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Capsule Endoscopy in the Assessment of Obscure Gastrointestinal Bleeding: An Evidence-Based Analysis

Health Quality Ontario

February 2015

Ontario Health Technology Assessment Series; Vol. 15: No. 1, pp. 1–55, February 2015

Suggested Citation

This report should be cited as follows:

Health Quality Ontario. Capsule endoscopy in the assessment of obscure gastrointestinal bleeding: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2015 February;15(1):1–55. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/capsule-endoscopy-gi-bleeding.

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Abstract

Background

Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent bleeding associated with negative findings on upper and lower gastrointestinal (GI) endoscopic evaluations. The diagnosis and management of patients with OGIB is particularly challenging because of the length and complex loops of the small intestine. Capsule endoscopy (CE) is 1 diagnostic modality that is used to determine the etiology of bleeding.

Objectives

The objective of this analysis was to review the diagnostic accuracy, safety, and impact on health outcomes of CE in patients with OGIB in comparison with other diagnostic modalities.

Data Sources

A literature search was performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published between 2007 and 2013.

Review Methods

Data on diagnostic accuracy, safety, and impact on health outcomes were abstracted from included studies. Quality of evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results

The search yielded 1,189 citations, and 24 studies were included. Eight studies reported diagnostic accuracy comparing CE with other diagnostic modalities. Capsule endoscopy has a higher sensitivity and lower specificity than magnetic resonance enteroclysis, computed tomography, and push enteroscopy. Capsule endoscopy has a good safety profile with few adverse events, although comparative safety data with other diagnostic modalities are limited. Capsule endoscopy is associated with no difference in patient health-related outcomes such as rebleeding or follow-up treatment compared with push enteroscopy, small-bowel follow-through, and angiography.

Limitations

There was significant heterogeneity in estimates of diagnostic accuracy, which prohibited a statistical summary of findings. The analysis was also limited by the fact that there is no established reference standard to which the diagnostic accuracy of CE can be compared.

Conclusions

There is very-low-quality evidence that CE has a higher sensitivity but a lower specificity than other diagnostic modalities. Capsule endoscopy has few adverse events, with capsule retention being the most serious complication. Capsule endoscopy is perceived by patients as less painful and less burdensome

compared with other modalities. There is low-quality evidence that patients who undergo CE have similar rates of rebleeding, further therapeutic interventions, and hospitalization compared with other diagnostic modalities.

Plain Language Summary

Obscure gastrointestinal bleeding is defined as bleeding where the cause is not determined from initial medical procedures examining the gastrointestinal tract. Visualizing this part of the body is very difficult and capsule endoscopy is one method that allows for the examination of the entire small intestine to determine the cause of the bleeding. This diagnostic method involves swallowing a pill-sized camera, which has its own light source and takes pictures of the small intestine as it passes through. These pictures are sent to a small recording device worn on the body, for interpretation by a doctor.

This review demonstrated that capsule endoscopy tended to have a higher sensitivity than some other diagnostic methods and, as such, correctly returned a positive test result in a greater proportion of individuals with bleeding. However, capsule endoscopy also had a lower specificity than some other methods and, therefore, correctly classified a smaller proportion of individuals without bleeding as having a negative test result.

There is the potential for the capsule to be stuck at a narrowed spot in the digestive tract. This review identified that few patients experienced capsule retention, which may require surgery or procedures using long endoscopes to remove the capsule.

Patients tended to prefer capsule endoscopy over other methods. With capsule endoscopy, they reported less pain and less burden with the preprocedure preparation. This review found no difference in the rates of further bleeding, hospitalization, or more interventions in patients who underwent capsule endoscopy compared with patients who underwent other diagnostic methods.

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List of Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	Assessment of Multiple Systematic Reviews
ASGE	American Society for Gastrointestinal Endoscopy
BSG	British Society of Gastroenterology
CE	Capsule endoscopy
CI	Confidence interval
CT	Computed tomography
DBE	Double-balloon enteroscopy
EGD	Esophagogastroduodenoscopy
ESGE	European Society of Gastrointestinal Endoscopy
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HTA	Health technology assessment
LR	Likelihood ratio
MRE	Magnetic resonance enteroclysis
OGIB	Obscure gastrointestinal bleeding
OHIP	Ontario Health Insurance Plan
PE	Push enteroscopy
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
SBFT	Small-bowel follow-through

Background

Objective of Analysis

The objective of this analysis was to review the diagnostic accuracy, safety, and impact on health outcomes of capsule endoscopy (CE) in comparison with other diagnostic modalities in patients with obscure gastrointestinal bleeding (OGIB).

Clinical Need and Target Population

Epidemiology of Obscure Gastrointestinal Bleeding

Obscure gastrointestinal bleeding is defined as persistent or recurrent bleeding associated with negative findings on upper and lower gastrointestinal (GI) endoscopic evaluations. OGIB can be further classified into overt or occult bleeding depending on the presence or absence of clinically evident bleeding. (1) Overt OGIB is defined as visible GI bleeding (e.g., melena or hematochezia) and can be categorized as active (i.e., there is evidence of ongoing bleeding) or inactive bleeding. OGIB is classified as occult when there is no evidence of visible GI bleeding (e.g., unexplained iron deficiency anemia suspected to be caused by GI blood loss). (2)

Gastrointestinal bleeding is a common clinical presentation, with about 100 episodes per 100,000 persons per year. (3) OGIB represents about 5% of all cases of GI bleeding, with small bowel as the presumed source. This has led to the use of the new term "mid-gastrointestinal bleeding" to describe bleeding that occurs between the papilla and the ileocecal valve. (4)

The diagnosis and management of patients with OGIB is particularly challenging because of the length and complex loops of the small intestine. (5) The presenting symptoms can help to direct the plan of investigation. Hematemesis can indicate upper GI bleeding, whereas melena can suggest bleeding anywhere from the nose to the large bowel. Conversely, hematochezia is suggestive of either a lower GI bleed or a fast upper GI bleed.

Causes of Obscure Gastrointestinal Bleeding

Obscure gastrointestinal bleeding can arise from any lesion throughout the GI tract, although the majority arise in the small bowel and predominantly include vascular lesions. (6) The etiology of bleeding in the small bowel is varied and may be dependent on the age of the patient (Table 1). (1)

Table 1: Causes of Obscure Gastrointestinal Bleeding in the Small Bowel

In Patients Aged Less Than 40 Years
Tumours
Meckel's diverticulum
Dieulafoy's lesion
Crohn's disease
Celiac disease
In Patients Aged 40 Years and Older
Angiectasia
Nonsteroidal anti-inflammatory drug enteropathy
Celiac disease
Uncommon Causes
Hemobilia
Hemosuccus pancreaticus
Aortoenteric fistula

Technologies

There is a range of diagnostic and therapeutic modalities that are used to investigate the small bowel; these are described below.

Capsule Endoscopy

Capsule endoscopy was first introduced by Given Imaging Ltd. (Yokneam, Israel) in 2001. Since that time, a third-generation product has been licenced and four other manufacturers now produce CE devices. The introduction of CE has allowed for the visualization of the entire GI tract. It is a relatively simple and non-invasive test (provided the patient can swallow the capsule) that enables patients to continue with normal activities of daily living. (7) The primary limitation of the technology is that it is a purely diagnostic test and offers no therapeutic benefit such as obtaining biopsies or administering therapy, besides directing further therapeutic measures.

Health Canada licences CE devices from five manufacturers for the examination of the small bowel (Table 2).

Table 2: Small-Bowel Endoscopy Capsules Licenced for Use in Canada

Company Name	Licence No.	Date Issued	Class	Device Name	Intended Use
CapsoVision, Inc.	89763	2012-09-26	2	CapsoCam	Visualization of the small-bowel mucosa
Chongqing Jinshan Science & Technology (Group) Co., Ltd.	86038	2011-05-06	2	OMOM Smart Capsule	Diagnosis of small-intestinal diseases such as obscure abdominal pain, distension, diarrhea, gastrointestinal bleeding, small-bowel tumour, and suspected Crohn's disease
Given Imaging Inc.	69804	2005-11-25	2	PillCam SB	Visualization of the small-bowel mucosa including assessment for severity and extent of small-bowel abnormalities
Given Imaging Inc.	69804	2007-06-18	2	PillCam SB2	Visualization of the small-bowel mucosa including assessment for severity and extent of small-bowel abnormalities
Given Imaging Inc.	69804	2013-03-13	2	PillCam SB3	Visualization of the small-bowel mucosa including assessment for severity and extent of small-bowel abnormalities
IntroMedic Co., Ltd.	77649	2008-07-23	2	MiroCam Capsule Endoscope	Visualization of the small-bowel mucosa as an adjunctive tool in the detection of abnormalities in the small bowel
IntroMedic Co., Ltd.	86466	2011-06-29	2	MiroCam Capsule Endoscope	Visualization of the small-bowel mucosa as an adjunctive tool in the detection of abnormalities in the small bowel
Olympus Medical Systems Corp.	75207	2009-05-05	2	Capsule Endoscope System	Visualization of the small-bowel mucosa

In general, a CE system consists of four main parts: (1) a disposable capsule, (2) an image recorder, (3) a portable real-time monitor, and (4) a computer workstation. The capsule is swallowed and is propelled through the GI tract via bowel peristalsis. The capsule contains a video camera, a light source, a radio transmitter, and batteries. The various capsules differ in size, frame rate, and field of view (Table 3). Once the capsule is swallowed by a patient, it begins to acquire images and transmit them to the sensor array attached to the patient's abdomen; this sensor subsequently sends the data to the recorder (worn as a belt around the patient's waist). The data are then downloaded to a computer workstation, and the images are evaluated by a physician using a computer software. Each manufacturer provides its own software to process the data downloaded from the data recorder.

Table 3: Specifications of Small-Bowel Endoscopy Capsules Licenced for Use in Canada

Capsule	Size (mm)	Frame Rate (fps)	Field of View (degrees)	Communication
PillCam SB	11 x 26 mm	2	140	RF
PillCam SB2	11 x 26	2	156	RF
PillCam SB3	11 x 26	2–6	172	RF
MiroCam	10.8 x 24.5	3	170	HBC
Capsule Endoscope System	11 x 26	2	145	RF
OMOM	13 x 27.9	2	140	RF
CapsoCam	11 x 31	20	360	Onboard storage

Abbreviations: fps, frames per second; HBC, human body communication (transmits data through the field generated by the electrodes on the capsule and the direct contact between cellular tissue or bodily fluid and the electrodes attached to the human body); RF, radio-frequency.

The capsule endoscopy procedure usually begins in a doctor's office; once the patient has ingested the capsule, he or she can leave the office and resume normal activities, while the capsule examination takes place. The capsule is excreted usually after 8 to 72 hours, although occasionally excretion can take longer. Three capsules use radio-frequency technology to transmit data, whereas the MiroCam capsule (IntroMedic Co., Ltd., Seoul, Korea) transmits data through a field generated by electrodes on the capsule and the direct contact between cellular tissue or bodily fluid and the electrodes attached to the human body. For all devices except the CapsoCam capsule (CapsoVision, Inc., Silicon Valley, California), the capsule is discarded after excretion. The CapsoCam capsule does not generate or transfer radio-frequency signals, and all the data are stored onboard the capsule. Therefore, the patient is not required to wear any external devices or wires but is required to retrieve the capsule for data extraction.

In patients with dysphagia, gastroparesis, or known or suspected anatomical abnormalities that would preclude the safe ingestion of the capsule, the capsule can be placed into the stomach or small bowel. These delivery methods include overtubes to deliver the capsule into the stomach, and standard polypectomy snares and nets to deliver the capsule into the duodenum. (7) A capsule endoscope delivery device (US Endoscopy, Mentor, Ohio) can also be used; in this case, a disposable sheath is preloaded through the working channel of a standard endoscope and allows the activated video capsule endoscope to be delivered directly to the desired anatomical area.

A patency capsule is also available (Agile Patency System, Given Imaging) and is used to identify patients at high risk of capsule retention. This is a nonvideo capsule composed of lactose and barium that dissolves within 30 to 100 hours of entering the GI tract. Timer plugs on the capsule facilitate the controlled disintegration of the capsule body. The capsule contains a radio-frequency identification tag that can be used to determine the capsule location.

Contraindications for the use of CE include known bowel strictures or swallowing disorders and a history of bowel obstruction. Recent abdominal surgery is also a relative contraindication. (8)

Ontario Context

The cost for the time required for a clinician to read the results of CE is funded by the Ontario Health Insurance Plan (OHIP; fee code G332, introduced February 2008). Funding is provided only when the procedure is rendered for the purpose of identifying GI bleeding of obscure origin when all appropriate conventional techniques have failed to identify a source. (9) There are some instances where the use of

the technology is outside of this definition (e.g., the examination of the small bowel with no evidence of bleeding); these are funded by the patient or by a hospital's operating budget.

Small-Bowel Radiological Investigations

Small-Bowel Follow-Through

Small-bowel follow-through (SBFT) is a radiographic examination of the small bowel. The patient swallows a barium contrast medium and is then examined by a radiologist using a fluoroscope to acquire radiographic (x-ray) images.

Computed Tomography

Computed tomography (CT) is a noninvasive radiological technique that provides multi-planar images of the small bowel with high spatial resolution. The procedure can provide detailed information on the bowel wall and structures, but visualization of superficial lesions is limited. Exposure to ionizing radiation is also a concern. Distension of the small bowel is achieved via infusion of contrast material through a nasojejunal tube (enteroclysis) or through the administration of oral contrast material (enterography).

Magnetic Resonance Imaging

Magnetic resonance imaging is a noninvasive cross-sectional imaging technique. The technique can allow for the visualization of any thickening of the intestinal wall. There is no radiation exposure; however, poorer-resolution images are obtained compared with CT. Contrast agents are administered through a nasojejunal tube (enteroclysis) or orally (enterography).

Angiography

Angiography is a radiographic study of the blood vessels in which a radio-opaque contrast medium is used to identify the vessels.

Deep Enteroscopy

Push Enteroscopy

Push enteroscopy (PE) involves the oral insertion of a long dedicated enteroscope and allows for the examination of the upper GI tract up to the proximal jejunum, about 50 to 100 cm distal to the ligament of Treitz. (6) It is performed as an outpatient procedure under general or conscious sedation.

Balloon-Assisted Enteroscopy

Balloon-assisted enteroscopy allows for the examination of the entire small bowel for both diagnostic and therapeutic purposes. The procedure involves the use of a special enteroscope and an overtube, both of which have balloons at the distal end. The system using 2 balloons is called double-balloon enteroscopy (DBE), and the system using a single balloon is called single-balloon enteroscopy. The enteroscope is advanced in short stages through the small bowel through alternating steps of inflating and deflating the balloons, alternating the insertion of the enteroscope and overtube, and pulling back the enteroscope and overtube. By repeating this series of push and pull, a longer distance in the small bowel can be traversed compared with conventional endoscopy techniques. Access is either from the foregut (antegrade) or colon (retrograde). Both routes need to be combined in order to allow for complete enteroscopy of the small bowel. (10) The procedure requires sedation and can take several hours. It can be used to obtain tissue

biopsies for histological analysis, and can also provide other therapeutic options such as hemostasis of bleeding, polypectomy, balloon dilation, and foreign-body extraction. In addition, this procedure can be used to mark pathology with India ink to direct later surgery. (10)

Surgery

Intraoperative enteroscopy allows for the entire small intestine to be explored, and this procedure was once regarded as the gold standard for small-bowel evaluation. It is a more invasive technique and requires general anesthesia. Currently it is rarely done because of the associated laparotomy risks and significant morbidity and mortality. (11)

Evidence-Based Analysis

Research Question

What are the diagnostic accuracy, safety, and impact on health outcomes of CE for the diagnosis of OGIB compared with other diagnostic modalities?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 3, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and all EBM databases, for studies published from January 1, 2007, to December, 3 2013. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria or where a decision could not be made based solely on title or abstract, full-text articles were obtained. Articles that cited or were cited by the included studies were also examined to identify any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- articles published between January 1, 2007, and December 3, 2013
- systematic reviews and meta-analyses
- randomized controlled trials (RCTs) where patients were randomized within a study to CE or another diagnostic modality
- direct (head-to-head) observational studies where both CE and another diagnostic modality were evaluated in the same patient population
- studies of patients with OGIB

Exclusion Criteria

- noncomparative observational studies
- case reports and case series
- studies that present preliminary results in abstract form
- narrative reviews
- editorials
- studies in pediatric populations
- studies in nonhumans

Outcomes of Interest

- diagnostic accuracy (sensitivity, specificity)
- adverse events
- patient health outcomes
- impact on patient management

Index Test

Capsule endoscopy was the index test of interest. The analysis was not restricted to any specific model or manufacturer of capsule. Capsule endoscopy technologies developed for the investigation of the esophagus (PillCam ESO) and the colon (PillCam COLON) were excluded.

Comparator Tests

The comparator tests considered were these:

- CT enteroclysis or enterography
- magnetic resonance enteroclysis (MRE) or enterography
- PE
- double- or single-balloon enteroscopy
- angiography
- SBFT
- intraoperative enteroscopy

Reference Standard

A single reference standard for evaluating OGIB has not been established. Therefore, the definitions of the reference standard and of a positive test result as described by the study authors were accepted.

Data Extraction

Measures of diagnostic accuracy reported by the included studies were used to reconstruct 2-by-2 tables containing the numbers of true-positive, false-positive, false-negative, and true-negative results. The sensitivity, specificity, and their 95% confidence intervals (CIs) were calculated for each 2-by-2 table. Sensitivity describes the proportion of patients with disease who have a positive test result, whereas specificity is the proportion of patients without disease who have a negative test result. Data reported on diagnostic yield (the number of lesions detected divided by the number of tests undertaken) were not included in this summary.

Data on adverse events and patient outcomes were recorded as described by the authors. The failure of authors to report any event did not imply that no adverse events had occurred.

Statistical Analysis

Where the data allowed, likelihood ratios (LRs) were calculated to summarize the predictive value of CE and other diagnostic modalities. The LR is a measure that combines sensitivity and specificity and provides a summary of how much more or less likely a patient with the disease is to have a particular test result compared with patients without the disease. (12) The positive likelihood ratio (LR+) is calculated as sensitivity/(1 − specificity) and represents the odds that a positive test result would be found in a

patient with, versus without, a disease. The negative likelihood ratio (LR−) is calculated as (1 − sensitivity)/specificity and represents the odds that a negative test result would be found in a patient with, versus without, a disease. These values allow for the translation of population characteristics (i.e., sensitivity and specificity) to individual patients. An LR of 1.0 indicates that a test does not have a diagnostic value; in general, a large LR+ (> 10) significantly increases the probability of disease, while a small LR− (< 0.10) provides strong evidence to rule out the chance the patient has the disease. Where appropriate, meta-analysis of sensitivity and specificity was performed using Meta-DiSc software, version 1.4.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (13) The quality of evidence for each diagnostic accuracy study was examined using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. (14) The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (15) The overall quality was determined to be high, moderate, low, or very low using a stepwise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality. For diagnostic tests, cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard are considered high quality. (16) Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (15) For more detailed information, please refer to the latest series of GRADE articles. (15)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Evidence-Based Analysis

The database search yielded 1,189 citations published between January 1, 2007, and December 3, 2013, (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

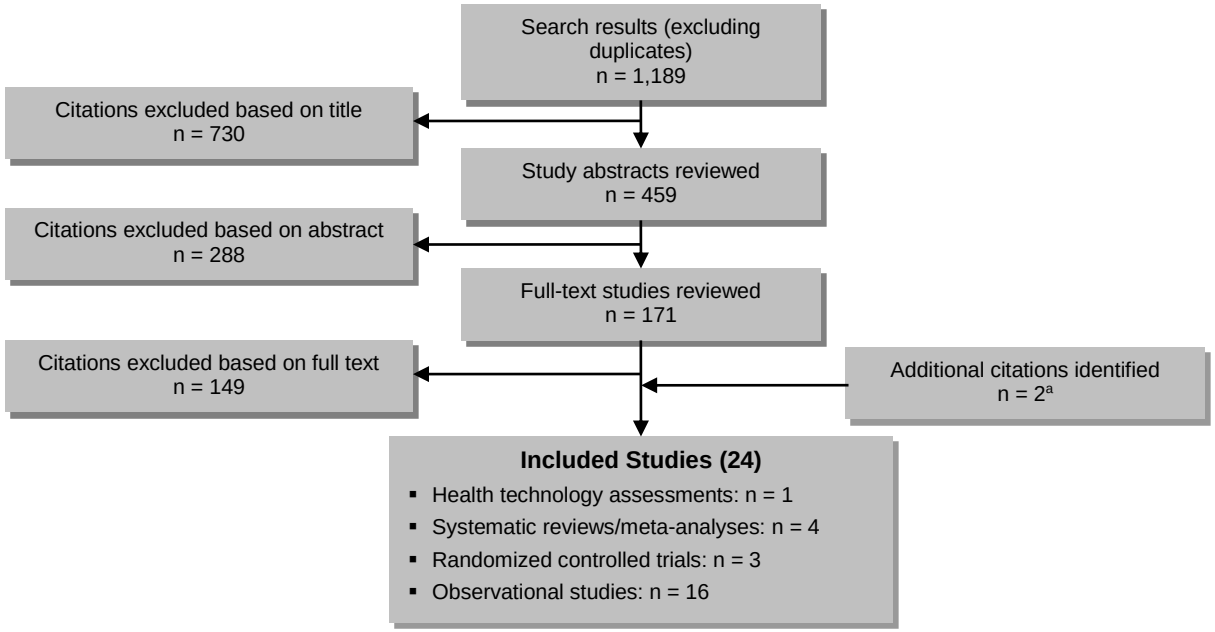
Twenty-three studies (3 systematic reviews, 1 meta-analysis, 3 RCTs, and 15 observational studies) met the inclusion criteria. The reference lists of the included studies and health technology assessment (HTA) websites were hand-searched to identify other relevant studies, and 1 additional HTA citation and observational study was included, for a total of 24.

For each included study, the study design was identified and is summarized below in Table 4, a modified version of a hierarchy of study design by Goodman. (17)

Table 4: Body of Evidence Examined According to Study Design

Study Design	No. of Eligible Studies
RCTs	
Systematic review of RCTs	0
Large RCT	0
Small RCT	3
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	5
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	16
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	**24**

Abbreviation: RCT, randomized controlled trial.



Reasons for exclusion

Abstract review (n = 288)

Wrong study type (n = 259)

- case series (n = 38)
- narrative review (n = 79)
- abstract only (n = 127)
- transit time/bowel preparation study (n = 15)

Wrong patient population (n = 16)

CE not index test (n = 6)

No comparator modality (n = 7)

Full-text review (n = 149)

Wrong study type (n = 28)

- economic analysis (n = 8)
- case series (n = 2)
- narrative review (n = 18)

Non-English language (n = 4)

Wrong patient population (n = 7)

No outcome data presented (n = 1)

Duplicate/earlier publication (n = 4)

CE not index test (n = 9)

No comparator modality (n = 80)

Only diagnostic yield data presented (n = 16)

Figure 1: Citation Flow Chart

Abbreviation: CE, capsule enteroscopy.

[a]One health technology assessment report and 1 observational study were identified via hand searching and bibliographic review.

Diagnostic Accuracy

Existing Health Technology Assessment Reports, Meta-Analyses, and Systematic Reviews

The search yielded 3 HTA reports, (18-20) 4 meta-analyses, (21-24) and 2 systematic reviews. (25, 26) Two HTA reports were excluded as the full reports were not available in English, (19, 20) and the 4 meta-analyses and 1 systematic review were excluded as they presented data on only diagnostic yield. (21-24, 26) The characteristics of the included HTA report and systematic reviews are summarized in Appendix 2.

The 2008 HTA report by the Italian National Agency for Regional Health Services summarized data on the diagnostic accuracy and safety of CE in OGIB and other small-bowel diseases. (18) A shortened version of the report was later published as a systematic review in 2009. (27) The HTA report identified 6 studies comparing the diagnostic accuracy of CE with that of PE in OGIB. (28-33) However, only 2 of these studies, (31, 33) did indeed present accuracy data and were eligible for inclusion. The other 4 studies presented data on only diagnostic yield and were excluded. The authors did suggest that PE may not be a suitable or fair comparator for CE as the former does not allow the visualization of the entire small bowel. The report also identified 5 studies of patients with OGIB comparing the diagnostic accuracy of CE with DBE. (34-38) Again, although the authors identified these as diagnostic accuracy studies, all of the studies presented data on only diagnostic yield. Finally, the report identified 5 further studies comparing CE with other diagnostic modalities. (39-43) Only the prospective study by Hartmann and colleagues (43) reported diagnostic accuracy data. The sensitivity and specificity of CE were reported using intraoperative enteroscopy as the reference standard (95% and 75%, respectively). However, no accuracy data for an additional comparator diagnostic modality were presented; therefore, the study by Hartmann et al was not included in this analysis.

Overall, the Italian HTA report (18) concluded that findings and subsequent conclusions from the identified literature regarding diagnostic accuracy should be regarded as uncertain because of the low quality of evidence. The authors suggested that the only reliable results are from the randomized trial by de Leusse and colleagues, (33) although they acknowledged the study's small sample size.

The systematic review by Varela Lema and Ruano Ravina (25) summarized an earlier Spanish-language HTA report (44). The authors identified 4 studies that reported data on the diagnostic accuracy of CE. (43, 45-47) Three studies did not present any comparative diagnostic accuracy data and were therefore not relevant to this analysis. (43, 45, 47) In the fourth study, Pennazio and colleagues (46) presented diagnostic accuracy data for only CE using a combination of surgery, PE, and other means as a reference standard. No pooled analysis was undertaken in the systematic review, and no conclusions on the overall diagnostic accuracy of the technology were made. The authors identified that the lack of a valid reference standard allowing for the confirmation of the CE results is an important limitation on ascertaining the true diagnostic value of CE and whether it could replace other techniques. Other important challenges highlighted by the report were (1) the difficulty in assessing accuracy as bleeding frequently disappears or diminishes by itself in many cases of OGIB, and (2) difficulties in determining a positive result. The authors concluded that CE may occupy a preferential place in the diagnosis of OGIB, although the evidence is insufficient to establish whether it could be used as the diagnostic test of first choice.

Primary Studies

Eight studies were identified by this analysis that reported the diagnostic accuracy of CE in determining the etiology of OGIB compared with other diagnostic modalities. The characteristics of the studies are described in Table 5. Capsule endoscopy was compared with a range of diagnostic modalities, and a variety of reference standards were used. All but 2 of the studies included an entirely adult population

(48, 49); the 2 studies included patients aged less than 18 years (the proportion of the study cohort aged less than 18 was not reported). All study participants underwent esophagogastroduodenoscopy (EGD) and colonoscopy prior to undergoing any further diagnostic modalities.

The results of the studies reporting on the diagnostic accuracy of CE for OGIB are presented in Table 6. Overall, most studies had negative LRs of > 0.10, the threshold for providing convincing evidence to exclude disease. The negative LRs ranged from 0.15 to 0.79, suggesting that patients without the condition may be up to 15 to 80% more likely to have a negative test than patients with the condition.

Capsule Endoscopy Versus Magnetic Resonance Enteroclysis

Two studies compared the accuracy of CE with that of MRE. (49, 50) The study by Wiarda and colleagues (50) reported that the sensitivity and specificity of CE were 61% (95% CI, 36–81) and 85% (95%, CI 61–96), respectively; the sensitivity and specificity of MRE were 21% (95% CI, 7–46) and 100% (95% CI, 79–100), respectively. No statistical comparisons were undertaken by the authors. In the larger study by van Weyenberg and colleagues, (49) the sensitivity for CE was similar to that for MRE (74% [95% CI, 58–86] compared with 79% [95% CI, 63–90]; $P = 0.591$). The specificity of MRE was statistically significantly higher than that of CE (97% [95% CI, 85–100] compared with 84% [95% CI, 68–0.93]; $P = 0.047$). Although both studies did use results obtained from DBE as a component of the reference standard, the overall methods to assess the final diagnosis between the 2 studies differed.

Capsule Endoscopy Versus Computed Tomography

Four included studies provided direct comparative data on the diagnostic accuracy of CE versus CT. (48, 51-53) Three studies presented a greater sensitivity of detecting lesions using CE compared with CT, while 1 study reported the opposite. (51) CT enterography demonstrated statistically significant greater sensitivity than CE in 2 subgroups: patients with small-bowel masses ($P = 0.03$) and patients with small-bowel lesions ($P = 0.008$). Only 2 studies presented comparative specificity data, (48, 52) with 1 study reporting a higher sensitivity for CE compared with CT, and another reporting a lower sensitivity. A third study described sufficient data for the specificity to be calculated, so that overall CE had a lower specificity than CT (49% compared with 67%). (51) All 4 studies differed in the methods in which the reference standard was assessed.

Capsule Endoscopy Versus Push Enteroscopy

One randomized trial and 1 observational study compared the diagnostic accuracy of CE with PE. In the randomized trial, the sensitivity of CE (79% [95% CI, 60–86]) for the detection of all lesions was statistically significantly higher than that of PE (41% [95% CI, 30–53]; $P = 0.025$). (33) For all lesions, the specificity for CE was lower than that for PE (87% [95% CI, 67–90] compared with 100% [95% CI, 91–100]), although the difference was not statistically significant. Similar results were obtained when the analysis was restricted to small-bowel lesions. Saurin and colleagues undertook a retrospective analysis to assess the diagnostic accuracy of CE compared with PE, using a 1-year follow-up as the reference standard. (31) Capsule endoscopy had a higher sensitivity than PE (92% [95% CI, 82–100] compared with 69% [95% CI, 53–87]), but a lower specificity (48% [95% CI, 32–68] compared with 80% [95% CI, 64–94]) ($P < 0.01$). Both studies used different reference standards.

Table 5: Characteristics of Included Studies Reporting on the Diagnostic Accuracy of Capsule Endoscopy and Other Modalities in Obscure Gastrointestinal Bleeding

Study	Design	N	Population	Index Test	Comparator Test	Reference Standard
de Leusse et al, 2007 (33) France	Randomized prospective controlled trial (crossover if negative)	78	Patients with overt bleeding within previous 6 mo or a chronic (> 3 mo) IDA without obvious bleeding Mean age 54 ± 16 y (range 22–85 y); 30 female, 48 male Prior tests: any of EGD, colonoscopy, and SBFT or CT enteroclysis (all findings negative)	CE (PillCam SB)	Push enteroscopy	At the end of the 1-y follow-up, diagnosis was confirmed by surgery or any other examination
Huprich et al, 2011 (51) United States	Prospective observational study	58	Patients with recurrent or persistent IDA or overt bleeding with no source of blood loss identified Mean age 65 y (range 23–88 y); 29 female, 29 male Prior tests: EGD, colonoscopy (all findings negative)	CE (PillCam M2A)	Multi-phase CT enterography	Determined by consensus review of all clinical records, including those from subsequent tests and clinical visits (could include results from DBE or surgery)
Khalife et al, 2011 (52) France	Retrospective observational study	32	Patients with bleeding of unknown origin that persisted or recurred Mean age 55.9 ± 20.3 y (range 18–87 y); 13 female, 19 male Prior tests: EGD, colonoscopy (all findings negative)	CE (PillCam SB)	64-section CT enteroclysis	The following tests, alone or in combination, were used: colonoscopy with ileoscopy, DBE, histopathological findings after surgery, or enteroscopic biopsy specimens
Kulkarni et al, 2012 (48) India	Prospective observational study	50	Patients with clinically evident GI bleeding or IDA Mean age 58 y (range 3–82 y); 20 female, 30 male Prior tests: EGD, colonoscopy (all findings negative)	CE (type not described)	Multi-detector CT	The final diagnosis was achieved when the findings were unequivocal on CT scan or when equivocal findings on CT scan were confirmed by another modality or by surgical/histopathological findings

Study	Design	N	Population	Index Test	Comparator Test	Reference Standard
Saurin et al, 2005 (31) France	Prospective observational study	60	Patients with OGIB Mean age 58 ± 18 y (range 21–79 y); 33 female, 27 male Prior tests: upper gastrointestinal endoscopy and colonoscopy (both negative) and SBFT barium series without enteroclysis	CE (PillCam M2A)	Push enteroscopy	Follow-up data after 1 y
van Weyenberg et al, 2013 (49) Netherlands	Retrospective analysis of patient records	77	Patients with small-bowel disease, of whom 34 (44.2%) had suspected OGIB Mean age 51 y (range 4–87 y); 35 female, 42 male Prior tests: EGD, colonoscopy	CE (PillCam SB or MiroCam)	Magnetic resonance enteroclysis	Histopathology findings obtained via DBE or surgery; absence of findings at DBE or if no DBE or surgery was performed, then the results of clinical follow-up lasting at least 24 mo
Wiarda et al, 2012 (50) Netherlands	Prospective observational study	38	Patients with OGIB Mean age 58 y (range 28–75 y); 20 female, 18 male Prior tests: EGD, colonoscopy (all findings negative)	CE (PillCam SB)	Magnetic resonance enteroclysis	DBE and expert panel consensus
Zhang et al 2010, (53) China	Prospective observational study	123 (49[a])	Patients presenting with hematochezia, chronic intermittent melena, or hypohemoglobinemia of varying severities and had a history of active (overt) hemorrhage within 1 wk prior to CE Mean age 54.88 ± 15.69 y (range 17–87 y); 64 female, 59 male Prior tests: EGD, colonoscopy (all findings negative)	CE (PillCam; model not described)	Multi-detector CT	Surgery

Abbreviations: CE, capsule endoscopy; CT, computed tomography; DBE, double-balloon enteroscopy; EGD, esophagogastroduodenoscopy; IDA, iron deficiency anemia; OGIB, obscure gastrointestinal bleeding; SBFT, small-bowel follow-through.

[a]Patients who had the index test, comparator, and the reference standard.

Table 6: Diagnostic Accuracy of Capsule Endoscopy in Obscure Gastrointestinal Bleeding Compared With Other Diagnostic Modalities

Study	Sensitivity, % (CI)		Specificity, % (CI)		TP:FP		FN:TN		LR+[a]		LR−[a]	
	CE	Comp	CE	Comp	CE	Comp	CE	Comp	CE	Comp	CE	Comp
CE versus MRE												
van Weyenberg et al, 2013 (49)	74 (58–86)	79 (63–90)	84 (68–0.93)	97 (85–100)	29:6	31:1	10:32	8:37	4.71	30.2	0.30	0.21
Wiarda et al, 2012 (50)	61 (36–81)	21 (7–46)	85 (61–96)	100 (79–100)	11:3	4:0	7:17	15:19	4.07	N/A	0.46	0.79
CE versus CT												
Huprich et al, 2011 (51)												
Overall	26 (10–51)	79 (54–94)	49 (32–65)[b]	67 (54–94)[b]	5:20	15:13	14:19	4:26	0.51	2.37	1.51	0.32
In patients with small-bowel bleeding source	38 (18–61)	88 (64–97)	NR	NR	NR	NR	NR	NR				
In patients with small-bowel masses	33 (12–65)	100 (70–100)	NR	NR	NR	NR	NR	NR				
Khalife et al, 2011 (52)	87 (62–98)	69 (41–89)	81 (54–96)	100 (79–100)	14:3	11:0	2:13	5:16	4.67	N/A	0.15	0.31
Kulkarni et al, 2012 (48)	71 (48–94)	72 (60–84)	100 (NR)	43 (NR)	10:0	26:6	4:1	10:8		1.69		0.49
Zhang et al, 2010 (53)	82 (NR)	67 (NR)	NR	NR	40:NR	33:NR	9:NR	16:NR				
CE versus PE												
Saurin et al, 2005 (31)	92 (82–100)	69 (53–87)	48 (32–68)	80 (64–94)	19:8	N/A[c]	6:23	N/A[c]	1.77	3.45	0.17	0.39
de Leusse et al, 2007 (33)												
Overall (all lesions)	79 (60–86)	41 (30–53)	87 (67–90)	100 (91–100)	N/A[c]	N/A[c]	N/A[c]	N/A[c]	6.08	N/A	0.24	0.59
Small-bowel lesions	100 (61–100)	33 (21–43)	90 (77–92)	100 (93–100)	N/A[c]	N/A[c]	N/A[c]	N/A[c]	10	N/A	0	0.67

Abbreviations: CE, capsule endoscopy; comp, comparator; CT, computed tomography; FN, false negative; FP, false positive; LR, likelihood ratio; MRE, magnetic resonance enteroclysis; N/A, not available; NR, not reported; PE, push enteroscopy; TN, true negative; TP, true positive.

[a]Calculated from raw data or from reported sensitivity and specificity when raw data were not provided in the study.

[b]Not reported in study, but calculated based on raw data provided in study.

[c]Could not obtain these values based on data provided that matched the stated specificity and sensitivity values.

Safety

Existing Health Technology Assessment Reports, Meta-Analyses, and Systematic Reviews

One HTA report, (18) 1 meta-analysis, (24) and 3 systematic reviews (25, 26, 54) were identified that reported safety data on the use of CE in patients with OGIB. The characteristics of the included HTA report, meta-analysis, and systematic reviews are summarized in Appendix 2.

The 2008 Italian HTA report provided a summary of 11 studies and the complications associated with CE. (18) The authors identified 5 studies comparing CE with DBE that reported safety data. Data on adverse events were also identified from 3 studies comparing CE with PE and a further 3 studies comparing CE with intraoperative endoscopy. The authors undertook a pooled analysis of the safety data and reported that 9% and 3% of the 863 patients who underwent CE experienced technical problems or adverse events, respectively. Technical problems were defined as events indirectly related to safety (e.g., battery failure or battery expiry), while adverse events were those directly related to patient safety (e.g., self-resolving symptoms, surgery, or mortality).

The meta-analysis by Chen and colleagues presented a summary of the complications from 8 studies comparing CE with DBE. (24) The authors identified no DBE-related adverse events and reported that 3 of the 277 patients (1.1%) enrolled in the analysis experienced capsule retention.

The systematic review by Varela Lema and Ruano Ravina included a narrative summary of the safety and adverse effects of CE in small-bowel disease. (25) The authors reported that most studies documented the existence of nonpermanent retentions or delays, in a range of patients (4.7%–80%). The most severe complication associated with CE was related to the need to undergo laparotomy because of permanent retention of the capsule. In patients with OGIB, this percentage did not exceed 5%.

The systematic review by Westerhof and colleagues (26) identified 9 studies comparing CE with DBE. They summarized that in all studies the complication rates were low and that capsule retention occurred in up to 5% of patients. They identified some minor complications associated with DBE including abdominal pain, nausea, a painful throat or mucosal injury due to contact with the overtube. They also summarized data from a single study of 479 patients where the major complications for DBE included pancreatitis (1.7%) and perforations (0.8%).

Finally, 1 systematic review was identified that reported solely on the rates of capsule retention. (54) Liao and colleagues examined 104 prospective studies and 46 retrospective studies, and calculated a pooled retention rate of 1.4% (95% CI, 1.2–1.6). The rate of capsule retention was lower when the analysis was restricted to the 47 studies of patients with OGIB (1.2%; 95% CI, 0.9–1.6). The majority of the retained capsules (58.7%) were removed surgically, with 15.8% excreted spontaneously or by drug stimulation, and 12.5% removed endoscopically.

Primary Studies: Comparative Safety

Thirteen studies were identified by this analysis that presented safety data for CE compared with other diagnostic modalities. Only studies where adverse events were described or where authors stated that no adverse events had occurred were included. Capsule retention was the only adverse event reported for CE, and a range of mild to moderate adverse events was reported for the comparator modalities (Table 7). Three studies reported that no patients experienced any procedure-related complications or adverse events. These studies included a trial of 136 patients with OGIB randomized to undergo either CE or small-bowel radiography (55). No adverse events were reported in 2 small observational studies comparing CE with DBE (56) and comparing CE with CT or angiography. (42)

A prospective study of patients with OGIB compared CE with DBE. (57) Data on diagnostic yield as well as complications were presented. Of the 162 patients who underwent DBE, 1 patient experienced a perforation episode and another patient experienced acute pancreatitis. Capsule retention occurred in 4 (5.4%) of the 74 patients who underwent CE.

Kamalaporn and colleagues undertook a retrospective review of patients who underwent CE followed by DBE. (58) No complications were reported for CE or DBE. However, 2 cases of the capsule not reaching the small bowel and 19 cases of the capsule not reaching the cecum within 8 hours were reported.

An observational study of 32 patients with OGIB examined using both CE and DBE reported 2 cases of capsule retention. (59) The authors reported that no major complications relating to DBE were experienced, except for "slight abdominal pain, nausea, or mucosal injury due to contact with the overtube." The number of patients experiencing these adverse events was not reported.

A large observational study reported that 4% of patients who underwent CE experienced capsule retention. (38) A range of mild adverse events were experienced by over three quarters of the patients who underwent DBE, although the authors did not provide data on each individual adverse event.

Table 7: Adverse Events Reported in Studies Comparing Capsule Endoscopy with Other Diagnostic Modalities in Patients with Obscure Gastrointestinal Bleeding

Study	Design	N	Capsule Endoscopy		Comparator Modality	
CE vs SBFT						
Laine et al, 2010 (55)	RCT	136	Adverse events	0/66	Adverse events	0/70
CE vs DBE						
Arakawa et al, 2009 (57)[a]	Retrospective observational study	162	Capsule retention	4/74 (5.4%) Removed by: 1—gastroscopy 1—surgery 2—DBE	Perforation Acute pancreatitis	1/162 (0.62%) 1/162 (0.62%)
Kamalaporn et al, 2008 (58)	Retrospective observational study	202	Capsule retention Capsule not reaching cecum within 8 h Capsule not reaching small bowel	0/181 19/202 (9.4%) 2/202 (1.0%)	Significant complications	0/51
Kameda et al, 2008 (59)	Prospective single-blinded trial	32	Capsule retention	2/32 (6.3%) Capsule removed by: 2—DBE	Major complications "Slight abdominal pain, nausea, or mucosal injury due to contact with the overtube"	0/32 (NR/32)

Study	Design	N	Capsule Endoscopy		Comparator Modality	
Li et al, 2007 (38)	Prospective observational study	218	Capsule retention	7/164 (4.3%) Capsule removed by: 2—surgery 5—not described	Dizziness, light pharyngalgia, distension, light abdominal pain, nausea, or vomiting Procedure-related complications	39/51 (76.5%) 0/51
Lin et al, 2008 (56)	Prospective observational study	10	Complications	0/10	Complications	0/10
Marmo et al, 2009 (60)	Prospective observational study	193	Capsule retention	6/165 (3.6%) Capsule removed by: 3—DBE 1—surgery	Major complications Transient oxygen desaturation	0/193 2/193 (1.0%)
Shishido et al, 2012 (61)[b]	Prospective observational study	118	Capsule retention	1/118 (0.8%) Capsule removed by: 1—DBE	Aspiration pneumonia Injury to the duodenal mucosa due to insertion of the endoscopic overtube Acute pancreatitis Perforation	4/118 (3.3%) 1/118 (0.8%) 0 0
CE vs MRE						
van Weyenberg et al, 2013 (49)	Retrospective analysis of patient records	77	Capsule retention	2/77 (2.6%) Capsule removed by: 2—DBE	Vomiting	4/77 (5.2%)
Wiarda et al, 2012 (50)	Prospective observational study	38	Capsule retention	0/38	Vomiting	3/38 (7.9%)
CE vs CT						
Zhang et al, 2010 (53)	Prospective observational study	123	Capsule retention	5/123 (4.1%) Capsule removed by: 5—surgery	NR	

Study	Design	N	Capsule Endoscopy		Comparator Modality	
CE vs CT or Angiography						
Saperas et al, 2007 (42)	Prospective observational study	28	Complications	0/28	Complications with CT	0/25
					Complications with angiography	0/25
CE vs PE						
de Leusse et al, 2007 (33)	Randomized prospective controlled trial (crossover if negative)	78	Complications	0	Significant complications	0
			Capsule retention	0		
			Capsule did not reach cecum during the recording time	6/69 (9%)		

Abbreviations: CE, capsule endoscopy; CT, computed tomography; DBE, double-balloon enteroscopy; MRE, magnetic resonance enteroclysis; NR, not reported; PE, push enteroscopy; SBFT, small-bowel follow-through.

[a]Safety data also previously presented in a smaller, earlier study by Ohmiya and colleagues. (62)

[b]Safety data also previously presented in a smaller, earlier study by Fukumoto and colleagues. (63)

Marmo and colleagues (60) undertook a prospective observational study of 193 patients with OGIB who first underwent CE and then DBE. A secondary objective of the study was to evaluate the safety of the 2 procedures. The authors reported that no major adverse event occurred after either examination. However, 6 patients (3.6%) experienced capsule retention, and 2 patients (1.0%) had transient oxygen desaturation during DBE.

The observational study of 118 consecutive patients treated by CE and DBE reported on procedure-related complications. (61) One patient experienced capsule retention. Aspiration pneumonia developed in 4 patients after antegrade DBE, and 1 patient experienced injury to the duodenal mucosa due to insertion of the endoscopic overtube. No patient experienced DBE-related acute pancreatitis or perforation.

The study by van Weyenberg and colleagues comparing CE with MRE (49) reported 2 cases of symptomatic capsule retention. For MRE, 4 patients vomited during the procedure; no other complications were reported.

In another study comparing CE with MRE, Wiarda and colleagues reported that no patients experienced capsule retention. (50) A small proportion of patients (7.9%) experienced vomiting due to MRE.

The study by Zhang and colleagues compared CE with CT. (53) They reported that 4% of patients experienced capsule retention, but provided no data on adverse events experienced due to CT.

The randomized trial by de Leusse and colleagues reported no complications in patients who underwent CE or PE. (33) No cases of capsule retention were observed; however, in 6 patients the capsule did not reach the cecum within the recording time.

Patient Perceptions and Acceptability

Existing Health Technology Assessment Reports, Meta-Analyses, and Systematic Reviews

The 2008 Italian HTA report assessed evidence on the acceptability of CE. (18) The authors identified 2 studies that reported data on acceptability and tolerability of CE in patients with OGIB. (28, 36) In the study by Mylonaki and colleagues, patients were interviewed 2 weeks or more after the examination and were asked to compare CE with PE and to indicate whether either examination was painful. (28) The authors reported that 49 of 50 patients said that they found CE preferable to PE; 2 of 50 found CE uncomfortable but only at the time of swallowing the capsule, and 34 of 50 found PE painful ($P < 0.05$). Hadithi and colleagues used a questionnaire to assess tolerability of CE compared with DBE in 35 patients. (36) Capsule endoscopy was found to be more tolerable to patients than DBE (94% compared with 40%; $P < 0.001$). Two patients (6%) described swallowing the video capsule as being uncomfortable.

Primary Studies

One observational study by Wiarda and colleagues compared the patient burden, pain, and preference for modality between CE, DBE, and MRE in 76 patients with suspected or known Crohn's disease or OGIB. (64) Patient burden was assessed using a nonvalidated questionnaire administered 1 day and 5 weeks after the procedures. The same questionnaire was used to assess each patient's assessment of pain 1 day after the procedures. Patients reported that the bowel preparation for CE was significantly less burdensome ($P = 0.000$) than preparation for MRE or DBE. MRE preparation was also significantly less burdensome ($P = 0.022$) than preparation for DBE. CE was significantly less painful ($P \leq 0.0001$) than MRE and DBE, and MRE was significantly less painful ($P = 0.007$) than DBE. Before and after all examinations, about half of the patients considered CE the most preferable first-order diagnostic modality, followed by MRE and DBE. After having undergone all examinations, the proportion of patients who preferred MRE as the first-order modality decreased from 15.7% to 2.6%. This study also presented safety data, which had been reported previously in a prior study. (50)

Patient Outcomes and Impact on Patient Management

Existing Health Technology Assessment Reports, Meta-Analyses, and Systematic Reviews

No HTA reports, meta-analyses, or systematic reviews were identified that investigated the impact on patient health outcomes or management of CE compared with other diagnostic modalities in patients with OGIB.

Primary Studies

This analysis identified 3 randomized trials that reported comparative data between CE and other diagnostic modalities on the impact on patient management (Table 8).

Leung and colleagues (65) undertook a small randomized study in 60 consecutive patients presenting with active overt OGIB who had undergone nondiagnostic EGD and colonoscopy. Patients were randomized to mesenteric angiography or CE and were followed up at 12-week intervals for the first year to monitor for rebleeding and hemoglobin levels; other outcomes were followed for 5 years. There was no statistically significant difference in the cumulative rates of rebleeding between the 2 groups in follow-up ($P = 0.23$). Patients who underwent CE were significantly more likely to undergo DBE. There were no differences between the 2 groups in further interventions required after the initial assessment.

The randomized trial by de Leusse and colleagues (33) presented data on patient outcomes and therapeutic management after CE and PE in patients with OGIB. A higher proportion of patients who underwent CE were in clinical remission after 1 year, and a higher percentage of patients had initiated treatment following the identification of a bleeding source. However, no statistically significant differences in the rates of outcomes were observed.

Laine and colleagues (55) undertook a randomized trial to determine whether CE influences the management and outcomes in patients with OGIB. Patients were randomized to CE or small-bowel radiography. The study follow-up was predefined as 1 year after random assignment. Follow-up included monthly visits with complete blood count for the first 3 months and then every 3 months thereafter for a total of 1 year. Patients were queried at follow-up visits about symptoms of bleeding and other health care interactions since the last visit. No statistically significant differences in bleeding outcomes or subsequent interventions were found, except in patients who initially presented with overt bleeding. These patients were statistically significantly less likely to have further bleeding or subsequent hospitalization for bleeding when assessed using CE compared with small-bowel radiography.

Table 8: Data on Patient Outcomes After Capsule Endoscopy Compared With Other Diagnostic Modalities

Study	Design	N	Outcome	Capsule Endoscopy	Comparator Modality	*P* Value/Mean % Difference
CE vs Angiography						
Leung et al, 2012 (65)	Randomized trial	60		**n (%)**	**n (%)**	***P* Value**
			DBE	7/30 (23.3)	1/30 (3.3)	0.05
			Surgery for small-bowel disease	3/30 (10)	2/30 (6.7)	1
			Further hospitalization for rebleeding or anemia	5/30 (16.7)	5/30 (16.7)	1
			Further transfusion	3/30 (10)	3/30 (10)	1
			Death (not related to bleeding)	4/30 (13.3)	4/30 (13.3)	1
CE vs PE						
de Leusse et al, 2007 (33)	Randomized trial	78		**% (95% CI)**	**% (95% CI)**	***P* Value**
			Clinical remission at 1 y[a]	70 (56–83)	58% (43–74)	NR
			Therapeutic impact[b]	43 (29–59)	34% (22–51)	NR
			Additional explorations	75 (62–87)	79% (66–90)	NR
			For diagnosis	13 (6–27)	3% (1–14)	NR
			For treatment	13 (6–27)	0% (0–9)	NR
CE vs SBFT						
Laine et al, 2010 (55)	Randomized trial	136		**n/N (%)**	**n/N (%)**	**Mean % Difference**
			Further bleeding			
			All patients	20/66 (30)	17/70 (24)	6 (−9 to 21)
			Overt bleeding	13/26 (50)	8/28 (29)	21 (4 to 47)
			Occult bleeding	7/40 (18)	9/42 (21)	−4 (−21 to 13)
			Subsequent interventions for diagnosis or treatment of bleeding			
			All patients	17/66 (26)	15/70 (21)	4 (−10 to 19)
			Overt bleeding	10/26 (38)	8/28 (29)	10 (−15 to 35)
			Occult bleeding	7/40 (18)	7/42 (17)	1 (−15 to 17)
			Subsequent hospitalization for bleeding			
			All patients	8/66 (12)	4/70 (6)	6 (−3 to 16)
			Overt bleeding	8/26 (31)	2/28 (7)	24 (3 to 44)
			Occult bleeding	0/40	2/42 (5)	−5 (−16 to 5)
			Subsequent blood transfusion			
			All patients	5/66 (8)	4/70 (6)	2 (−7 to 10)
			Overt bleeding	5/26 (19)	2/28 (7)	12 (−6 to 30)
			Occult bleeding	0/40	2/42 (5)	−5 (−16 to 5)

Abbreviations: CE, capsule endoscopy; CI, confidence interval; DBE, double-balloon enteroscopy; NR, not reported; PE, push enteroscopy; SBFT, small-bowel follow-through.

[a]Defined as no recurrence of overt bleeding, and correction of the hemoglobin level and iron deficiency.

[b]Defined as the percentage of patients in whom the identification of a bleeding source led to a specific treatment, such as surgery, hemostatic endoscopy, proton pump inhibitor, or steroids.

Discussion

Capsule endoscopy allows for the visualization of the entire small bowel, an area that is challenging to examine because of its length and complex loops. In studies of patients with OGIB, direct comparisons between other diagnostic modalities indicate that there is very-low-quality evidence of greater sensitivity of CE (the ability to identify the etiology of the bleed). However, this may be limited by the lower specificity of the technology and the risk of a greater number of false positives. These false positives may have downstream effects through overdiagnosis and exposure to unnecessary treatments.

Considerable heterogeneity was found in the point estimates of diagnostic accuracy, with wide and often overlapping CIs for sensitivity and specificity between the CE and the comparator tests. This limited meta-analysis of the estimates. This heterogeneity may be have been because of the lack of an agreed reference standard in determining the etiology of OGIB.

Direct safety data comparing CE with other diagnostic modalities are limited. However, in general, CE is well tolerated by patients, with the most serious complication—capsule retention—occurring in 0% to 6% of patients with OGIB. Prior screening for strictures may partially mitigate the risks of capsule retention, but excluding patients because of known or historical obstructions may not entirely reduce this risk. Patients reported that CE was significantly less painful than other diagnostic modalities and that the preparation before the procedure was less burdensome. There is some low-quality evidence that patients with OGIB experienced similar or better health outcomes following CE than with other diagnostic modalities.

Limitations

There are some limitations to this analysis that should be acknowledged. First, the study designs of the included studies had some serious limitations that decreased the level of evidence. Second, the safety analysis was perhaps limited by the known poor reporting of adverse events in clinical trials. Most studies did not describe how adverse events were monitored or defined. Often, studies used a generic statement such as "no complications were experienced," which does not provided any detail on the types of events monitored. Third, the diagnostic accuracy studies in OGIB were unable to provide any detail on potential differences in the sensitivity or specificity of CE in patients with occult or overt OGIB. The subtype of OGIB may require a different diagnostic algorithm; therefore, it is unclear whether the diagnostic accuracy results can be applied to both types of OGIB. Fourth, diagnostic accuracy data for CE were obtained entirely from 1 manufacturer (Given Imaging), except for 1 study that also included the MiroCam capsule (IntroMedic). The accuracy of CE across the entire device class must then be assumed. Finally, several studies that reported data on only the diagnostic yield of CE compared with another diagnostic modality were excluded from the analysis. This decision was made a priori as, although a high diagnostic yield indicates that a test can identify a large number of positive tests, this result does not provide any indication of the rate of false positives attributed to the test. Indeed, when diagnostic yield is used as an outcome measure, it is difficult to differentiate true positives from false positives. However, it is unclear whether diagnostic yield may have some value in a clinical context, as clinicians may wish to place a greater value on a test that has a high yield and not be concerned if the test generates considerable false-positive results.

Conclusions

Clinical guidelines generally support the use of CE as the first diagnostic test for OGIB following negative findings on upper and lower endoscopies. Indeed, CE is a sensitive technology for determining the etiology of OGIB. Its sensitivity tends to be higher than that for other modalities, but its specificity is also lower. The technology is limited by its lack of biopsy or therapeutic capabilities. Therefore, it cannot entirely act as a replacement for other diagnostic modalities, particularly ones such as PE that have therapeutic capabilities. Instead, CE may be used as a tool for triage—guiding decisions on the need for further workup—or as a complementary tool to be used in combination with other diagnostic modalities based upon institutional expertise and availability.

In the determination of the etiology of OGIB, CE:

- has a higher sensitivity than MRE, computed tomography, or PE (GRADE: very low);
- has a lower specificity than MRE, computed tomography, or PE (GRADE: very low);
- has a good safety profile with few adverse events (GRADE: very low), although there is a risk of capsule retention and comparative safety data with other diagnostic modalities are limited;
- is perceived by patients to be more tolerable and less burdensome than PE, DBE, or MRE (GRADE: very low); and
- is associated with no difference in patient health-related outcomes such as rebleeding or follow-up treatment compared with PE, SBFT, or angiography (GRADE: low).

Existing Guidelines for Technology

Published international guidelines were identified through a search of the following websites and databases (Table 9) using a combination of text words (*capsule* or *bleeding*).

Table 9: Websites and Databases Searched to Identify International Guidelines

Organization	Website
National Guideline Clearinghouse (United States)	www.guideline.gov
Canadian Medical Association Infobase: Clinical Practice Guidelines (Canada)	www.cma.ca/index.php/ci_id/54316/la_id/1.htm
National Institute for Health and Care Excellence Guidance (United Kingdom)	http://guidance.nice.org.uk/index.jsp?action=find
National Health and Medical Research Council Clinical Practice Guidelines Portal (Australia)	www.clinicalguidelines.gov.au
Scottish Intercollegiate Guidelines Network (Scotland)	www.sign.ac.uk/guidelines/index.html
Institute for Clinical Systems Improvement (United States/International)	https://www.icsi.org/guidelines__more/
DynaMed	https://dynamed.ebscohost.com
Trip database	www.tripdatabase.com/

Recommendations and algorithms suggested by a single author or groups of authors were excluded. (5, 6, 26, 66, 67) One guideline was excluded as no evidence-based recommendations were provided, (68) while another potentially relevant guideline was excluded as it was not written in English. (69)

The methodological rigour and transparency of clinical practice guidelines were determined using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. (70) AGREE II is composed of 6 domains that capture guideline quality, including scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. Emphasis was placed on the rigour of development domain score as it reflects the strength of the methods to search for evidence and to make recommendations.

Five relevant guidelines were identified. Quality assessment using the AGREE domain scores for each guideline is presented in Table 10. The overall quality of the guidelines varied considerably, both within and across the 6 AGREE II domains. No guideline scored well in all domains of quality. Scores for the rigour of development were generally low and ranged between 20 and 39%, with the Korean Society of Gastrointestinal Endoscopy (71) and British Society of Gastroenterology (BSG) guidelines (72) scoring the highest. Applicability and editorial independence were the 2 domains with the lowest scores across the guidelines.

Table 10: AGREE II Domain Scores for the Use of Capsule Endoscopy in Obscure Gastrointestinal Bleeding

Guideline, Year	AGREE II Domain (Maximum Possible Score)					
	Scope and Purpose (Out of 21)	Stakeholder Involvement (Out of 21)	Rigour of Development (Out of 56)	Clarity of Presentation (Out of 21)	Applicability (Out of 28)	Editorial Independence (Out of 14)
KSGE, 2013 (71)	19	11	21	9	4	8
ASGE, 2010 (2)	9	9	14	13	4	2
ESGE, 2009 (73)	8	9	14	8	4	8
BSG, 2008 (72)	8	5	22	8	10	8
AGA, 2007 (1)	8	6	13	5	4	2

Abbreviations: AGA, American Gastroenterological Association; AGREE, Appraisal of Guidelines for Research and Evaluation; ASGE, American Society for Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy; KSGE, Korean Society of Gastrointestinal Endoscopy.

The recommendations regarding the use of CE in patients with OGIB are summarized in Table 11. Four guidelines presented algorithms for the assessment of OGIB. (1, 2, 71, 72)

The guidelines relating to OGIB differed in the number of the recommendations, with some issuing 7 and another issuing 14. There was no single recommendation where the guidelines differed; instead, there were several instances where 1 guideline made a recommendation that was not replicated in any other guideline. Only the 2010 American Society for Gastrointestinal Endoscopy (ASGE) guideline differentiated between occult and overt OGIB in their recommendations, presenting 2 individual pathways that should be undertaken depending on the nature of the OGIB. (2)

All studies recommended CE as a first-line diagnostic tool after negative findings on EGD and colonoscopy. Other commonalities between guidelines were also evident. Two guidelines (ASGE and BSG) agreed that when there is a high suspicion for an upper GI lesion, a second EGD should be undertaken. (2, 72) The European Society of Gastrointestinal Endoscopy (ESGE), ASGE, and BSG guidelines all stated that deep or flexible enteroscopy should be considered in patients with suspected stenosis, obstructive symptoms, or surgically altered anatomy. (2, 72, 73) The ASGE and BSG guidelines both recommended repeating CE in patients with negative findings on CE and further bleeding. The ESGE and BSG guidelines agreed that patients with bleeding sites identified on CE should subsequently undergo flexible enteroscopy (either PE or DBE via an oral/anal route depending on location/site of bleeding). The ASGE guideline did not issue a formal recommendation, but instead stated in the document that appropriate endoscopic, angiographic, medical, or surgical interventions should be instituted upon detection by CE of a culprit lesion. Finally, both the ESGE and BSG guidelines stated that intraoperative endoscopy should be reserved for patients with persistent OGIB in whom the bleeding source remains undiagnosed by flexible enteroscopy treatment.

Table 11: Existing Guidelines for the Use of Capsule Endoscopy in Patients with Suspected Obscure Gastrointestinal Bleeding

Organization, Year	Guidelines	Strength of Evidence[a]	Strength of Recommendation[a]
Korean Society of Gastrointestinal Endoscopy, 2013 (71)	CE is an effective initial diagnostic method for evaluating patients with OGIB.	Moderate	Strong
	CE is an effective initial diagnostic method for evaluating patients with IDA if no bleeding focus can be found outside the GI tract.	Moderate	Strong
	CE has higher diagnostic yield than small-bowel barium radiography in patients with OGIB.	Moderate	Strong
	CE is more effective than enteroclysis in determining the cause in patients with OGIB.	Moderate	Strong
	CE could be more helpful than CT angiography in determining the cause in patients with OGIB.	Low	Weak
	CT enterography/CT enteroclysis as a complementary examination to CE could be helpful in determining the cause in patients with OGIB.	Low	Weak
	CE has a higher diagnostic yield than PE in patients with OGIB.	Low	Strong
	Performing CE as soon as possible in OGIB is effective in improving the diagnostic yield.	Moderate	Strong
	CE and DBE provide similar diagnostic yields in patients with OGIB.	Low	Strong
	It is recommended to perform CE prior to DBE for the diagnosis of patients with OGIB.	Low	Strong
American Society for Gastrointestinal Endoscopy, 2010 (2)	After appropriate resuscitation, we recommend emergent endoscopy or angiography in patients with massive OGIB.	Low	
	We recommend urgent EGD in patients with active overt OGIB and a clinical presentation suggestive of upper GI bleeding.	Moderate	
	For those with signs or symptoms of lower GI bleeding, we suggest repeating colonoscopy.	Low	
	Otherwise, recommended diagnostic options include PE, CE, and tagged red blood cell scintigraphy.	NR	
	For those patients with inactive overt OGIB, we suggest CE, deep enteroscopy, PE, and/or colonoscopy.	Low	
	In patients with occult OGIB and a high clinical suspicion for an upper GI lesion, we suggest repeating EGD before small-bowel evaluation.	Low	
	For those with a suspected lower GI lesion, we suggest repeating colonoscopy prior to small-bowel evaluation.	Low	
	In the absence of localizing signs or symptoms, we recommend small-bowel evaluation.	Moderate	
	We recommend CE as the first-line diagnostic tool for evaluation of the small bowel in patients with OGIB.	Moderate	

Organization, Year	Guidelines	Strength of Evidence[a]	Strength of Recommendation[a]
	We suggest that in select circumstances (e.g., where there is a high level of suspicion of small-bowel angiectasias or in patients with surgically altered anatomy), deep enteroscopy may be considered as the initial small-bowel diagnostic procedure in patients with OGIB.	Low	
	We recommend that patients with occult OGIB and a negative CE evaluation who remain clinically stable be treated with iron therapy if evidence of iron deficiency is present.	Moderate	
	We suggest that, in patients with negative CE and continued bleeding, repeat CE be considered, particularly if the clinical state changes from obscure to overt bleeding or if the hemoglobin level drops by ≥ 4 g/dL.	Low	
	We suggest that small-bowel follow-through and enteroclysis have a limited role in the evaluation of OGIB, given their low yields for identifying lesions.	Low	
European Society of Gastrointestinal Endoscopy, 2009 (73)	CE is the first-line examination in OGIB after a negative upper and lower GI endoscopy.	2b	B
	Patients with unexplained IDA should undergo small-bowel CE examination.	2b	B
British Society of Gastroenterology, 2008 (72)	If there is a high suspicion of bleeding from an upper GI source, a second look endoscopy should be undertaken prior to CE to ensure no pathology has been missed.	B	
	Patients presenting with OGIB with a negative gastroscopy and colonoscopy should undergo CE if no contraindications exist.	B	
	All patients undergoing CE for any indication should be appropriately counselled on the risks of capsule retention.	C	
	Non-passage of a capsule may occur in the presence of a normal radiological contrast study.	B	
	Those patients with pathology/bleeding sites identified on CE should subsequently undergo either a PE or DBE (oral/anal route) depending on location/site of bleeding.	B	
	In patients with a negative CE and persistent OGIB, a second look CE may be considered. If this is negative they should be referred for DBE.	C	
American Gastroenterological Association, 2007 (1)	In the patient presenting with OGIB with either positive fecal occult blood testing and associated anemia or overt bleeding with melena or maroon blood per rectum, colonoscopy and upper endoscopy should be performed.	NR	
	CE should be the third test in the evaluation of patients with GI bleeding, once findings on upper endoscopy and colonoscopy are negative.	NR	
	In the patient with active bleeding, CE can confirm the small bowel as the site of bleeding, providing a location. Even if the study findings are negative for the small bowel in the actively bleeding patient, the study may indicate that the bleeding is actually colonic or even gastric in origin.	NR	

Organization, Year	Guidelines	Strength of Evidence[a]	Strength of Recommendation[a]
	In the face of continued bleeding and initially negative findings on colonoscopy and upper endoscopy, repeated endoscopic examinations can be worthwhile. Repeated barium studies are not indicated.	NR	
	In the patient with active bleeding within the small intestine, the capsule will guide further evaluation and therapy.	NR	
	A patient with a small bowel tumor detected by CE will proceed directly to laparoscopic surgery.	NR	
	If the site of bleeding is identified in the proximal small bowel and there is no mass, PE will be used to reidentify the site and cauterize the lesion.	NR	
	In cases where a distal small bowel site is identified, surgical intervention coupled with intraoperative enteroscopy or DBE will be necessary.	NR	
	In patients with isolated IDA or a more occult or intermittent type of bleeding, CE should be used similarly to identify an intestinal bleeding lesion and thereby direct subsequent testing or treatment.	NR	

Abbreviations: CE, capsule endoscopy; CT, computed tomography; DBE, double-balloon enteroscopy; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; IDA, iron deficiency anemia; NR, not reported; OGIB, obscure gastrointestinal bleeding; PE, push enteroscopy.

[a]See Table 12 for a description of the used to assess the strength of evidence and strength of recommendation.

A range of evidence assessment tools was used by the published guidelines to assess quality. These are summarized in Table 12.

Table 12: Summary of Evidence Assessment Methods Used by the Included Guidelines

Organization, Year	Guidelines		
Korean Society of Gastrointestinal Endoscopy, 2013 (71) American Society for Gastrointestinal Endoscopy, 2010 (2)	**Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group**		
	High quality	Further research is very unlikely to change our confidence in the estimate of effect.	
	Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	
	Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	
	Very low quality	Any estimate of effect is very uncertain.	
European Society of Gastrointestinal Endoscopy, 2009 (73)	**Grade of recommendation**	**Types of study**	
	A	1a	Systematic review of randomized controlled trials of good methodological quality and with homogeneity
		1b	At least 1 randomized controlled trial with narrow confidence interval
	B	2a	At least 1 well-designed controlled study without randomization
		2b	Noncontrolled cohort studies
		3a	Systematic review of case-control studies (with homogeneity)
		3b	Individual case-control study
	C	4	Case series/poor-quality cohort or case-controlled studies
	D	5	Expert committee reports or opinions, or clinical experiences of respected authorities
British Society of Gastroenterology, 2008 (72)	Grade A	Requires at least 1 randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence categories Ia and Ib)	
	Grade B	Requires the availability of clinical studies without randomization on the topic of consideration (evidence categories IIa, IIb, and III)	
	Grade C	Requires evidence from expert committee reports or opinions or clinical experience of respected authorities, in the absence of directly applicable clinical studies of good quality (evidence category IV)	
American Gastroenterological Association, 2007 (1)	Method of assessing evidence was not described		

Acknowledgements

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Appendices

Appendix 1: Literature Search Strategies

Search date: December 3, 2013
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Embase, all EBM databases (see below)

Q: What are safety, accuracy, and cost-effectiveness of CE for the diagnosis of OGIB compared with other diagnostic modalities?
Limits: 2007–current; English
Filters: none

Database: EBM Reviews—Cochrane Database of Systematic Reviews <2005 to October 2013>, EBM Reviews—ACP Journal Club <1991 to November 2013>, EBM Reviews—Database of Abstracts of Reviews of Effects <4th Quarter 2013>, EBM Reviews—Cochrane Central Register of Controlled Trials <October 2013>, EBM Reviews—Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews—Health Technology Assessment <4th Quarter 2013>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2013>, Embase <1980 to 2013 Week 48>, Ovid MEDLINE(R) <1946 to November Week 3 2013>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <December 02, 2013>

Search Strategy:

#	Searches	Results
1	exp *Gastrointestinal Hemorrhage/	57797
2	(OGIB or ((GI or gastrointestin* or gastro-intestin*) adj2 (bleed* or blood or lesion* or h?emorrhag* or rebleed*))).ti,ab.	49956
3	or/1-2	84578
4	exp Capsule Endoscopy/	6258
5	exp Capsule Endoscopes/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	361
6	exp capsule endoscope/ use emez	583
7	(((capsule* or videocapsule* or wireless) adj2 (endoscop* or enteroscop*)) or pillcam* or pill cam* or (capsule* adj2 (wireless or camera* or video or disposable* or ingestible* or m2a or olympus)) or videocapsule* or endo?capsule* or WCE or (given adj (imaging or diagnostic*)) or mirocam or capsocam or intromedic or omom).ti,ab.	25201
8	or/4-7	26775
9	3 and 8	2711
10	limit 9 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	2407
11	limit 10 to yr="2007 -Current" [Limit not valid in DARE; records were retained]	1852
12	remove duplicates from 11	1189

Appendix 2: Included Health Technology Assessment Reports, Meta-Analyses, and Systematic Reviews

Table A1: Characteristics of Included Health Technology Assessment Reports, Meta-Analyses, and Systematic Reviews

Author, Year	Objective and Methods	Included Studies	AMSTAR Score
AGENAS, 2008 (18)	**Objective:** to identify and summarize available evidence about the diagnostic accuracy and safety of CE for OGIB, Crohn's disease, familial polyposis, and celiac disease in the small bowel **Method:** systematic review Time period: January 2001 to July 2007 Inclusion criteria: comparative studies on patients with OGIB, Crohn's disease, familiar polyposis, and celiac disease in the small bowel, reporting on the prespecified outcomes comparing CE with different diagnostic techniques Exclusion: editorials, letters, news articles, clinical guidelines, conference papers, interviews, surveys, opinion pieces, anonymous articles, and nonsystematic reviews; studies with fewer than 10 participants; studies in nonhumans Outcomes: diagnostic performance, effect on clinical management and/or health outcome, tolerability, efficiency, and direct and indirect outcomes Language(s): English	Patients with small-bowel disease Total of 27 studies	8
Varela Lema and Ruano Ravina, 2008 (25)	**Objective:** to assess the effectiveness, safety, and clinical use of CE in the diagnosis of small-bowel diseases **Method:** systematic review Time period: January 2003 to December 2005 Inclusion criteria: original, published, peer-reviewed studies; prospective or retrospective diagnostic studies, systematic reviews, or meta-analyses; ≥ 20 patients for CD studies; ≥ 1 comparator; comparison test performed within 6 mo of CE; reports on yield, accuracy, safety, reliability, or clinical management Outcomes: diagnostic accuracy, yield, change in management, adverse events Language(s): English, Spanish, French, Italian, Portuguese	Patients with OGIB 11 studies	6
Chen et al, 2007 (24)	**Objective:** to compare the diagnostic yield of CE with that of double-balloon enteroscopy **Method:** meta-analysis Time period: up to February 2007 Inclusion criteria: comparative studies Outcomes: yield, complications Language(s): English	Patients with OGIB 8 studies	5

Author, Year	Objective and Methods	Included Studies	AMSTAR Score
Westerhof et al, 2009 (26)	**Objective:** to perform a systematic literature search on studies in which CE was compared with DBE in patients with OGIB **Methods:** systematic review Time period: [month not given] 2000 and 31 December 2008 Inclusion criteria: only articles in which patients with OGIB had undergone both techniques, and of whom information regarding the findings was provided Exclusion criteria: not described Outcomes: yield, complications Language(s): English	Patients with OGIB 9 studies	1
Liao et al, 2010 (54)	**Objective:** to provide systematically pooled results on the indications and detection, completion, and retention rates of small-bowel CE **Methods:** systematic review Time period: [month not given] 2000 and January 2009 Inclusion criteria: studies in which CE was used alone or with other diagnostic tools for indications of small-bowel diseases Exclusion criteria: studies in which CE was performed to evaluate esophageal, gastric, or colonic diseases; duplicates or earlier versions of included studies Outcomes: indication, detection rates, completion rates, retention rates, clinically significant findings Language(s): English	Patients with OGIB 227 original articles (149 prospective studies, 78 retrospective studies)	2

Abbreviations: AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali; CD, Crohn's disease; CE, capsule enteroscopy; OGIB, obscure gastrointestinal bleeding.

Appendix 3: Evidence Quality Assessment

Table A2: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
AGENAS, 2008 (18)	8	✓	×	✓	✓	✓	✓	✓	✓	×[b]	×	✓
Varela Lema and Ruano Ravina, 2008 (25)	6	✓	×	✓	✓	×	×	✓	✓	×[b]	×	✓
Chen et al, 2007 (24)	5	×	✓	✓	✓	×	×	×	×	✓	✓	×
Westerhof et al, 2009 (26)	1	✓	×	×	×	×	×	×	×	×[b]	×	×
Liao et al, 2010 (54)	2	✓	✓	×	×	×	×	×	×	×[b]	×	×

Abbreviations: AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali; AMSTAR, Assessment of Multiple Systematic Reviews.

[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al. (13)

[b]Did not state that a meta-analysis was not planned or why a meta-analysis was not conducted.

Table A3: GRADE Assessment on the Comparison of Capsule Endoscopy With Other Diagnostic Modalities for Obscure Gastrointestinal Bleeding

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
True Positives (Patients With Clinical Indication and Positive Result)							
7 observational accuracy studies, 1 RCT	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected[d]	None	⊕ Very Low
True Negatives (Patients Without Clinical Indication and Negative Result)							
6 observational accuracy studies, 1 RCT	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected[d]	None	⊕ Very Low
False Positives (Patients Without Clinical Indication and Positive Result)							
6 observational accuracy studies, 1 RCT	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected[d]	None	⊕ Very Low
False Negatives (Patients With Clinical Indication and Negative Result)							
7 observational accuracy studies, 1 RCT	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected[d]	None	⊕ Very Low
Adverse Events							
2 RCTs, 11 observational studies	No serious limitations	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[e]	Undetected[d]	None	⊕ Very Low
Patient Perceptions							
3 observational studies	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[f]	Undetected[d]	None	⊕ Very Low
Patient Health Outcomes							
3 RCTs	No serious limitations	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected[d]	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

[a]In 4 of 8 studies reporting any diagnostic accuracy data, the patients were not selected consecutively; in 4 of 8 studies the reference standard was interpreted/generated with knowledge of the index test.

[b]Inconsistency between the estimates was a concern and limited meta-analysis of the estimates.

[c]Confidence intervals were very wide in all studies.

[d]Possibility of publication bias was not excluded, but considered insufficient to downgrade the evidence.

[e]Poor reporting of adverse events (lack of detail on definition of events, monitoring of events).

[f]Confidence intervals not presented in studies.

Table A4: Risk of Bias for the Assessment of Diagnostic Accuracy of Capsule Endoscopy With Other Diagnostic Modalities for Obscure Gastrointestinal Bleeding (QUADAS-2)

Author, Year	Patient Selection	Index Test	Reference Standard	Flow and Timing
de Leusse et al, 2007 (33)	Low risk	Low risk	High risk[a]	High risk[b,c]
Huprich et al, 2011 (51)	Low risk	Low risk	High risk[a]	High risk[b]
Khalife et al, 2011 (52)	High risk[d]	Low risk	Low risk	High risk[b]
Kulkarni et al, 2012 (48)	Low risk	Low risk	High risk[a]	High risk[b,c]
Saurin et al, 2005 (31)	High risk[d]	Low risk	Low risk	High risk[b,c]
van Weyenberg et al, 2013 (49)	High risk[d]	Low risk	Low risk	High risk[b]
Wiarda et al, 2012 (50)	Low risk	Low risk	High risk[a]	Low risk
Zhang et al, 2010 (53)	High risk[d]	Low risk	Low risk	High risk[c]

Abbreviations: QUADAS-2, revised Quality Assessment of Diagnostic Accuracy Studies.
[a]Reference standard results interpreted with knowledge of the results of the test.
[b]Not all patients received the same reference standard.
[c]Not all patients were included in the analysis.
[d]Patients not selected randomly or consecutively.

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ISSN 1915-7398 (online)
ISBN 978-1-4606-4916-9 (PDF)