysis of diagnostic test accuracy	Coeliac and CE	2	461	6	166 pts	►Pooled CE Sens: 89% (95%CI: 82%-94%) and Spec: 95% (95%CI: 89%-98%), AuROC: 0.9584; ►Although not as accurate as pathology, CE a reasonable alternative method of diagnosing coeliac disease
Koulaouzidis *et al*[32]	Diagnostic yield of SBCE in patients with IDA: A systematic review	Jan 2001 - Nov 2011	Systematic review of evidence base	IDA and CE	2	1225	24	1960 pts	►Pooled SBCE-DY in IDA: 47% (95%CI: 42%-52%), with significant heterogeneity among included studies (I^2 = 78.8%, P < 0.0001); ►Pooled SBCE-DY (subgroup 1: 4 studies focused solely on IDA pts): 66.6% (95%CI: 61.0%-72.3%, I^2 = 44.3%) ►Pooled SBCE-DY (subgroup 2: 20 studies not focusing only on IDA pts): 44% (95%CI: 39%-48%, I^2 = 64.9%); ►SBCE in subgoup 1: more vascular (31% *vs* 22.6%, P = 0.007), inflammatory (17.8% *vs* 11.3%, P = 0.009), neoplastic (7.95% *vs* 2.25%, P < 0.0001) lesions detected

CE: Capsule endoscopy; N/A: Not available or not applicable; Sens: Sensitivity; Spec: Specificity; AuROC: Area under Receiver operation characteristics curve; DBE: Double-balloon enteroscopy; OGIB: Obscure gastrointestinal bleeding; DY: Diagnostic Yield; pts: Patients; IY: Incremental yield; GTT: Gastric transit time; SBTT: Small bowel transit time; SBCE: Small-bowel capsule enteroscopy; OR: Odds ratio; RR: Relative risk; C + IL: Colonoscopy with ileoscopy; PE: Push enteroscopy; SBCD: Small bowel Crohn's disease; CT: Computed tomography; IDA: Iron deficiency anemia; FEM: Fixed effect model.

Table 4 Studies evaluating the clinical application of faecal calprotectin in the setting of small-bowel capsule endoscopy

Ref.	Country	Centre	Study type	Design	Participants	FC	CE	Objective(s)	Outcome(s)
Goldstein *et al*[41]	United States	Multi-centre	Prospec-tive	Double-blind, triple-dummy, placebo controlled	334 healthy subjects	N/A	M2A®; Given® Imaging, Yokneam, Israel	Evaluate incidence of SB injury and correlation with FC in healthy subjects on celecoxib or ibuprofen + omeprazole	►Mean increase in FC higher in subjects on ibuprofen+omeprazole compared with celecoxib alone ($P < 0.001$); ►No correlation between FC and SB mucosal breaks
Hawkey *et al*[42]	Germany, United Kingdom	Multi-centre	Prospec-tive	Double-blind, double-dummy, placebo controlled	139 healthy subjects	Phical Calprotectin Test Kit NovaTec Immunodiag-nostica, GmbH Dietzenbac, Germany	M2A®; Given® Imaging, Yokneam, Israel	Investigate SB injury lumiracoxib reduces *vs* naproxen + omeprazole	►More SB mucosal breaks on naproxen+omeprazole (77.8% *vs* 40.4%, $P < 0.001$); ►Furthermore, higher FC *vs* placebo (96.8 *vs* 14.5 μg/g, $P < 0.001$); ►27.7% on lumiracoxib had SB mucosal breaks (*vs* placebo, $P = 0.196$; *vs* naproxen, $P < 0.001$) ►No increase in FC (-5.7 μg/g; *vs* placebo, $P = 0.377$; *vs* naproxen, $P < 0.001$)
Smecuol *et al*[43]	Argentina, Spain, Canada	Multi-centre	Prospec-tive	Non-blinded study	20 healthy subjects	Calprest® Eurospital SpA, Trieste, Italy	M2A®; Given® Imaging, Yokneam, Israel	Determine SB damage by low-dose ASA (on a short-term basis)	►Short-term administration of low-dose ASA associated with mucosal abnormalities of the SB mucosa; ►Median baseline FC (6.05 μg/g; range: 1.9-79.2 μg/g) increased significantly after ASA use
Werlin *et al*[44]	United States, Israel, United Kingdom	Multi-centre	Prospec-tive	N/A	42 pts with CF* (aged 10-36 yr); 29 had pancreatic insufficiency	Calprest® Eurospital SpA, Trieste, Italy	PillCam®SB; Given® Imaging, Yokneam, Israel	Examine the SB of pts with CF without overt evidence of GI disease using CE	►Varying degrees of diffuse areas of inflammatory findings in the SB: oedema, erythema, mucosal breaks and frank ulcerations; ►No adverse events recorded; FC markedly high in pts with pancreatic insufficiency, 258 μg/g (normal < 50)
Koulaouzidis *et al*[45]	United Kingdom	Single centre	Retro-spective	Chart review	70 pts with suspected CD and (-) ve bi-directional endoscopy	CALPRO NovaTec Immunodiag-nostica GmbH, Dietzenbac, Germany	(1) PillCam® SB; Given® Imaging, Yokneam, Israel; (2) MiroCam®; IntroMedic Co., Seoul, South Korea	Value of FC as selection tool for further investigation of the SB with SBCE, in a cohort of pts with suspected CD	►FC = 50-100 μg/g: normal SBCE, despite symptoms suggestive of IBD; ►FC > 100 μg/g: good predictor of positive SBCE; ►FC > 200 μg/g: associated with higher SBCE DY (65%); confirmed CD in 50%; ►Measurement of FC prior SBCE: useful tool to select patients for referral. If FC < 100 μg/g: SBCE is not indicated (NPV 1.0)
Jensen *et al*[46]	Denmark	Single centre	Prospec-tive	Blinded study	83 pts from GI OPD clinics with suspected CD	Calprotectin ELISA, BÜHLMANN Laboratories AG, Basel, Switzerland	PillCam®SB; Given® Imaging, Yokneam, Israel	Determine FC levels in CD restricted to SB compared to colonic CD, in pts on first diagnostic work-up; Assess the Sens and Spec of FC in suspected CD	►In pts with SB or colonic CD FC is equal: median 890 μg/g *vs* 830 mg/kg, respectively ($P = 1.0$); ►FC cut-off = 50 μg/g: 92% and 94% Sens for SB and colonic CD, respectively; ►Overall, Sens and Spec for FC: 95% and 56%; ►CD was ruled out with NPV of 92%; ►In suspected CD, FC is effective marker to r/o CD and select patients for endoscopy

Koulaouzidis *et al*[47]	United Kingdom	Single centre	Retro-spective	Chart review	49 pts; known or suspected CD	CALPRO NovaTec Immuno-diagnos-tica GmbH, Dietzenbac, Germany	PillCam®; Given® Imaging, Yokneam, Israel; MiroCam®; IntroMedic Co., Seoul, South Korea	Assess performance of 2 SBCE inflammation scoring systems (LS and CECDAI) correlating them with FC; Define threshold levels for CECDAI	►LS performs better than CECDAI in describing SB inflammation, especially at FC < 100 μg/g ►CECDAI levels of 3.8 and 5.8 correspond to LS thresholds of 135 and 790, respectively
Sipponen *et al*[48]	Finland	Single centre	Pro-spective	Blinded study	84 pts; known or suspected CD	Calprest® Eurospital SpA, Trieste, Italy	PillCam®; Given® Imaging, Yokneam, Israel; MiroCam®; IntroMedic Co., Seoul, South Korea	Study the role of FC and S100A12 in predicting SB inflammatory lesions	►CE abnormal in 35/84 (42%) pts: 14 CD, 8 NSAID-enteropathy, 8 angioectasias, 4 polyps/tumours, 1 ischemic stricture ►Median FC/S100A12: 22 μg/g (range: 2-342 μg/g)/0.048 μg/g (range: 0.003-1.215 μg/g) ►FC significantly higher in CD pts (median 91, range: 2-312) compared with pts with normal CE or other abnormalities (P = 0.008) ►Faecal S100A12 (0.087 μg/g, range: 0.008-0.896 μg/g): no difference between the groups (P = 0.166) ►Sens, Spec, PPV, NPV in detecting SB inflammation; FC (cut-off 50 μg/g): 59%, 71%, 42%, 83%; S100A12 (cut-off 0.06 μg/g): 59%, 66%, 38%, 82%, respectively

CF: Cystic Fibrosis; CD: Crohn's disease; GI: Gastrointestinal; OPD: Out-Patient Department; SB: Small-bowel; FC: Faecal calprotectin; ASA: Acetyl-salycylic acid; CE: Capsule endoscopy/e; Pts: Patients; Sens: Sensitivity; Spec: Specificity; SBCE: Small-bowel capsule endoscopy; LS: Lewis score; CECDAI: Capsule endoscopy Crohn's disease activity index; NPV: Negative predictive value; PPV: Positive predictive value; N/A: Not available or not applicable; NSAID: Non-steroidal anti-inflammatory drug.

Table 5 Studies looking at the identification rate of the ampulla in capsule endoscopy

Ref.	CE	Type of CE model; Company	AoV seen, *n* (%)	Reviewers	Reviewing speed (fps)	Frames AoV visible[2]	Comments
Wijeratne *et al*[53]1	138	NS	9 (6.0)	1	NS	NS	4 FAP patients (AoV not seen)
Kong *et al*[54]	110	M2A®; Given®Imaging Ltd.	48 (43.6)	2	15	3.5 ± 2.5	
Clarke *et al*[55]	125	M2A®; Given®Imaging Ltd.	13 (10.4)	2	5	NS	
Iaquinto *et al*[56]	23	PillCam®SB; Given®Imaging Ltd.	0 (0.0)	2	NS	N/A	FAP patients (11/23 had duodenal polyps)
Metzger *et al*[57]	20	PillCam®SB1; Given®Imaging Ltd.	1 (5.0)	NS	NS	NS	Repeat examinations
		PillCam®SB2; Given®Imaging Ltd.	5 (25.0)	NS	NS	NS	
Katsinelos *et al*[58]	14	NS	0 (0.0)	1	NS	N/A	FAP patients
Nakamura *et al*[59]	96	PillCam®SB1; Given®Imaging Ltd.	18 (18.0)	2	10	NS	
Karagiannis *et al*[60]	10	PillCam®Colon; Given®Imaging Ltd.	6 (60.0)	NS	NS	NS	Two-headed PillCam®
Lee *et al*[61]1	30	PillCam®SB; Given®Imaging Ltd.	13 (43.3)	NS	NS	NS	
	30	PillCam®SB2; Given®Imaging Ltd.	15 (50.0)	NS	NS	NS	
	50	PillCam®SB1; Given®Imaging Ltd.	0 (0.0)	2	NS	N/A	
Selby *et al*[62]	50	PillCam®SB2; Given®Imaging Ltd.	9 (18.0)	2	NS	NS	
	8	PillCam®ESO1; Given®Imaging Ltd.	0 (0.0)	2	NS	N/A	Two-headed PillCam®
	12	PillCam®ESO2; Given®Imaging Ltd.	1 (8.0)	2	NS	NS	Two-headed PillCam®
Koulaouzidis *et al*[63]	11	PillCam®ESO1; Given®Imaging Ltd.	4 (36.4)	1	7	NS	Two-headed PillCam®
	7	PillCam®ESO2; Given®Imaging Ltd.	1 (14.3)	1	9	NS	Two-headed PillCam®
Park *et al*[64]	30	PillCam®SB; Given®Imaging Ltd.	13 (43.3)	6	7	3.1 ± 1.1	
	30	PillCam®SB2; Given®Imaging Ltd.	15 (50.0)	6	9	3.1 ± 1.5	
	262	PillCam®SB1; Given®Imaging Ltd.	28 (10.7)	1	6	36.35 ± 73.24	
Koulaouzidis *et al*[65]	148	PillCam®SB2; Given®Imaging Ltd.	13 (8.8)	1	6	42.46 ± 69.3	
	209	MiroCam®; IntroMedic Ltd.	18 (8.6)	1	6	87.20 ± 248.4	
Friedrich *et al*[66]	25	CapsoCam®SV1; Capsovision Ltd.	22 (71)	3	NS	3.1 ± 1.8	

[1]Published only as abstracts; [2]mean ± SD. CE: Capsule endoscopy; NS: Not stated; N/A: Not available or not applicable; AoV: Ampulla of Vater; fps: Frames per second; FAP: Familial adenomatous polyposis syndrome.

CAPSULE ENDOSCOPE ASPIRATION; HOW COMMON IS THIS?

Capsule enteroscopy is generally considered safe, having an overall complication rate of about 1%-3%[13,14]. Undoubtedly, the most feared complication of CE is capsule retention in the small bowel (overall retention rate 1.5%-2%), which seems directly related with the clinical indication for SBCE[13,14,40]. Interestingly enough, other possible complications - which were postulated at the time of CE introduction (*i.e.*, retention inside colonic diverticula, interaction with pacemakers, *etc.*) to represent

potential hurdles for the method, were shown to be very infrequent and/or without clinically relevant consequences[67-71]. Conversely, capsule aspiration - an unexpected complication - has been reported with increasing frequency (Table 6)[72-93]. Overall, this is probably related to the increase in the mean age of patients undergoing CE. In fact, capsule aspiration occurs in 1 out of 800-1000 procedures[88], mostly in elderly male patients with co-morbidities and/or swallowing disorders. In the majority of cases capsule aspiration resolves quickly, because patients expectorate the capsule. However, in selected cases, emergency bronchoscopy is required. Thus far, only one fatality-directly associated with capsule aspiration- has been reported[90].

CAN WE SHORTEN OUR READING TIME IN CAPSULE ENDOSCOPY?

Few will disagree with the notion that CE is a time-consuming procedure. In fact, although capsule administration and swallowing requires only a couple of minutes, SBCE transit through the small bowel, although variable, on overage lasts about 2-5 h[94]. This results in 14400-72000 frames, depending on capsule frame rate (Table 1). This large amount of visual information requires careful evaluation by the CE reader. In addition, any small-bowel lesion may only be visible in just a few or even in a single frame[95]. Therefore, focused and undivided attention is required for the entire duration of each CE video evaluation. In light of all that, several attempts have been made to develop technical software features, in order to make CE video analysis easier and shorter (without jeopardising its accuracy). The first software feature designed for this purpose was the Suspected Blood Indicator (SBI), an automatic system able to pick up, in a completely automatic fashion, frames containing several red pixels and, therefore (theoretically), to detect blood and or other red-coloured lesions. Nevertheless, the accuracy profile of this tool (Table 7) is suboptimal and, at present time[96-102], it can be used only as supportive tool[102].

Given®Imaging Ltd. has also introduced another software tool, which aims specifically at shortening the CE reading time, the QuickView. This sampling tool is able to select one frame every X CE frames (the sampling rate can be set by the reader) and therefore present, with the click of a tag-button, a shortened CE video which can be reviewed in a few minutes. Although the sampling method of the QuickView system is only quantitative, it has showed a promising sensitivity and specificity in identifying small-bowel lesions (Table 8), and reveals promising potential when coupled with other image enhancing systems[104-112]. Olympus has similar software function (express mode) and we are aware of a single relevant study with very similar results[113].

In the last few years, Given®Imaging Ltd., through a collaboration with Fujinon Inc., Japan introduced the electronic chromo-endoscopy (Fujinon Intelligent Chromo Endoscopy, FICE) in the field of capsule enteroscopy. Data available thus far, show that application of FICE in SBCE videos, leads to improved image quality and definition of the surface texture of small-bowel lesions (Table 9)[114-120]. Although this seems to facilitate the detectability of small-bowel findings, it is still under question whether it proves to be clinically significant[121]. Similar function from Olympus Inc., shows promising results[122].

WHAT'S NEW ON THE FIELD OF SMALL-BOWEL CAPSULE ENDOSCOPY?

As aforementioned, there are differences among different capsule models (Table 1). Since its introduction in clinical practice in 2001, CE technology has been significantly. For instance, battery life is longer, image capture frame rate has increased, angle of view is now wider, light control has been optimized, and many real time viewing systems are now available. Nevertheless, these impressive advancements, do not allow overcoming the main current limitation of CE, *i.e.*, uncontrolled propulsion; CE relies totally on natural bowel peristalsis, *i.e.*, it still remains a rather "passive" diagnostic technique.

Several research groups are working to design brand new capsules able to actively move or to be remotely manoeuvred through their descent in the small bowel[123]. These new capsules would allow not only recognizing a small bowel lesion but also, in a near future, to collect targeted tissue samples or to deliver drugs (Table 10)[124-141].

CONCLUSION

Since CE introduction in clinical practice in 2001, over 1500 papers, focused on SBCE, have been published (PubMed search 17/03/2012; keyword term: "small bowel capsule endoscopy"; available from: http://www.ncbi.nlm.nih.gov/pubmed/?term=small+bowel+capsule+endoscopy).

Out of those, < 20% are clinical trials; case reports and reviews account for about 40% of published evidence. As the amount of information has increased exponentially, and in fact continues to do so[12], it is often difficult for the busy clinician to retrieve and filter data or extract answers to questions arising from the daily clinical practice. In the present review, we opted to answer certain pertinent questions on contentious and important issues in CE through comprehensive tables. Essentially, we aim to present an easy-to-read review with all the necessary evidence to support opinions expressed herein.

The analysis of the publications listed in the tables clearly demonstrates how SBCE, although much "younger" than other endoscopic techniques, has found a definite role in the diagnostic work-up of certain patient-subgroups. Further success of this modality depends not only on continuous technological progress (*i.e.*, introduction of new capsule models, improved battery life and/or development of new reading software features)[142] but also on the search for new diagnostic strategies, aiming to select for SBCE those patients with higher potential for positive DY[32,45,81,111,117].

Table 6 Case reports of aspiration of capsule endoscopes

Ref.	Case (age/gender)	Comorbidities	CE model/ company	Swallowing difficulties	No. of attempts to swallow CE/ gagging or coughing	Aspiration time/where in bronchial tree CE seen	Capsule removal (if employed)	Final diagnosis
Schneider *et al*[72]	64/male	Mechanical MV on phenprocoumon, BMI 15.5	M2A®; Given®Imaging Ltd.	No Hx of dysphagia	4/gagging and spitting capsule - last attempt recurrent coughing (aspiration presumed)	2 min/trachea-bronchi	Spontaneous resolution	NS
Fleischer *et al*[73]	76/male	HHT	M2A®; Given®Imaging Ltd.	No Hx of dysphagia	1/lodged in his throat - no respiratory difficulty, could talk, vital signs normal	60 min/ cricopharyngeus	Endoscopy-Roth net; 6 d post-dilation, patient ingested capsule with no problem	Spasticity, prominence of cricopharyngeus; endoscopy and oesophageal dilation 1 wk later
Sinn *et al*[74]	69/female	On phenprocoumon	M2A®; Given®Imaging Ltd.	No Hx of dysphagia	1/coughed several times	50 s/bifurcation of the trachea	Spontaneous resolution	NS
Tabib *et al*[75]	87/female	Recent onset IDA, CHF, IHD, AF, bladder cancer, CRF	M2A®; Given®Imaging Ltd.	No Hx of dysphagia, pre-CE barium meal	2/choking, dyspnoea, CE felt lodged in the throat	NS/right main-stem bronchus - bronchus intermedius	Rigid bronchoscopy	NS
Buchkremer *et al*[76]	74/male	Recent diagnosis of coeliac disease; past Hx of ankylosing spondylitis	M2A®; Given®Imaging Ltd.	No Hx of dysphagia	NS/dyspnoea started after CE ingestion	NS/right main-stem bronchus	Flexible bronchoscopy	NS
Rondonotti *et al*[77]	NS	NS	M2A®; Given®Imaging Ltd.	NS	NS/coughed several times	NS/NS	Spontaneous resolution	NS
Nathan *et al*[78]	93/male	No significant past medical Hx	M2A®; Given®Imaging Ltd.	No Hx of dysphagia	1/coughed hours post-ingestion	Approximately 8 h/ bronchial tree	Spontaneous resolution	NS
Shiff *et al*[79]	75/male	NS	M2A®; Given®Imaging Ltd.	No Hx of dysphagia	2/some coughing	NS/bronchi	Spontaneous resolution Eventually, CE endoscopic placement	NS
Sepehr *et al*[80]	67/male	HTN, DM, CVA	NS	Hx of dysphagia (intermittent)	1/coughing, tachypnoea, and tachycardia	NS/trachea	Endoscopy-Roth net	NS
Koulaouzidis *et al*[81]	76/male	NS	PillCam®SB; Given®Imaging Ltd.	No Hx of dysphagia	1/coughed weakly	15 s/trachea	Spontaneous resolution	NS
Guy *et al*[82]	90/male	Ischaemic CVA	NS	No Hx of dysphagia	NS/no symptoms	NS/bronchial tree	Rigid bronchoscopy - stone retrieval basket	NS
Leeds *et al*[83]	85/male	NS	NS	No Hx of dysphagia	NS/difficulty swallowing CE, slightly painful	8 h/lobar bronchus	Spontaneous resolution	NS
Bredenoord *et al*[84]	65/male	Sigmoid colectomy for diverticulae; Ileal carcinoid resected	NS	Hx of dysphagia	Lengthy swallowing attempt/ coughing noted	NS/right main bronchus	Spontaneous resolution, eventually, CE was swallowed on same session	Normal small-bowel
Choi *et al*[85]	75/male	Prior CVA	PillCam®SB; Given®Imaging Ltd.	No Hx of dysphagia	NS/coughed several times	2 h/left main bronchus	Flexible Bronchoscopy-Roth net and bronchial wall irrigation to induce cough	NS, patient declined further investigations
Depriest *et al*[86]	90/male	IHD, AF, PVD (warfarin + clopidogrel)	PillCam®SB; Given®Imaging Ltd.	No Hx of dysphagia	NS/some cough	NS/left main bronchus, then right main bronchus	Chest percussive therapy + postural drainage; Flexible bronchoscopy + extraction basket + Roth net	NS
Depriest *et al*[86]	90/male	IHD, AF, PVD (warfarin + clopidogrel)	PillCam®SB; Given®Imaging Ltd.	No Hx of dysphagia	NS/some cough	NS/left main bronchus, then right main bronchus	Chest percussive therapy + postural drainage; flexible bronchoscopy + extraction basket + Roth net	NS

Kurtz *et al*[87]	73/male	Renal cell cancer, MV (bovine), hyperlipidaemia, melaena	NS	No Hx of dysphagia	Sips of water, 1st attempt, 2 min later non-productive cough (20 s)	Level of carina; then right main stem bronchus	Bronchoscopy-retrieval basket (multiple spontaneous ejections from trachea prior bronchoscopy)	NS
Lucendo *et al*[88]	80/male	Advanced PD, DM, walking + speech difficulties	PillCam®SB; Given®Imaging Ltd.	No Hx of dysphagia	Several attempts/persistent coughing and some dyspnoea	20 s/tracheobronchial tree	Spontaneous resolution	Oesophageal ulcer + ileal ulcer
Pezzoli *et al*[89]	82/male	Unexplained anemia, HTN	NS	No Hx of dysphagia	NS/asymptomatic (minimal cough)	3 d/in the right bronchus	Spontaneous resolution	NS
Parker *et al*[90]	77/female	Hysterectomy	NS	No Hx of dysphagia	Initial attempt unsuccessful/chocking episode, CE coughed-up	NS/NS	Spontaneous resolution, endoscopic placement with AdvanCE® device	Patient suffered intracranial bleed, eventually succumbed
Despott *et al*[91]	65/male	COPD, cirrhosis, pancreatitis	NS	No Hx of dysphagia	NS/asymptomatic	NS/right main bronchus	Rigid bronchoscopy-Roth net	Endoscopic placement with AdvanCE® device
	73/male	COPD	NS	NS	NS/brief coughing	NS/left main bronchus	Bronchoscopy-snare + Roth net	Endoscopic placement with AdvanCE® device
	81/male	NS	NS	NS	NS/fleeting choking sensation	NS/right main bronchus	Rigid bronchoscopy-crocodile grasping forceps	NS
Girdhar *et al*[92]	83/male	COPD, GORD	PillCam®SB; Given®Imaging Ltd.	No Hx of dysphagia	Difficult, requiring multiple sips of water/some cough, after 1 h mild shortness of breath	NS/left main bronchus	Flexible bronchoscopy + rat-tooth alligator forceps + stiff-wire basket with a pin-vise handle	NS
Poudel *et al*[93]	80/male	AF, IHD, CVA on anti-coagulants, anaemia + melaena	M2A®; Given®Imaging Ltd.	NS	NS	24 h/left main stem bronchus; then right bronchus	Flexible bronchoscopy + net + snare forceps + tripod; eventually, grasped with basket	NS

MV: Mitral valve; BMI: Body mass index; HHT: Hereditary haemorrhagic telangiectasia; IDA: Iron deficiency anaemia; CHF: Chronic heart failure; IHD: Ischaemic heart disease; AF: Atrial fibrillation; CRF: Chronic renal failure; Hx: History; Ns: Not stated; HTN: Hypertension; DM: Diabetes mellitus; CVA: Cerebrovascular accident; PVD: Peripheral vascular disease; PD: Parkinson's disease; COPD: Chronic obstructive pulmonary disease; GORD: Gastro-oesophageal reflux disease; CE: Capsule endoscopy.

Table 7 Studies looking at the clinical validity of Suspected Blood Indicator, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy

Ref.	Country	Centre	Objective(s)	Study type	Design	CE type	Outcome(s)	Conclusions
Gross *et al*[96]	United States	Single centre	Accuracy of SBI to number of blood transfusions	Retrospective	►Gold standard for lesions detected by experienced CE reviewer	M2A; Given® Imaging Ltd.	►Gold standard: 72 pts; ►pts received blood transfusions ranging between 0-16 units; ►Overall: A total of 17 pts had positive SBI. Active bleeding in 16 pts, who were transfused an average of 8 units before the study; ►55 pts had a negative SBI and no active bleeding was seen on their capsule studies. In this group, the average number of PRBC transfused was 1 unit. There was one patient who had a false positive SBI with no active bleeding seen in the capsule study review	Pts receiving blood transfusions are more likely to have a positive SBI correlating with the localization of active bleeding
Liangpunsakul *et al*[97]	United States	Single centre	Assess accuracy of SBI	Retrospective	►Gold standard for lesions detected by experienced CE reviewer; ►Significant lesions considered AVMs, ulcers, erosions, active bleeding; ►Reviewing speed: 15fps	M2A; Given® Imaging Ltd.	►Gold standard: 109 lesions; ►SBI: 31 potential areas of blood; correctly identified lesions: 28; ►Overall: SBI (Sens, PPV, accuracy): 25.7%, 90%, 34.8%, respectively; ►For actively bleeding SB lesions only: SBI (Sens, PPV, accuracy): 81.2%, 81.3%, 83.3%, respectively	SBI has good Sens and PPV for actively bleeding SB lesions

D'Halluin *et al*[98]	France	Multi-centre (7 centres)	Assess Sens/Spec of SBI (in OGIB)	Retro-spective	►Gold standard for lesions detected by experienced CE reviewer, SBI tags marked by another investigator; ►Significant lesions considered Bleeding or having a bleeding potential: high (P2), low (P1), or absent (P0); ►Concordance: same time code in frames selected by expert reader and those tagged by SBI; ►Reviewing speed: NS	M2A; Given® Imaging Ltd.	►156 SBCE recordings evaluated: In 83 (normal): either no lesion (n = 71) or P0 lesion (n = 12); in 73 abnormal: P2 (n = 114) and P1 (n = 92) lesions; ►154 red tags analysed: SBI (Sens, Spec, PPV, NPV) for P2 or P1: 37%, 59%, 50%, 46%, respectively	►SBI-based detection of SB lesions (with bleeding potential) is of limited clinical value
Singnorelli *et al*[99]	Italy	Single centre	Assess Sens/Spec of SBI per lesion, overall, according to red findings (identified by the reader), and per patient	Retro-spective	►Gold standard for lesions detected by four experienced CE reviewers; ►Outcomes: Sens, Spec and accuracy calculated both per lesion/patient; ►Reviewing speed: NS	M2A; Given® Imaging Ltd.	►95 patients; 209 red findings; ►Overall Sens: 28%; ►Sens higher for identification of blood (61%) than for nonbleeding "red" findings, *e.g*., AVMs (26%); ►Per-patient Sens, Spec: 41%, 70%, respectively	►SBI has low Sens/Spec in per-lesion and per-patient SBCE evaluation; ►Complementary/rapid screening tool; ►Complete review of the recordings is still necessary
Ponferrada *et al*[100]	Spain	Single centre	Assess accuracy/performance of SBI	Prospec-tive	►Gold standard for lesions detected by experienced CE reviewers	M2A; Given® Imaging Ltd.	►57 consecutive patients; ►Indications: OGIB (64.9%), CD (14%), malabsorption (14%), suspicion of SB tumour (7.1%); ►SBI Sens, Spec, PPV, NPV: 58.3%, 75.5%, 38.8%, 87.2%, respectively	
Buscaglia *et al*[101]	United States	Single centre	Assess accuracy/performance of SBI according to CE indications	Retro-spective	►Gold standard for lesions detected by experienced CE reviewer; ►Significant lesions:AVMs, varices, venous ectasias, red spots, ulcers, erosions, blood, blood clots ►Concordant and discordant findings between CE reviewer and SBI; ►Reviewing speed: 8-15 fps	M2A; Given® Imaging Ltd.	►CE indications: OGIB (n = 112), suspected CD (n = 122), anaemia of unknown origin (n = 53), other (n = 4); ►221 lesions with bleeding potential; ►Overall: SBI (Sens, Spec, PPV, NPV): 56.4%, 33.5%, 24.0%, 67.3%, respectively; ►For actively bleeding lesions: SBI (Sens, PPV): 58.3%, 70%, respectively; ►For suspected CD: SBI (Sens, NPV): 64%, 80.4%, respectively; ►For OGIB: SBI Sens 58.3%; ►For anaemia: SBI Sens 41.3%;	►SBI performance characteristics suboptimal/insufficient to screen for SB lesions with bleeding potential; ►Even in pts with active intestinal bleeding, SBI Sens was only < 60%
Park *et al*[102]	South Korea	Single centre	Investigate whether SBI is affected by background colour and CE velocity	Experi-mental	►Paper-made phantom SB models in a variety of colours to simulate the background colours observed in CE; ►Red spots were attached inside them; ►CE manually passed through models; ►SBI red spots detection rate was evaluated based on colours of SB models and CE velocities (0.5, 1, 2 cm/s)	M2A; Given® Imaging Ltd.	►SBI red spots detection rate differed significantly per background colour of SB model, P < 0.001; ►SBI red spots detection rate highest for very pale magenta, burnt sienna, yellow background; ►SBI red spots detection rate lowest for dark brown, very pale yellow background ►SBI red spots detection rate decreases at rapid CE passage (1-2 cm/s) compared to slower (0.5 cm/s) for very pale yellow (P = 0.042), yellow (P = 0.001), very pale magenta (P = 0.002), burnt sienna (P = 0.001) background; ►Red spots detection rate no different according to velocity for light greyish pink (P = 0.643) or dark brown (P = 0.396) background	►SBI Sens affected by background colour and capsule passage velocity in the models

PRBC: Pack red blood cells; fps: Frames per second; SBI: Suspected Blood Indicator; CE: Capsule endoscopy; AVM: Arterio-venous malformations; SB: Small-bowel; Sens: Sensitivity; Spec: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; OGIB: Obscure gastrointestinal bleeding; CD: Crohn's disease.

Table 8 Studies looking at the clinical validity of QuickView, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy

Ref.	QuickView sampling rate	QuickView reading frame mode/ reading speed (fps)	Average reading time (mean)	Comparison with/ reading frame mode/ reading speed used (fps)	Rapid® Reader version	Reviewers	Cases					QuickView		Lesions missed
							Total	OGIB	CD	Polyposis	Other	Sensitivity (%)	Specificity (%)	
Ponferrada *et al*[100]	NS	25, 15, 5	NS	Conventional/NS/15, 15, 5		2	57	37	8	N/A	12	96.5 (5 fps)	NS	NS
Schmelkin[104]	NS	NS	NS	NS	4.0	1	47	47	N/A	N/A	N/A	100	100	N/A
Appalaneni *et al*[105]	NS	Single frame, 25	3 min	NS	NS	2	50	NS	NS	NS	NS	NS	NS	2
Westerhof *et al*[106]	High (17)	NS	4.4 min (median)	Conventional/dual view/18	4.0	2	100	56	30	2	12	NS	NS	13
Shiotani *et al*[107]	High (17)	Single, 6	17.9 min	NS	5.0	3	44	NS	NS	NS	14	NS	NS	10
Hosoe *et al*[108]	Normal	NS	NS	NS	5.0	3	45	NS	NS	NS	14	NS	NS	NS
Saurin *et al*[109]	NS	NS	11.6 min	Conventional/NS/NS	5.0	12	106	106	N/A	N/A	N/A	89.2	Jul-84	8
Shiotani *et al*[110]	5, 15, 25, 35	Single, NS	NS	NS	6.5	4	87	NS	NS	NS	NS	NS	NS	NS
Koulaouzidis *et al*[111]	35 18	Dual view (WL + BM)	475 s (QuickView WL) 450 s (QuickView BM)	Conventional/ single or dual view/12-20	7.0	1	200	106	81	4	9	92.3 (QVWL P1 + P2) 91 (QVBM P1+P2)	96.3 (QVWL P1 + P2) 96 (QVBM P1 + P2)	
Kyriakos *et al*[112]	NS	NS, 3	16.3 min (6.7)	Conventional/NS/NS	5.0	2	100	55	22	3	20	NS	NS	12

NS: Not stated; NA: Not applicable; fps: Frames per second; QVWL; QuickView with white light; QVBM: QuickView with blue mode; OGIB: Obscure gastrointestinal bleeding; CD: Crohn's disease; P1, P2: Classification as per probability of bleeding.

Table 9 Studies looking at the clinical validity of Fujinon® intelligent chromoendoscopy enhancement/Blue mode, feature of capsule endoscopy reading software, in small-bowel capsule endoscopy

Ref.	Country	Centre	Study type	Objective(s)	Design	Images	FICE	CE	Outcome(s)
Imagawa *et al*[114]	Japan	Single centre	Retrospective	Assess whether visualization of SB lesions improves with FICE	►5 experienced readers compared CE-WL images to their FICE counterparts	►Angiectasis (n = 23); ►Erosion/ ulcers (n = 47); ►Tumour (n = 75)	FICE 1,2,3	PillCam®SB1; Given®Imaging Ltd.	►FICE 1: AVMs: improvement in 87% (20/23) cases; erosion/ulceration: improvement 53.3% (26/47) cases; tumour images: improvement 25.3% (19/75) cases; ►FICE 2: AVMs: improvement in 87% (20/23) cases; erosion/ulceration: improvement in 25.5% (12/47) cases; tumour images: improvement in 20.0% (15/75) cases; ►FICE 3: All images groups: only equivalence achieved in all cases; intra-observer agreement: good to satisfactory (5.4 or higher)
Imagawa *et al*[115]	Japan	Single centre	Prospective	Assess whether FICE improves detection rate of SB lesions in CE	►A CE reader reviewed CE-WL videos; ►Another reader, reviewed CE-FICE videos with FICE 1,2,3	50 pts	FICE 1,2,3	PillCam®SB1; Given®Imaging Ltd.	►Angioectasias detection: CE-WL: 17 AVMs; CE-FICE 1: 48 AVMs; CE-FICE 2: 45 AVMs; CE-FICE 3: 24 AVMs; significant CE-FICE 1 and 2 (P = 0.0003 and P < 0.0001, respectively) ►Detection rate for erosion, ulceration and tumour did not differ statistically between CE-WL and CE-FICE 1,2,3; ►Similar interpretation time (CE-WL: 36 ± 6.9 min; CE-FICE 1: 36 ± 6.4 min; FICE 2: 38 ± 5.8 min; FICE 3: 35 ± 6.7 min)

Gupta *et al*[116]	Belgium	Single centre	Retrospective	Assess potential benefit of FICE for SB lesion detection in patients with OGIB	CE videos analysed by 2 GI fellows with and without FICE 1,2,3; Reference standard: Senior consultant described findings as P0, P1 and P2 lesions	60 pts with OGIB	FICE 1,2,3	PillCam®SB1; Given®Imaging Ltd.	►Overall, 157 lesions diagnosed with CE-FICE *vs* 114 with CE-WL ($P = 0.15$); ►For P2 lesions; CE-FICE Sens/Spec: 94%/95% *vs* CE-WL Sens/Spec: 97%/96%, respectively; 5/55 AVMs better characterized with CE-FICE than CE-WL ►More P0 diagnosed by CE-FICE than CE-WL (39 *vs* 8, $P < 0.001$); ►Intra-class kappa correlations between fellows and reference: CE-FICE *vs* CE-WL for P2 lesions: 0.88 *vs* 0.92; CE-FICE *vs* CE-WL for P1 lesions: 0.61 *vs* 0.79
Krystallis *et al*[117]	United Kingdom	Single centre	Retrospective	Assess FICE and Blue mode visualisation of SB lesions in CE	►2 experienced reviewers CE-WL images to FICE/Blue mode counterparts	►Angioectasias ($n = 18$); ►Erosion/ulcers ($n = 60$); ►Villi oedema ($n = 17$); ►Cobblestone ($n = 11$); ►Blood lumen ($n = 15$); ►LICS/other ($n = 46$)	Blue mode; FICE 1,2,3	Pillcam®SB1/SB2; Given®Imaging Ltd.	►Total of 167 images, for all lesion categories: ►Blue mode *vs* WL: image improvement in 83%; $\kappa = 0.786$ ►FICE 1 *vs* WL: image improvement in 34%; $\kappa = 0.646$ ►FICE 2 *vs* WL: image improvement in 8.6%; $\kappa = 0.617$ ►FICE 3 *vs* WL: image improvement in 7.7%; $\kappa = 0.669$
Duque *et al*[118]	Portugal	Single centre	Prospective	Assess reproducibility and diagnostic accuracy of CE-FICE	►4 physicians reviewed 150 FICE images; ►2 experienced physicians analysed 20 CE; 1 interpreted CE-WL; the other, CE-FICE videos	20 patients with OGIB	Blue mode; FICE 1,2,3	PillCam®SB2; Given®Imaging Ltd.	►Concordance between the 4 gastroenterologists: 0.650; ►CE-WL identified 75 findings and the CE-FICE 95; ►CE-FICE did not miss any lesions identified by CE-WL and allowed the identification of a higher number of AVMs (35 *vs* 32) and erosions (41 *vs* 24)
Nakamura *et al*[119]	Japan	Single centre	Prospective	Assess preview of angioectasias by CE-FICE preview (compared to CE-WL)	►One experienced physician analysed CEs in QuickView mode; ►Mean reading time, sensitivity and specificity for angiodysplasia detection were evaluated including SBI	50 pts with angiodysplasia were randomly assigned to 2 equally sized groups of CE-WL reading and CE-FICE reading	SBI; Blue mode; FICE 1,2,3	PillCam®SB2; Given®Imaging Ltd.	►Mean reading time: 14min for both CE-WL and CE-FICE reading; ►The two previews for angiodysplasia were significantly superior to the function of SBI ($P < 0.01$); ►Sens and Spec of CE-WL: 80% and 100%, respectively; ►Sens and Spec of CE-FICE: 91% and 86%, respectively; ►FICE reading was superior in Sens, while it resulted in more false (+) ve lesion findings and lower Spec
Sakai *et al*[120]	Japan	Single centre	Prospective	►Assess whether CE-FICE improves detectability of SB lesions by CE trainees and if it contributes to reducing the bile-pigment effect; ►Evaluate whether poor bowel preparing affects the accuracy of lesion recognition by FICE	►4 gastroenterology trainees interpreted 12 CE videos with WL and FICE 1,2,3; ►Lesion detection rate under each of the three FICE settings was compared with that by conventional CE-WL	►60 AVMs; ►82 erosions/ulcers	FICE 1,2,3	PillCam®SB2; Given®Imaging Ltd.	►60 angioectasias; CE trainees identified: 26 by CE-WL, 40 by CE-FICE1, 38 by CE-FICE2, 31 by CE-FICE3; ►82 erosions/ulcerations, CE trainees identified: 38 by CE-WL, 62 by CE-FICE1, 60 CE- FICE2, 20 by CE-FICE3; ►CE-FICE 1 and 2 significantly improved detectability of angioectasias ($P = 0.0017$ and $P = 0.014$, respectively) and erosions/ulcers ($P = 0.0012$ and $P = 0.0094$, respectively); ►Detectability of SB lesions by CE-FICE1 was not affected ($P = 0.59$) by the presence of bile-pigments; ►Detectability of SB lesions by CE-WL ($P = 0.020$) and CE-FICE2 ($P = 0.0023$) was reduced by the presence of bile-pigments; ►In poor bowel visibility conditions, CE-FICE yielded a high rate of false-positive findings

FICE: Fujinon® Intelligent chromoendoscopy enhancement; CE: Capsule endoscopy; SB: Small bowel; WL: White light; OGIB: Obscure gastrointestinal bleeding; SBI: Suspected Blood Indicator; AVM: arterio-venous malformation; κ: Inter-observer agreement; LICS: Lesions of indeterminate clinical significance; Sens: Sensitivity; Spec: Specificity.

Table 10 Experimental and models in development for capsule-endoscopy the future?

Ref.	Project	Status	Active actuation	Magnetic propulsion	Therapeutic capabilities
Johannessen *et al*[124]	IDEAS: A miniature lab-in-a-pill multi-Sens or microsystem	Prototype	No	Yes	Yes
Karagozler *et al*[125]	Miniature endoscopy capsule robot using biomimetic micro-patterned adhesives	Prototype	Yes	No	No
Quirini *et al*[126]	An approach to capsular endoscopy with active motion	Prototype	Yes	No	No
Valdastri *et al*[127]	Wireless therapeutic endoscopic capsule: *in vivo* experiment	Prototype	No	Yes	Yes
Glass *et al*[128]	A legged anchoring mechanism for capsule endoscopes using micro-patterned adhesives	Prototype	Yes	No	No
Valdastri *et al*[129]	An endoscopic capsule robot: a meso-scale engineering case study	Concept	Yes	No	No
Tortora *et al*[130]	Propeller-based wireless device for active capsular endoscopy in the gastric district	Prototype	Yes	No	No
Valdastri *et al*[131]	A magnetic internal mechanism for precise orientation of the camera in wireless endoluminal applications	Prototype	No	Yes	No
Ciuti *et al*[132]	Robotic magnetic steering and locomotion of capsule endoscope for diagnostic and surgical endoluminal procedures	Prototype	No	Yes	Yes
Bourbakis *et al*[133]	Design of new-generation robotic capsules for therapeutic and diagnostic endoscopy	Concept	Yes	No	Yes
Gao *et al*[134]	Design and fabrication of a magnetic propulsion system for self-propelled capsule endoscope	Concept	No	Yes	No
Simi *et al*[135]	Design, fabrication, and testing of a capsule with hybrid locomotion for gastrointestinal tract exploration	Concept	No	Yes	No
Morita *et al*[136]	A further step beyond wireless capsule endoscopy	Concept	No	Yes	No
Yang *et al*[137]	Autonomous locomotion of capsule endoscope in gastrointestinal	Concept	Yes	No	No
Filip *et al*[138]	Electronic stool (e-Stool): A novel self-stabilizing video capsule endoscope for reliable non-invasive colonic imaging	Prototype	Yes	No	No
Yim *et al*[139]	Design and rolling locomotion of a magnetically actuated soft capsule endoscope	Prototype	Yes	No	No
Kong *et al*[140]	A robotic biopsy device for capsule endoscopy	Prototype	Yes	No	Yes
Woods *et al*[141]	Wireless capsule endoscope for targeted drug delivery: Mechanics and design considerations	Prototype	Yes	No	Yes

Certain issues (*i.e.*, best small-bowel preparation for CE[143,144], occurrence of some potentially life-threatening complications, visualisation quality of the proximal small-bowel) remain open and they will surely be the target of further clinical studies and technical improvements.

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