

***Capsule endoscopy
for the diagnosis of
suspected small
bowel Crohn's
disease***

July 2011

MSAC application no 1146

Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by Heather Gilbert, Samara Lewis and Merel Kimman from the NHMRC Clinical Trials Centre with the assistance of an Advisory Panel of experts. The report was commissioned by the Department of Health and Ageing on behalf of MSAC. It was edited by Louise Scahill of WordFix.

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Executive summary

The procedure

Capsule endoscopy is a non-invasive diagnostic test, usually conducted in an outpatient setting, in which the gastrointestinal system is visualised via a camera inside an ingested capsule. The test visualises the gastrointestinal tract mucosa to diagnose a range of conditions such as obscure gastrointestinal bleeding (OGIB), celiac disease, small bowel tumours and Peutz-Jeghers syndrome (PJS). The indication for this assessment is the diagnosis of patients with suspected small bowel Crohn's disease.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

Assessment of capsule endoscopy

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease was received from Given Imaging Pty Ltd by the Department of Health and Ageing in February 2010.

A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of the literature and an economic evaluation of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease.

This report assesses capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease. The specific research question to be addressed is:

In symptomatic patients with suspected but unconfirmed Crohn's disease, what is the value of capsule endoscopy compared with either abdomen computed tomography (CT) with or without enterography, magnetic resonance imaging (MR) with or without enterography, or empirical treatment for the diagnosis of suspected small bowel Crohn's disease?

Crohn's disease is a chronic inflammatory bowel disease that may affect any portion of the gastrointestinal tract but, in cases of small bowel involvement, typically affects the terminal ileum (Yamada 2009). Most patients with isolated small bowel Crohn's disease are diagnosed using colonoscopy with ileoscopy; however diagnosis can be difficult due to the inaccessibility of the small bowel. Capsule endoscopy is able to visualise areas of the proximal small bowel inaccessible to upper and lower endoscopy; this may lead to earlier diagnosis and treatment and a small increase in the detection and treatment of previously undetected Crohn's disease (Satsangi et al 2006)

Resources used in this procedure's delivery include diagnostic tests to identify appropriate patients such as colonoscopy with ileoscopy and small bowel radiology tests such as small bowel follow-through (SBFT), abdominal CT, computed tomography enterography (CTE), magnetic resonance imaging without enterography (MRI) and magnetic resonance enterography (MRE); gastroenterologist or consultant physician attendance to administer the procedure and interpret its results; and pharmaceutical treatment for diagnosed patients including corticosteroids, anti-inflammatories and biological agents. See Table 1 for a list of associated MBS and Pharmaceutical Benefits Scheme (PBS) items.

Table 1 MBS and PBS items associated with capsule endoscopy for small bowel Crohn's disease

MBS/PBS item no.	Item name
<i>Prior diagnostic tests¹</i>	
32090	Colonoscopy
58915	Small bowel series
56507	Abdomen CT
66512	Blood tests
<i>Treatment of diagnosed patients – PBS items</i>	
1936X	Prednisone (Corticosteroids)
2687K	Azathioprine (Anti-inflammatory)
9206M	Mesalazine (Anti-inflammatory)
5754W	Infliximab (Biological agent)
13918	Administration cost – IV infusion – Infliximab
9188N	Adalimumab (Biological agent)
<i>Treatment of diagnosed patients – MBS items</i>	
110/116	Consultant physician, referred consultation
AAC27	Casualty visits (ED)
G05B ²	Hospitalisation (for small bowel procedure)
23	General practitioner
66512	Blood tests: LFT, U&E, CRP

CT= computed tomography, ED = emergency department, LFT = liver function test, U&E = Urea, electrolytes, creatinine, CRP = C-reactive protein

1. MRI and MRE are not currently funded through the MBS.
2. National Hospital Cost Data Collection

Although not directly specified in the application, the MBS item descriptor implied by the application is summarised in Table 2. Capsule endoscopy is usually performed in an outpatient setting. Consistent with other MBS listings of capsule endoscopy, it is presumed that capsule endoscopy services will only be reimbursed for public funding when performed by a specialist or consultant physician with endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy (and Medicare Australia is notified of that recognition).

Table 2 Proposed MBS item descriptor

Category 2 - DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
<p>CAPSULE ENDOSCOPY to evaluate suspected small bowel Crohn's disease, using a capsule endoscopy device approved by the Therapeutic Goods Administration. This is restricted to patients with no known Crohn's disease (ie, it is not for patients with known Crohn's disease with suspected small bowel involvement). The procedure includes the administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered (not being a service associated with double balloon enteroscopy).</p> <p>Medicare benefits are only payable for this item if:</p> <p>(a) the service is performed by a specialist or consultant physician with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy and Medicare Australia notified of that recognition; and</p> <p>(b) the patient to whom the service is provided:</p> <p>(i) is aged 10 years or over; and</p> <p>(ii) has suspected Crohn's disease on the basis of evidence of underlying inflammation, as indicated by elevated Erythrocyte Sedimentation Rate and/or C-Reactive Protein or other inflammatory markers tested at least twice over at least six weeks, and ongoing symptoms of diarrhoea and/or abdominal pain; and</p> <p>(iii) no evidence of strictures on small bowel radiology; and</p> <p>(c) a colonoscopy with attempted ileoscopy and small bowel radiology have been performed on the patient and have not confirmed the diagnosis of Crohn's disease; and</p> <p>(d) the service is performed within 6 months of the colonoscopy, attempted ileoscopy and small bowel radiology</p>
Fee: \$1,961.95 Benefit: 75% = \$1,471.50, 85% = \$1,890.75

Capsule endoscopy is being assessed for the diagnosis of small bowel Crohn's disease. As such, it should only be used once per patient per lifetime. However, some patients for whom the test is equivocal may undergo repeat testing. The MBS item descriptor should therefore either restrict performance of capsule endoscopy for this indication to once per year, or make no restriction. It should be noted that there are sometimes cases of technical failures of the capsule endoscopy in which the patient may require a repeat procedure.

Current arrangements for public reimbursement

Capsule endoscopy is an outpatient procedure and is available in private rooms (or clinics). It is funded through the MBS for two indications: the investigation of OGIB (MBS item 11820) and for small bowel surveillance of patients with PJS (MBS item 11823) (see Table 3). Capsule endoscopy for the present indication is financed through self-pay and is usually performed as an outpatient procedure in private rooms or clinics.

Table 3 MBS items for capsule endoscopy

MBS item	Descriptor ^a	Fee	Benefit	Indication	Date listed/approved
11820	CAPSULE ENDOSCOPY to investigate an episode of obscure gastrointestinal bleeding, using a capsule endoscopy device approved by the Therapeutic Goods Administration (TGA) (including administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered), (not being a service associated with double balloon enteroscopy), if: (a) the service is performed by a specialist or consultant physician with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and (b) the patient to whom the service is provided: (i) is aged 10 years or over; and (ii) has recurrent or persistent bleeding; and (iii) is anaemic or has active bleeding; and (c) an upper gastrointestinal endoscopy and a colonoscopy have been performed on the patient and have not identified the cause of the bleeding; and (d) the service is performed within 6 months of the upper gastrointestinal endoscopy and colonoscopy	\$1,961.95	\$1,471.50 (75%) \$1,890.75 (85%)	OGIB	Interim funding: 1 May 2004 Approved for ongoing funding: 23 November 2007
11823	CAPSULE ENDOSCOPY to conduct small bowel surveillance of a patient diagnosed with Peutz-Jeghers syndrome, using a capsule endoscopy device approved by the TGA. The procedure includes the administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered (not being a service associated with double balloon enteroscopy). Medicare benefits are only payable for this item if: 1. the service has been performed by a specialist or consultant physician with endoscopic training that is recognised by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and 2. the patient to whom the service is provided has been conclusively diagnosed with Peutz-Jeghers syndrome. This item is available once in any two year period.	\$1,961.95	\$1,471.50 (75%) \$1,890.75 (85%)	Surveillance of PJS	Listed: 1 March 2009

^a – Further details associated with these listings can be found in the explanatory notes D1.22 and D1.23 which are accessible via the Medicare Benefits Schedule.

Source: Medicare Benefits Schedule (Commonwealth of Australia 2011a)

Background

MSAC has previously considered capsule endoscopy for two indications: OGIB and PJS. MSAC recommended interim funding for capsule endoscopy for patients with confirmed recurrent OGIB following previous colonoscopy and endoscopy without identifying the bleeding source (endorsed by the Minister for Health and Ageing on 7 September 2003). Following review in November 2007, full public funding was approved. On 21 May 2008 the Minister for Health and Ageing accepted MSAC's recommendation that public funding be supported for performing capsule endoscopy no more than once in any two-year period for small bowel surveillance in patients diagnosed with PJS.

MSAC has not previously considered capsule endoscopy for Crohn's disease.

Clinical need

Incidence data for Crohn's disease are scarce; however, one Australian study in the regional Victorian city of Geelong found a crude annual incidence of 17.4 (95% CI =13 to 23) per 100,000 in 2008 (Wilson et al 2010). In 2007-08 there were 13,915 hospital separations with the principal diagnosis of Crohn's disease (ICD code K50) (AIHW 2011). Between 1998-99 and 2007-08, hospital separations with the principal diagnosis of Crohn's disease more than doubled, increasing from 6,485 to 13,915 (AIHW 2011). Inflammatory bowel disease (which includes Crohn's disease and ulcerative colitis) accounted for 0.5% of the total disease burden in Australia in 2003 (Begg et al 2007).

The estimated utilisation of capsule endoscopy for the diagnosis of small bowel Crohn's disease unconfirmed on prior tests lies between 664 and 1,431 per year (see 'Estimated utilisation of capsule endoscopy' on page 23). This estimate refers to the estimated number of patients who will use the test per year, not the number of tests per year.

The clinical flow chart showing both the current management and proposed management of suspected but unconfirmed small bowel Crohn's disease is presented in **Error! Not a valid bookmark self-reference.** (see page 1).

Capsule endoscopy will be used to provide an additional diagnostic modality to those currently available for the diagnosis of Crohn's disease. In the clinical flow chart, capsule endoscopy is a replacement test for repeat radiology (CT or MR with enterography) and a replacement for treating the patient empirically based on a suspicion of Crohn's disease which could not be confirmed (ie incremental to prior testing).

Comparator

The comparators to capsule endoscopy are empirical treatment, MR (with or without enterography) and CT (with or without enterography). In the comparison of capsule endoscopy to empirical treatment, capsule endoscopy is incremental to prior tests such as small bowel radiology and colonoscopy with ileoscopy.

Colonoscopy is an endoscopic procedure used primarily to visualise the large bowel or colon. To diagnose small bowel Crohn's disease, the endoscopist may attempt to reach the ileum during the colonoscopy (colonoscopy with ileoscopy). Most occurrences of small bowel Crohn's disease occur in the terminal ileum and hence are successfully diagnosed using colonoscopy with ileoscopy. Colonoscopy is publically funded under MBS item 32090 (fee \$321.65) and is being reviewed under the MBS Quality Framework review process.

MR is an imaging technique that enables cross-sectional imaging of the small bowel. MR can be administered without contrast agents (MRI), with contrast agents administered orally (MRE), or with contrast agents administered via a naso-gastric tube (magnetic resonance enteroclysis). Compared with CT, which uses x-ray attenuation, MR uses multiple tissue parameters to build an image. MR is not currently funded through the MBS for small bowel Crohn's disease.

Abdomen CT is a radiological technique used in the diagnosis of small bowel Crohn's disease. It provides multiplanar images of the lumen, wall and mesentery of the small bowel and usually involves the ingestion of contrast by the patient, either orally (enterography) or via a naso-gastric tube (enteroclysis). In some Australian settings,

abdomen CT has superseded barium imaging as the main form of radiological imaging used in the diagnosis of Crohn's disease (Morrison et al 2009). Abdomen CT is funded under MBS item 56507 with a fee of \$480.05.

Scientific basis of comparison

The scientific basis of the comparison of the effectiveness and cost-effectiveness of capsule endoscopy with that of ET, MRI/MRE and CT/CTE was a systematic review that yielded 22 studies. A linked analysis was performed that considered:

- the safety of the test – 14 studies (5 accuracy studies, 8 diagnostic yield studies and 1 case series)
- the accuracy of the test – 5 studies of the accuracy of capsule endoscopy including 2 studies of the comparative accuracy of capsule endoscopy versus MRI or MRE
- impact of availability of results from the test on clinical management – no studies identified
- impact of changes in management on patient outcomes – no studies identified and linked evidence case unable to be made.

Comparative safety

Key results

Safety data for capsule endoscopy for patients with suspected small bowel Crohn's disease were reported in 14 studies; none were comparative.

Seven studies reported no adverse events and one study reported two moderate to severe adverse events resolved within 24 hours (one with severe nausea with vomiting resolved with anti-nausea medication, 1/120, <1%; one with moderate pain, 1/120, <1%). These rates are comparable to those reported in previous MSAC assessments of capsule endoscopy, suggesting that adverse events are similar across indications.

Thirteen studies reported data on the delayed passage or retention of the capsule; the rate of retention ranged from 0% to 15%. In included studies where the rates of capsule retention and surgical removal were reported, 7 of 12 subjects with retained capsules underwent surgery during which the capsule was removed. In comparison with the use of capsule endoscopy for the indications previously assessed by MSAC, the use of capsule endoscopy for the present indication appears to have a higher rate of capsule retention and a higher rate of surgical removal of retained capsules (MSAC 2003; MSAC 2007). Prior screening for strictures on small bowel radiology partially, but not completely, mitigates these risks.

Key uncertainties

The large range of rates of retention reported may be partially explained by the small sample size of the studies; 9 of the 13 studies had sample sizes <40. The range of rates may also be explained by variations in the type and extent of prior screening for

strictures. Reporting of safety data was absent or inadequate in a number of studies. There were no comparative safety studies.

Overall conclusion with respect to comparative safety

Capsule endoscopy is considered:

- safe
- to have a low risk of adverse events, such as nausea, vomiting and pain, similar to that observed for other indications
- to lead to capsule retention in up to 15% of cases, approximately half of which may have surgery at which the capsule is removed; these risks can be partially, but not completely, mitigated by screening for strictures on small bowel radiology. These rates are potentially higher than for other indications
- to have no exposure to ionising radiation, compared with CT, and a potential clinical pathway that minimises the repetition of ionising radiation exposure, given the occurrence of prior small bowel radiology.

Comparative effectiveness

Key results

Direct evidence

No direct evidence was found comparing the health outcomes of patients with suspected small bowel Crohn's disease assessed with and without capsule endoscopy.

Linked evidence

In the absence of direct evidence of the effectiveness of capsule endoscopy, evidence of accuracy, change in management and the expected benefit of changes in management on health outcomes is presented to evaluate the effectiveness of capsule endoscopy using a linked evidence approach. This is discussed below under 'Diagnostic accuracy', 'Impact on patient management' and 'Impact on health outcomes'.

Diagnostic accuracy

Five primary studies provided accuracy data for capsule endoscopy. Two included studies compared capsule endoscopy with MRI or MRE. Five provided evidence for a comparison of capsule endoscopy and empirical treatment (ie capsule endoscopy as an incremental test over prior tests). No studies compared the accuracy of capsule endoscopy and CT/CTE.

Capsule endoscopy versus empirical treatment

Three fair quality and two poor quality studies provided evidence for a comparison of the accuracy of capsule endoscopy and empirical treatment (capsule endoscopy as an incremental test over prior tests).

In studies using a threshold of at least ≥ 2 ulcers or Crohn's disease specific lesions, the sensitivity of capsule endoscopy ranged from 47% (95% CI 22-73%) to 92% (95% CI 62-100%) and the specificity ranged from 89% (95% CI 81-94%) to 100% (95% CI 7-

100%). The negative likelihood ratio (LR) ranged from 0.08 to 0.58. For the threshold of any small bowel ulcers, the sensitivity of capsule endoscopy ranged from 85% (95% CI 58-96%) to 100% (95% CI 72-100%) and the specificity ranged from 74% (95% CI 64-82%) to 92% (95% CI 73-99%). The negative LR ranged from 0 to 0.21. Overall, most studies had negative LRs <0.10, the threshold for providing convincing evidence to exclude disease; however, two studies had negative LRs which were above the negative LR threshold for providing strong evidence for excluding disease <0.20. This included the largest study which had a negative LR >0.20 at both thresholds.

Capsule endoscopy versus MRI/MRE

One fair quality and one poor quality study compared the accuracy of capsule endoscopy and MRI or MRE respectively (against the reference standard of long-term follow-up >12 months).

There were no significant differences found between the sensitivity and specificity of capsule endoscopy and MRE. Capsule endoscopy and MRE were found to have similar sensitivities and specificities using either the threshold of >3 small bowel ulcers (sensitivity 91% [95% CI 57-100%] versus 100% [95% CI 82-100%] and specificity 100% [95% CI 87-100%] versus 98% [87-100%]) or the less stringent threshold of any small bowel ulcers (sensitivity 100% [95% CI 72-100%] versus 100% [95% CI 82-100%] and specificity 92% [95% CI 73-99%] versus 98% [95% CI 87-100%]).

Capsule endoscopy versus CT/CTE

The systematic review identified no studies comparing the accuracy of capsule endoscopy and CT/CTE for diagnosing suspected small bowel Crohn's disease.

Impact on patient management

No studies investigating the therapeutic impact of capsule endoscopy in patients with suspected small bowel Crohn's disease were identified.

Impact on health outcomes

In the absence of evidence that capsule endoscopy has significantly higher sensitivity or specificity than alternative tests (MR, CT) and of a subsequent change in management and improved health outcomes, a linked evidence case for improved health outcomes due to capsule endoscopy cannot be made.

Key uncertainties

There was no evidence on the accuracy of capsule endoscopy relative to CT/CTE and only two studies provided evidence on the comparative accuracy of capsule endoscopy relative to MR/MRE. Variations in accuracy across the studies may be partially explained by the variation in prior tests and selection criteria for patients across the studies. Poor reporting of these items meant that not all variations could be explained. In addition, most studies had negative LRs <0.10, the threshold for providing convincing evidence to exclude disease; however, two studies had negative LRs which were >0.20, including the largest study which had a negative LR >0.20 at both thresholds (Tukey et al 2009). While included studies suggest that capsule endoscopy is at least as accurate as MR at discriminating true disease status, the effect of this on patient management, and ultimately health outcomes, remains unknown. Overall, the evidence base was poor (level

IV studies or level III-2 with a high risk of selection and outcome bias) and only some variations in accuracy estimates between studies could be explained.

Overall conclusion with respect to comparative effectiveness

Capsule endoscopy is considered:

- likely to have at least comparable accuracy to MR;
- less likely to be predictive of the absence of Crohn's disease, when the capsule endoscopy is negative, in patient populations with negative or equivocal prior endoscopic and radiological tests;
- more likely to be predictive of the absence of Crohn's disease, when the capsule endoscopy result is negative, when a lower threshold is used to define a positive test; and
- not to be highly predictive of the absence of Crohn's disease in the largest and most applicable study.

There were no included studies that provided evidence on the comparative accuracy of capsule endoscopy and CT. The impact of capsule endoscopy findings on patient management is unknown and the resultant impact on health outcomes is uncertain.

Economic evaluation

The systematic review identified three economic studies that explored the costs or cost-effectiveness of imaging strategies, including capsule endoscopy, for diagnosing Crohn's disease. However, these could not be used as evidence of cost-effectiveness for the use of capsule endoscopy in Australia since they did not reflect the patient population or clinical pathway (page 1) under consideration in this report. In addition, none of the studies were conducted in Australia and substantial differences between health systems limit the transferability of economic studies.

Due to the lack of comparative effectiveness data it was also not warranted to perform a cost-effectiveness analysis to estimate the value for money of capsule endoscopy. The preferable approach to the economic evaluation was therefore a presentation of the costs and possible consequences of capsule endoscopy and comparators. A limited societal perspective was used, which included the cost to the MBS and patient copayments.

Overall conclusion with respect to economic evaluation

The average cost to society of capsule endoscopy ranged between \$1,924 per test when the costs of capsule retention were not taken into account, to \$2,085 per test when a 15% capsule retention rate was assumed but the costs of surgery to remove the retained capsule were not attributed to capsule endoscopy. The average cost of CT/CTE was \$434. MRI/MRE is currently not funded through the MBS as a diagnostic test for small bowel Crohn's disease.

Compared to a repeat CT/CTE or MRI/MRE, the consequences of capsule endoscopy for patient management are unknown and the resultant impacts on health outcomes are uncertain.

Financial/budgetary impacts

The financial implications of public funding for capsule endoscopy were estimated as the potential costs to the MBS as well as to society (including the cost to the MBS and patient copayments) compared with the costs of using repeat CT/CTE. The analysis should be interpreted cautiously given the limited epidemiological data.

Assuming an estimated range of 664 to 1,431 capsule endoscopies per year, the incremental cost to the MBS is estimated to be between \$983,982 and \$2,120,599 per year when capsule endoscopy replaces repeat CT/CTE. The incremental cost to society is estimated to be between \$989,049 and \$2,131,517 per year.

The cost impact is sensitive to the rate of capsule retention and whether costs of surgery to remove a retained capsule are classified as a cost of capsule endoscopy. Additionally, the implementation of public funding for capsule endoscopy may lead to a change in utilisation rate. It may lead to a modest increase in use; however, it could also lead to a modest decline in claims for MBS item 11820, capsule endoscopy for OGIB.

Introduction

MSAC has reviewed the use of capsule endoscopy, which is a diagnostic test for small bowel Crohn's disease. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the MBS in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for capsule endoscopy for the diagnosis of small bowel Crohn's disease.

Background

Capsule endoscopy

Crohn's disease is a chronic inflammatory bowel disease that may affect any portion of the gastrointestinal tract (Yamada 2009). The diagnosis of Crohn's disease relies on an endoscopy. However, Crohn's disease confined to the small bowel may be difficult to diagnose using this technique due to the location, length and complex looping structure of the small bowel. Within the last 10 years, capsule endoscopy has emerged as a new diagnostic technique in response to these challenges.

The test

First introduced onto the international market by Given Imaging Pty Ltd (Israel) in 2001, capsule endoscopy is a non-invasive diagnostic test in which the gastrointestinal system is visualised using a wireless micro video camera inside a capsule ingested by the patient (Munoz-Navas 2009). The test provides images of the mucosa of the gastrointestinal tract for use in the diagnosis or surveillance of a range of conditions. Current and potential indications include OGIB, celiac disease, small bowel tumours, evaluating the causes of iron deficiency anaemia, diagnosing small bowel Crohn's disease or evaluating a suspected recurrence, and the screening and surveillance of polyps in small bowel polyposis syndromes such as PJS (Ladas et al 2010; MSAC 2003; MSAC 2007; Munoz-Navas 2009; Sidhu et al 2008). In contrast to some diagnostic techniques such as colonoscopy, which may permit biopsy and adjunct therapeutic functions such as polypectomy, capsule endoscopy is confined to a diagnostic or surveillance role (Yamada 2009). Different versions of the PillCam® capsule are available for the oesophagus (PillCam® ESO2), the small bowel (PillCam® SB2) and the large bowel (PillCam® COLON) (Nakamura & Terano 2008). Three other video capsule technologies for the small bowel are currently manufactured: the EndoCapsule by Olympus (Japan); the MiRo-Cam by IntroMedic (Korea); and OMOM from the Chongqing Jinshan Science and Technology Group (China) (Ladas et al 2010). PillCam®SB is now in its second generation (Ladas et al 2010; Munoz-Navas 2009).

The procedure relies on three pieces of equipment – a video capsule, a data recorder and a workstation. The capsule is disposable and ingestible, approximately 26 mm x 11 mm in size, and contains micro imaging video technology which includes a battery, camera, transmitter, antenna and light emitting diodes (Sidhu et al 2008). The GIVEN® data recorder is a system worn at the waist that receives the transmitted images via radiofrequency data transmission. The workstation is a dedicated computer station to which data and images are uploaded for analysis by the clinician.

The procedure may be performed in an outpatient setting (Munoz-Navas 2009). After bowel preparation, where necessary, and fasting for 8 to 12 hours, the patient presents at the specialist's private room (or clinic) to have the data recorder fitted and to swallow the capsule (Sidhu et al 2008). The capsule moves through the gastrointestinal tract by peristalsis and transmits two images per second to the data recorder, producing eight hours of imaging (approximately 50,000 images) (Poelmans et al 2006). Around eight hours after ingesting the capsule, the patient returns to the specialist's private room (or clinic) and data are uploaded for analysis. The disposable capsule will usually be excreted naturally between 24 and 72 hours after ingestion.

Contraindications for capsule endoscopy include bowel obstruction, strictures, fistulae, swallowing disorders and pregnancy (Van Assche et al 2010). Pacemakers and implanted cardiac defibrillators have also been considered contraindicated due to theoretically possible risks, although this is yet to be assessed using large studies (Sidhu et al 2008). The main clinical risk is capsule retention. Technical failures that may affect the successful performance of the procedure include incomplete examination either due to the presence of bowel contents or failure to reach the caecum within the capsule's battery life; difficulty swallowing the capsule; and problems associated with missing footage, difficulties downloading the data and battery malfunction (Schnoll-Sussman & Kulkarni 2008).

Intended purpose

This report assesses capsule endoscopy for the evaluation of suspected small bowel Crohn's disease. The specific research question to be addressed is:

In symptomatic patients with suspected but unconfirmed Crohn's disease, what is the value of capsule endoscopy compared with abdomen CT with or without enterography, MR with or without enterography, or empirical treatment for the diagnosis of suspected small bowel Crohn's disease?

Crohn's disease

Crohn's disease is a chronic inflammatory bowel disease that may affect any part of the gastrointestinal tract, including the large and small bowel, mouth, tongue, oesophagus and stomach. As it is a chronic condition, patients with Crohn's disease usually present with more than six weeks of symptoms. The age of diagnosis of Crohn's disease peaks in the 20-24 year age group and an Australian incidence study found that 18% of incident Crohn's disease cases were 21 or younger (Wilson et al 2010). Symptoms may include abdominal pain, diarrhoea, rectal bleeding and weight loss, and extra-intestinal symptoms such as fever, cholangitis, skin lesions and arthritis (Yamada 2009). Crohn's disease may curtail life expectancy only slightly, but has a potentially chronic effect on a range of issues including quality of life, psychological and sexual dysfunction and employment (Baumgart & Sandborn 2007; Morrison et al 2009).

Crohn's disease has several characteristic features. It involves inflammation which may be patchy – affecting several discontinuous sites of the gastrointestinal tract (spatially discontinuous). The inflammation may also be transmural – extending through the intestinal wall from the mucosa to the serosa – thus potentially leading to complications such as fistulae and strictures (Yamada 2009). Crohn's disease may affect any portion of the gastrointestinal tract, but most commonly occurs in the ileum (part of the small bowel), the colon or both (Baumgart & Sandborn 2007).

The small bowel (also called the small intestine) is the longest section of the gastrointestinal tract and consists of three main parts: the duodenum, the jejunum and the ileum. Crohn's disease may affect any of these areas and may occur with or without large bowel involvement. However, isolated involvement of the jejunum and duodenum is rare. Patients with Crohn's disease localised to the small bowel are typically affected either solely in the terminal ileum, or in both the colon and ileum. The site of Crohn's disease changes during the course of the disease, but at diagnosis it has been found in the terminal ileum (47%), colon (28%), ileum and colon (21%) and upper gastrointestinal

tract (3%) (Baumgart & Sandborn 2007). It is possible that the reported occurrence of Crohn's disease above the ileum is an underestimate because this area is more difficult to visualise using conventional diagnostic tests (Satsangi et al 2006). Given that the terminal ileum is the typical pattern of small bowel involvement in Crohn's disease, the majority of patients with small bowel Crohn's disease are successfully diagnosed using colonoscopy with ileoscopy.

Current treatment

In Australia, contemporary treatment philosophy for small bowel Crohn's disease recognises that the disease cannot be cured, and instead aims to control symptoms, modify the natural history of the disease and prevent long-term complications (Morrison et al 2009). A long-term and multidisciplinary perspective on treatment is adopted that incorporates pharmaceutical, surgical and ancillary strategies.

Pharmaceutical treatment of small bowel Crohn's disease consists of two main stages – inducing remission and maintaining remission – and may involve a selection of anti-inflammatory, immunomodulatory and biological treatments. The induction of remission is an attempt to control the symptoms of small bowel Crohn's disease such as inflammation. The type of first line therapy chosen depends on clinical judgement, patient preference and the location and severity of the disease. The use of anti-inflammatories such as 5-aminosalicylic drugs as a first line therapy for small bowel Crohn's disease is common in Australia, despite poor patient compliance and controversies over its efficacy and which preparation to use in which circumstances (Geary et al 2007; Morrison et al 2009). Sulfasalazine (salazopyrin, pyralin-EN, salazopyrin-EN) is currently the only 5-aminosalicylic drug for which unrestricted access is available under the PBS. Mesalazine (mesasal, pentasa, salofalk) may be prescribed under special authority if the patient is hypersensitive to sulfonamides or intolerant to sulfasalazine, but evidence of its efficacy is inconsistent (Baumgart & Sandborn 2007; Geary et al 2007). Induction of remission in those with mild ileocaecal disease may involve between 2,000 and 4,000 mg of sulfasalazine daily (Baumgart & Sandborn 2007; Morrison et al 2009). Maintenance of remission may involve the continued use of 5-aminosalicylic drugs or immunomodulators such as azathioprine, 6-mercaptopurine or methotrexate. The effect of immunomodulators takes two to three months to occur (Morrison et al 2009).

If patients do not respond to 5-aminosalicylic drugs they may be treated with corticosteroids such as oral prednisolone or biological agents such as infliximab or adalimumab (Baumgart & Sandborn 2007; Morrison et al 2009). Corticosteroids are used to suppress the immune system (thereby reducing the inflammatory response) and are usually used for inducing remission rather than maintenance of remission as they have a number of short and long-term complications (Morrison et al 2009). The use of biological agents involves drugs that target molecules involved in the inflammatory pathways involved in Crohn's disease. Biological treatment may be used for both induction of remission and maintenance of remission in those with moderate to severely active disease that fails to respond to first line treatment (Morrison et al 2009). The concurrent use of immunomodulators alongside biological agents may improve the efficacy of the biological treatment but may also increase the risk of serious infections such as tuberculosis and skin cancer (Morrison et al 2009). Immunomodulators for the maintenance of remission are more often used in those with more active or severe forms of small bowel Crohn's disease.

In addition to pharmaceutical treatment, a range of issues such as sexual health, psychological health, anaemia, employment implications and nutrition need to be dealt with and may be managed by a multidisciplinary team.

Almost two-thirds of patients with Crohn's disease undergo surgery within 10 years of the diagnosis (Yamada 2009). The main surgical procedures vary depending on the patient's pathology, and may include single or multiple surgical resections (small bowel or ileocolonic) and single or multiple stricturoplasties. The indications for surgery include the treatment of complications of Crohn's disease such as fistulae, abscesses or strictures; intervention when medical management, such as corticosteroids, is associated with significant side-effects; or when medical management has failed to adequately control symptoms such as diarrhoea, weight loss and pain (Baumgart & Sandborn 2007; Yamada 2009). The decision to perform surgery, and the extent of tissue removed, is approached conservatively because surgery does not cure Crohn's disease and postoperative recurrence is probable (Yamada 2009). Fistulae are abnormal connections between organs that may form as a complication to Crohn's disease. Fistulae that may require surgery include passages formed between the intestine and the bladder and between the intestine and the skin of the abdomen (Baumgart & Sandborn 2007). Formation of fibrotic strictures – the development of fibrous tissue in the intestine as a reactive or reparative response to the disease and which may lead to symptoms of bowel obstruction – may also require surgery (Baumgart & Sandborn 2007). Surgery to induce remission when medical management fails to adequately control disabling symptoms or has unacceptable side-effects is the outcome of a decision that takes into account the morbidity of current treatment and the morbidity arising from surgery (Baumgart & Sandborn 2007).

Clinical need

Burden of disease

Data on the burden of disease specifically due to Crohn's disease are scarce. Begg et al (2007) reported that inflammatory bowel disease (which includes Crohn's disease and ulcerative colitis) accounted for 0.5% of the total disease burden in Australia in 2003.

Crohn's disease may carry a small increased risk of mortality (Osterman 2006) and a large effect on morbidity due to its negative influence on employment and social life, psychological distress and sexual dysfunction (Morrison et al 2009). Crohn's disease impairs quality of life due to the challenges associated with symptoms such as abdominal pain and diarrhoea. Factors that concern patients include the uncertainty of the disease, adverse effects of medication, having to use an ostomy bag, low energy levels and the possible need for surgery (Pihl-Lesnovska et al 2010).

In 2007-08, there were 13,915 hospital separations with the principal diagnosis of Crohn's disease (ICD code K50) (AIHW 2011). Between 1998-99 and 2007-08, hospital separations with the principal diagnosis of Crohn's disease (K50) more than doubled, increasing from 6,485 to 13,915 (AIHW 2011). This is consistent with reported global increases in the prevalence of Crohn's disease; however it could also represent an increased rate of admissions per patient (Gibson 2009; Morrison et al 2009; Wilson et al 2010). Note that hospital separations are recorded per episode of care rather than per patient and only record admitted patients.

Data on health system expenditure on Crohn's disease are scarce and health system expenditure data usually detail expenditure on digestive diseases as a group. In 2004-05, \$3,107 million was spent in Australia in relation to diseases of the digestive system. This amounts to 5.9% of total allocated health expenditure (where allocated health expenditure is that which was able to be allocated to disease – approximately 70% of total recurrent health expenditure) (AIHW 2010). The AIHW projected health expenditure by disease between 2002-3 and 2032-33. It was projected that health system and residential aged care expenditure on digestive disorders would increase from \$4,877 million to \$16,488 million (AIHW 2008). In percentage terms, this is the fourth highest projected increase (238%) and in dollar terms the sixth highest (\$11.61 billion) (AIHW 2008). Over half of the projected \$11.61 billion increase is attributed to an increase in the volume of services per case (AIHW 2008). The extent to which the expenditure specifically allocated to Crohn's disease will follow the overall trend in digestive disorders expenditure is unknown.

Incidence of Crohn's disease

The incidence of Crohn's disease varies widely by geographic location. The rates are highest in highly industrialised countries such as Australia, the UK, Canada and Northern Europe, where the incidence of Crohn's disease ranges from 7 to 23 per 100,000 per year (see Table 4). Table 4 lists studies that estimate Crohn's disease incidence rates.

Data on Crohn's incidence in Australia are scarce (see Table 4). One population-based prospective study reported a crude annual incidence of Crohn's disease in the regional Victorian city of Geelong of 17.4 (95% CI = 13.0-23.2) per 100,000 in 2008 (Wilson et al 2010).

Table 4 Studies reporting crude annual incidence rates for Crohn's disease

Source	Crude incidence (per 100,000 per year) (95% CI)	Age-standardised incidence (per 100,000 per year) (95% CI)	Location	Data type	Year of data collection
Shivananda et al (1996) ¹	7	7 (4-10)	Northern Europe	Prospective multicentre study	1991-93
Bernstein et al (1999) ²	15	nr	Manitoba, Canada	Insurance datasets	1989-94
Rubin et al (2000)	nr	8 (3-13)	Northern England	GP records	1990-94
Gearry et al (2006) ³	17 (13-20)	16	Canterbury, New Zealand	Population-based study	2004-05
Wilson et al (2010) ⁴	17 (13-23)	nr	Geelong, Victoria, Australia	Prospective cohort study	2008
Range	7-23	3-16			

1. The standardised incidence rates were directly age and sex standardised to the European Standard Population. Only cases aged 15-64 years were included. It is assumed that the incidence rates were annual incidence rates (this was not confirmed in the paper).

2. The results section of the study indicates that overall incidence rate was 14.6 per 100,000, and that it was not age standardised. However the Abstract states that the age and sex standardised annual incidence of Crohn's disease was 14.6 per 100,000 per year.

3. The incidence rate was age standardised to the WHO Standard Population. The age standardised incidence was listed as 16.3 per 100,000 per year in the results section but 16.5 per 100,000 per year in the abstract. It is assumed that the former is correct.

4. Data from this Australian study were used to derive estimates of utilisation and incidence in this review as the patient population is most applicable.

Taking the Australian incidence data from Wilson et al (2010) (17 per 100,000 per year) and multiplying it by the estimated annual resident population of Australia (21,875,000) as at 30 June 2009 would suggest that the annual incidence of Crohn's disease in Australia is approximately 3,719 cases (ABS 2009).

Crohn's disease locality may be classified into four locations according to the Vienna (subsequently Montreal) classification system: terminal ileum, colon, ileocolon and upper gastrointestinal (Satsangi et al 2006). In a Belgian study of 297 patients, 133 (45%) had Crohn's disease localised to the terminal ileum at diagnosis (Louis et al 2001). Assuming a similar rate in the Australian population, approximately 1,673 incident cases of Crohn's disease in Australia would be localised to the terminal ileum.

Estimated utilisation of capsule endoscopy

An estimate of the potential utilisation of capsule endoscopy, if public funding is approved, is difficult to derive from the available data. Figures on the use of capsule endoscopy for the present indication are not available directly. The potential utilisation of the test is estimated using limited available data, which includes the incidence of Crohn's disease found in the only Australian population-based incidence study by Wilson et al (2010) and the test's estimated diagnostic yield as reported by the largest accuracy study and the most applicable diagnostic yield study identified by the present review (see Box 1 for method and Table 4 and Table 5 for data sources).

The Advisory Panel estimated that approximately 95% of cases would be diagnosed by prior tests, leaving 5% of incident cases diagnosed by capsule endoscopy.

If the number of Australian cases of Crohn's disease is approximately 3,719 per year, and 5% (expert opinion of the Advisory Panel) of these are diagnosed by capsule endoscopy for the indication of small bowel Crohn's disease, then the estimated number of patients diagnosed with Crohn's disease by capsule endoscopy is approximately 186 per year. Using the diagnostic yield of capsule endoscopy reported in the largest accuracy study

and the most applicable (and only Australian) diagnostic yield study identified by the present review, the possible range of those with suspected small bowel Crohn's disease who are tested by capsule endoscopy and receive a positive diagnosis lies between 13% and 28% (see Table 5). Assuming a similar diagnostic yield applies to the patient population of this review, the estimated number of capsule endoscopy procedures performed – including those with a positive and negative result – can be estimated by dividing the anticipated number of patients diagnosed with Crohn's disease by capsule endoscopy (approximately 186 per year) by the estimated yield of the test (between 13% and 28%) and lies between 664 and 1,431 per year.

In an Australian incidence study by Wilson et al (2010), 5 of 45 (11%) incident Crohn's disease cases were diagnosed using capsule endoscopy for the investigation of anaemia or OGIB after an indeterminate or negative colonoscopy. This result was considered inapplicable to the estimation of test utilisation for the present indication: the patients in this study were being evaluated for a different indication (OGIB) and, contrary to the clinical flow chart for this assessment, were not required to have undergone small bowel radiology and attempted ileoscopy.

In summary, the estimated utilisation of capsule endoscopy for the diagnosis of small bowel Crohn's disease that was unconfirmed on prior tests lies between 664 and 1,431 per year. This estimate refers to the number of patients estimated to use the test per year, as opposed to the number of tests per year. Actual utilisation may be higher than this estimate if some patients who would otherwise be diagnosed with Crohn's disease while being evaluated for OGIB with capsule endoscopy will now be tested under the indication of suspected Crohn's disease. However, this would be balanced by a corresponding reduction in the utilisation of capsule endoscopy for OGIB.

Box 1 Estimation of the incidence of Crohn's disease and the utilisation of capsule endoscopy

<p>Number of Australian incident cases of Crohn's disease in 2009 = Crude Crohn's disease annual incidence rate * Australian population at 30 June 2009</p> <p>Proportion of incident cases of Crohn's disease diagnosed by capsule endoscopy = 0.05 (Expert opinion endorsed by the Advisory Panel)</p> <p>Estimated number of patients diagnosed with Crohn's disease by capsule endoscopy = Number of Australian incident cases Proportion diagnosed by capsule endoscopy</p> <p>Estimated utilisation of capsule endoscopy per year = Incidence of Crohn's disease not diagnosed by conventional techniques Diagnostic yield of capsule endoscopy</p>
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Diagnostic yield of capsule endoscopy in patients with suspected Crohn's disease

Source	% of patients with suspected Crohn's disease who test positive for Crohn's disease after capsule endoscopy	Diagnostic threshold
Selby et al (2008)	20% (24/120) (95% CI = 14- 28%)	≥ 3 ulcers
Tukey et al (2009)	19% (20/105) (95% CI = 13- 28%)	>3 ulcers

Existing tests

There is no pathognomonic marker – clinical, endoscopic, pathological – for Crohn's disease (Yamada 2009) that indicates by necessity that Crohn's disease is present and that all other diseases in the differential diagnosis are absent. Correspondingly, there is no

single and definitive diagnostic test for small bowel Crohn's disease. Instead, the diagnosis is reached using clinical judgement on the basis of the patient history and physical examination in combination with radiographic and endoscopic evidence and histological and laboratory findings (Baumgart & Sandborn 2007). Below is an overview of existing tests for the diagnosis of small bowel Crohn's disease – colonoscopy with attempted ileoscopy, abdomen CT and MR.

Endoscopic tests

Colonoscopy with attempted ileoscopy

Colonoscopy is an endoscopic procedure used to examine the terminal ileal, colonic and rectal mucosa. Colonoscopy with attempted ileoscopy involves the endoscopist attempting to reach the ileum: once the colonoscope reaches the caecum, the endoscopist locates the ileocaecal valve, positions the colonoscope at the correct angle and then the tip of the instrument passes through the valve (Chen & Khanduja 1997). It has been estimated that a skilled endoscopist can achieve this in 80% of cases (Yamada 2009). This procedure usually enables visualisation of only the first 5 to 10 centimetres of the terminal ileum but may extend to between 30 and 50 centimetres into the ileum (Yamada 2009). Deeper entry into the ileum is not often attempted since ileal Crohn's disease usually occurs within this portion of the terminal ileum.

Colonoscopy is publically funded under MBS item 32090 (fee \$321.65) and is being reviewed under the MBS Quality Framework review process.

Radiological tests

MR

MR is an imaging technique that enables cross-sectional imaging of the small bowel (Yamada 2009). Contrast agents can be administered orally (MRE) or through a naso-gastric tube (magnetic resonance enteroclysis) (Markova et al 2010). Compared with CT, which uses x-ray attenuation, MR uses multiple tissue parameters to build an image.

MR is not currently funded through the MBS for small bowel Crohn's disease.

Abdomen CT

Abdomen CT is a radiological technique used in the diagnosis of small bowel Crohn's disease. This test provides multiplanar images of the lumen, wall and mesentery of the small bowel. These images have a high degree of spatial resolution and are generated via the use of multidetector CT technology following the ingestion of a contrast agent by the patient, either orally (enterography) or via a naso-gastric tube (enteroclysis) (Fletcher 2009). In some Australian settings, CT has superseded barium imaging as the main form of radiological imaging used in the diagnosis of Crohn's disease (Morrison et al 2009).

Abdomen CT is funded under MBS item 56507 with a fee of \$480.05.

SBFT

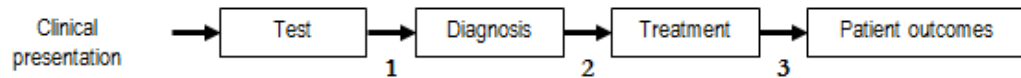
SBFT is a radiological technique for imaging the small bowel. Barium is either ingested by the patient or administered via enteroclysis and then x-ray images are taken of the abdomen. In some Australian settings, SBFT has been superseded by abdomen CT/CTE or MR/MRE (Morrison et al 2009); however, clinical practice varies across settings.

SBF^T is funded under MBS item 58915 with a fee of \$78.95.

Methodological considerations

The clinical value of a test depends on whether its use improves patient outcomes. This is determined by its ability to accurately detect or exclude disease, whether this information influences treatment decisions and the effectiveness of the treatment selected (see Figure 1).

Figure 1 Causal pathway and determinants of the clinical value of a test



1. Diagnostic accuracy
2. Therapeutic impact
3. Treatment effectiveness

If randomised controlled trials are not available to assess whether adopting a new test improves patient outcomes compared with standard testing practice, evidence from studies assessing test accuracy and therapeutic impact can be linked to evidence about treatment efficacy or improved prognosis to infer effectiveness in some situations.

There are guidelines for designing, conducting, reporting and appraising studies of test accuracy, treatment efficacy and patient prognosis (NHMRC 1999), but the methods for designing and interpreting therapeutic impact studies are less well established. The role of these studies is to provide evidence that the test information has an effect on clinical decision-making, for example by demonstrating changes in clinician diagnostic certainty, test ordering or treatment plans. This evidence is interpreted with evidence about the benefits or harms of these decisions, either through a simple descriptive assessment or quantitatively by using decision-analytic methods. This enables judgements to be made about the potential clinical value of the test or the need for further research to demonstrate effectiveness.

Demonstrating a change in diagnosis or treatment does not in itself provide evidence of effectiveness; therefore, therapeutic impact studies need to be carefully designed to answer a clearly defined question about the potential benefits of the test for clinical decision-making, with an explicit statement about existing evidence for the effectiveness or cost-effectiveness of these decisions (eg improved patient outcomes through reduction of invasive testing, increase in effective treatment, reduction in patient morbidity). Therapeutic impact studies can be designed as randomised trials to assess clinician diagnostic certainty, diagnosis and treatment selection with and without the new test, or as observational studies including pre- and post-test studies in which clinicians are asked to record their provisional diagnosis, diagnostic certainty and proposed management plan before and after testing. Data are analysed to report on changes in diagnostic thinking and therapeutic plans, and interpreted with information about the accuracy of the test and the true disease state of the subject in order to assess the benefits or harms of the information provided by the test.

Marketing status of the technology

PillCam® capsule endoscopy has been registered by the TGA since 30 August 2006 (see Table 6).

Table 6 Registration of PillCam® capsule endoscopy with the TGA

ARTG no	Product no	Product description	Device class	Sponsor
130833	215817	Given diagnostic system and PillCam® capsule endoscopy (capsule, non-digestible, electronic tracking)	Class IIa	Given Imaging Pty Ltd

Source: TGA (2011)

Current arrangements for public reimbursement

Capsule endoscopy is not listed on the MBS for the diagnosis of small bowel Crohn's disease. Capsule endoscopy is currently listed on the MBS for two indications: small bowel surveillance in patients diagnosed with PJS, and the investigation of OGIB when the cause of bleeding has not been identified by upper gastrointestinal endoscopy and colonoscopy. Details of these MBS items are listed in Table 7. Capsule endoscopy for the present indication is financed through self-pay and is usually performed as an outpatient procedure in private rooms or clinics.

Table 7 MBS items for capsule endoscopy

MBS item	Descriptor ^a	Fee	Benefit	Indication	Date listed/approved
11820	<p>CAPSULE ENDOSCOPY to investigate an episode of obscure gastrointestinal bleeding, using a capsule endoscopy device approved by the Therapeutic Goods Administration (TGA) (including administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered), (not being a service associated with double balloon enteroscopy), if:</p> <p>(a) the service is performed by a specialist or consultant physician with endoscopic training that is recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and</p> <p>(b) the patient to whom the service is provided:</p> <p>(i) is aged 10 years or over; and</p> <p>(ii) has recurrent or persistent bleeding; and</p> <p>(iii) is anaemic or has active bleeding; and</p> <p>(c) an upper gastrointestinal endoscopy and a colonoscopy have been performed on the patient and have not identified the cause of the bleeding; and</p> <p>(d) the service is performed within 6 months of the upper gastrointestinal endoscopy and colonoscopy</p>	\$1,961.95	<p>\$1,471.50 (75%)</p> <p>\$1,890.75 (85%)</p>	OGIB	<p>Interim funding: 1 May 2004</p> <p>Approved for ongoing funding: 23 November 2007</p>
11823	<p>CAPSULE ENDOSCOPY to conduct small bowel surveillance of a patient diagnosed with Peutz-Jeghers syndrome, using a capsule endoscopy device approved by the TGA. The procedure includes the administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered (not being a service associated with double balloon enteroscopy). Medicare benefits are only payable for this item if:</p> <p>1. the service has been performed by a specialist or consultant physician with endoscopic training that is recognised by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy; and</p> <p>2. the patient to whom the service is provided has been conclusively diagnosed with Peutz-Jeghers syndrome.</p> <p>This item is available once in any two year period.</p>	\$1,961.95	<p>\$1,471.50 (75%)</p> <p>\$1,890.75 (85%)</p>	Surveillance of PJS	Listed: 1 March 2009

^a – Further details associated with these listings can be found in the explanatory notes D1.22 and D1.23 which are accessible via the Medicare Benefits Schedule.

Source: Medicare Benefits Schedule (Commonwealth of Australia 2011a)

Approach to assessment

Objective

The objective of this assessment is to undertake a structured evaluation of the clinical need, safety, effectiveness and cost-effectiveness of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease.

Research question

A specific research question to assess the value of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease was developed by the evaluators in consultation with the Advisory Panel. This research question was structured according to the 'PPICO' (Population, Prior tests, Intervention, Comparator, Outcomes) framework for well-built clinical questions (Richardson et al 1995). The research question was developed *a priori* on the basis of information in the application and advice provided by the Advisory Panel about the characteristics of small bowel Crohn's disease, current practice and the intended purpose of capsule endoscopy in clinical practice as depicted in the clinical flow chart (see **Error! Not a valid bookmark self-reference.**).

The research question was:

In symptomatic patients with suspected but unconfirmed Crohn's disease, what is the value of capsule endoscopy compared with abdomen CT with or without enterography, MR with or without enterography, or empirical treatment for the diagnosis of suspected small bowel Crohn's disease?

The complete details of the research question can be found in the PPICO table and its accompanying footnotes (see Table 8).

Table 8 PPICO criteria and clinical question for the diagnosis of suspected small bowel Crohn's disease

Population	Prior tests	Intervention	Comparator	Reference standard	Outcomes
Patients with suspected but unconfirmed non-stricturing small bowel Crohn's disease, as indicated by ongoing symptoms suggestive of Crohn's disease such as abdominal pain, diarrhoea, extra-intestinal symptoms or raised inflammatory markers on blood tests. ¹	Conventional diagnostic tests: Colonoscopy <i>and</i> Attempted ileoscopy (as part of colonoscopy) <i>and</i> Small bowel radiology: SBFT <i>or</i> small bowel enteroclysis (SBE) <i>or</i> Abdomen CT +/- enterography <i>or</i> MR +/- enterography <i>and</i> Blood tests	Capsule endoscopy	Abdomen CT +/- enterography <i>or</i> MR +/- enterography <i>or</i> Empirical treatment	Long-term follow-up (>12 months) ² <i>or</i> Panel of tests <i>or</i> Abdomen CT with enterography or enteroclysis <i>or</i> MR with enterography or enteroclysis	Diagnostic performance <ul style="list-style-type: none"> • sensitivity • specificity • additional TP & FP • ROC AUC, Q*, DOR • diagnostic yield³ Impact on patient management <ul style="list-style-type: none"> • Crohn's disease progression⁴ • treatment morbidity • quality of life

Clinical question

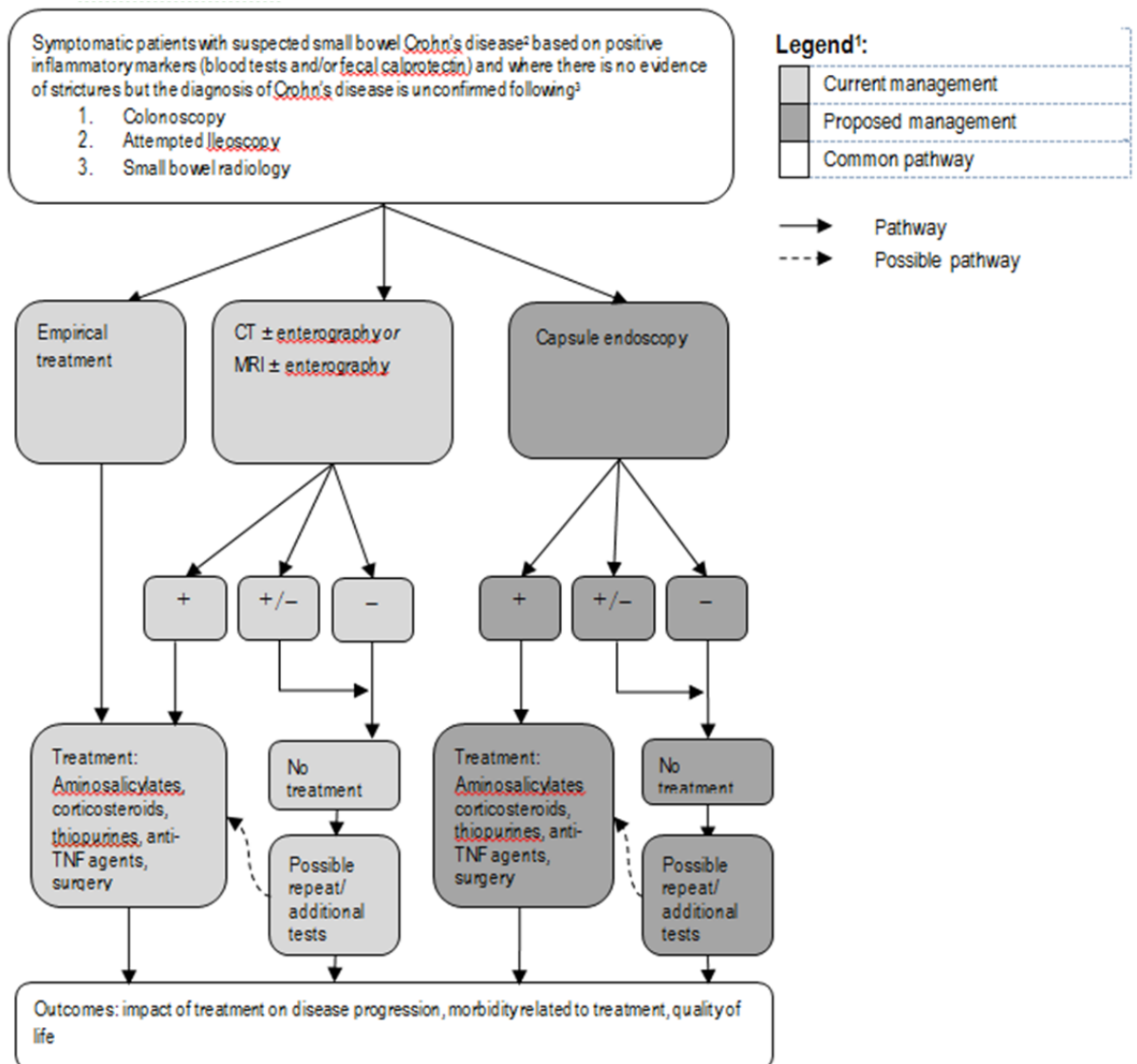
In symptomatic patients with suspected but unconfirmed Crohn's disease, what is the value of capsule endoscopy compared with abdomen CT with or without enterography, MR with or without enterography or empirical treatment for the diagnosis of suspected small bowel Crohn's disease?

1. The criteria for enrolling patients in the Multicenter Australian Capsule Endoscopy in Patients with Suspected Crohn's Disease Study (the MACCS study, Clinical Trials identifier: NCT00434551) (Selby et al 2008) may be used to further define this patient population. This study includes patients ≥10 years old, who have suffered from abdominal pain and/or diarrhoea for the last six weeks and/or have extra-intestinal manifestations of Crohn's disease, who have at least one of a number of signs over the preceding six months such as positive inflammatory markers on blood tests (C-reactive protein, erythrocyte sedimentation rate, abnormal white cell count or platelet count or low albumin) or fecal calprotectin or recurrent fever and in whom a diagnosis of Crohn's disease remains unconfirmed following prior tests conducted within six months prior to enrolment and blood tests within one month of enrolment. The study excludes patients with known intestinal obstruction, suspected strictures or strictures seen on SBFT; who are on nonsteroidal anti-inflammatory drugs (NSAIDs) during the three months preceding enrolment; who have indeterminate colitis being evaluated only to make a definitive diagnosis; are undergoing treatment for active inflammatory bowel disease; or that have suspected celiac disease (see Selby et al ((2008)) for the complete inclusion and exclusion criteria).
2. In the absence of studies that use long-term follow-up (>12 months) as a reference standard, studies using the other listed reference standards will be considered.
3. Diagnostic yield will only be used as an outcome if there are insufficient findings arising from studies that use measures of diagnostic accuracy.
4. Improvement in, or prevention of, Crohn's disease progression may be measured by the Crohn's Disease Activity Index or the Harvey Bradshaw Index.

Clinical decision pathway

A flow chart depicting the diagnosis of patients with suspected small bowel Crohn's disease was developed based on the information contained in the application submitted to MSAC and the advice of the Advisory Panel (see **Error! Not a valid bookmark self-reference.**). This clinical flow chart depicts the potential role of capsule endoscopy in the diagnosis of patients with suspected but unconfirmed small bowel Crohn's disease.

Figure 2 Clinical flow chart



- + refers to a diagnosis of definite Crohn's, +/- refers to a diagnosis of possible Crohn's and - refers to Normal (no findings). These choices are based on the criteria defined by Mow et al (2004).
- Patients with suspected small bowel Crohn's disease as indicated by ongoing symptoms suggestive of Crohn's disease such as abdominal pain, diarrhoea, extra-intestinal symptoms or raised inflammatory markers on blood tests (C-reactive protein, erythrocyte sedimentation rate, white cell or platelet count or low albumin) and/or fecal calprotectin for whom a definitive diagnosis of Crohn's disease (in any area of the bowel) remains unconfirmed following the above listed prior tests.
- This includes a diagnosis of Crohn's disease in areas other than the small bowel; a patient diagnosed with colonic Crohn's disease following a colonoscopy would be excluded from this patient population.

Comparator

This report compares capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease with three alternative tests:

- empirical treatment
- MR +/- enterography
- abdomen CT +/- enterography.

The reference standard

The diagnosis obtained at long-term follow-up (>12 months) was considered the most valid reference standard against which to determine the true disease status of patients for the assessment of capsule endoscopy in this assessment; however, given the lack of an agreed reference standard for capsule endoscopy, other reference standards were considered eligible for inclusion.

Given that a proposed benefit of capsule endoscopy is the earlier diagnosis of Crohn's disease, long-term follow-up (>12 months) is considered the most valid reference standard for this review. However, clinical follow-up is an imperfect reference standard. Crohn's disease has periods of activity and remission, and when restricted to the small bowel, is known to be difficult to diagnose (Satsangi et al 2006). Hence, the reference standard may not adequately discriminate between a true and false diagnosis: 12 months may not be sufficient time for a definitive diagnosis to occur. The validity of clinical follow-up as a reference standard is further compromised in circumstances where capsule endoscopy test results are not independent of the reference standard, resulting in incorporation bias and increasing the apparent sensitivity and specificity of the test. Variations in the extent of the follow-up used across the included studies, such as blinding, included tests and criteria for the diagnosis, are likely to contribute to variations in the reported accuracy of capsule endoscopy and its comparators. The reference standard could be improved by establishing *a priori* the specific tests and criteria which will be used to define a positive diagnosis of Crohn's disease at the 12-month follow-up and ensuring this is independent and blind to the test results.

Diagnostic assessment framework

In the absence of any direct evidence for the effectiveness of capsule endoscopy for the diagnosis of small bowel Crohn's disease, effectiveness evidence is presented using a linked evidence approach in which the evidence for accuracy, change in patient management and the expected benefit of changes in management on health outcomes are linked in order to draw inferences on the effectiveness of capsule endoscopy (see 'Methodological considerations', page 26).

Review of the literature

Literature sources and search strategies

A systematic review of the medical literature was conducted to identify relevant studies, systematic reviews and health technology assessment (HTA) reports published up to October 2010. Electronic databases of published research were searched for original research papers, including systematic reviews (see Table 9) and the websites of international HTA agencies were searched for existing HTA reports (Appendix C). Clinical trials databases were searched to identify ongoing studies (see Table 10) and specialty websites were searched for relevant grey literature (Appendix C).

Table 9 Electronic databases searched

Database	Period covered
EMBASE.com ¹	Up to October 2010
PreMEDLINE	Up to October 2010
All EBM ²	Up to October 2010

¹ Includes EMBASE and MEDLINE.

² Includes Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, HTA and Cochrane Methodology Register.

Table 10 Clinical trials databases searched to identify ongoing studies

Source	Location
Current Controlled Trials – International Standard Randomised Controlled Trial Number Register and <i>metaRegister</i> of Controlled Trials	http://www.controlled-trials.com
ClinicalTrials.Gov	http://www.clinicaltrials.gov
Australian New Zealand Clinical Trials Registry	http://www.actr.org.au
WHO International Clinical Trials Registry Platform	http://apps.who.int/trialsearch

A strategy for searching the medical literature was developed to identify literature on the safety, effectiveness and cost-effectiveness of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease. The search strategy was developed on the EMBASE platform (see Table 11) and adapted for the other databases listed in Table 9 where necessary.

Table 11 Search strategy for EMBASE.com (containing MEDLINE and EMBASE)

Element of clinical question	Search terms
Population	<ol style="list-style-type: none">1. 'enteritis'/exp OR 'enteritis'2. 'colitis'/exp OR 'colitis'3. 'crohn disease'/de OR 'crohn disease'4. crohn*5. enterocolitis:ab,ti6. 'small bowel'/de OR 'small bowel'7. (disease* OR inflammation*):ab,ti8. 6 and 79. Or/1-5,8
Intervention/test	<ol style="list-style-type: none">1. 'wireless capsule endoscopy'/exp OR 'wireless capsule endoscopy'2. 'capsule endoscopy'/exp OR 'capsule endoscopy'3. (capsule NEXT/3 (endoscop* OR enteroscop*)):tn,ab,ti4. 'videocapsule endoscopy' OR 'video capsule endoscopy'5. (wireless NEAR/3 (endoscop* OR record*)):tn,ab,ti6. ((disposable OR ingestible OR capsule) NEAR/3 imaging):tn,ab,ti7. (m2a NEXT/3 capsule):tn,ab,ti8. pillcam OR 'pill cam'9. (given NEXT/3 (imaging OR diagnostic*)):tn,ab,ti10. 'endo capsule' OR 'endocapsule'11. olympus NEAR/3 capsule12. OMOM NEAR/3 capsule13. MIRO NEAR/3 capsule14. or/1-1315. 14 AND [Population search string]

Selection criteria

The selection criteria outlined in Table 12 were developed *a priori* and were applied to all articles identified by the literature search.

Table 12 Selection criteria for the identification of relevant studies

Characteristic	Inclusion criteria
Publication type	<p>Clinical studies included. Non-systematic reviews, letters, editorials, animal, in-vitro, laboratory studies, conference abstracts and technical reports excluded.</p> <p>Systematic reviews Systematic reviews that have been superseded will be excluded</p> <p>Primary studies Primary studies published during the search period of included systematic reviews excluded. Accuracy studies excluded if:</p> <ul style="list-style-type: none"> patients were selected for inclusion in the study based on their known disease (case-referent, case-control studies) <p>Diagnostic yield studies excluded if:</p> <ul style="list-style-type: none"> retrospective or non-consecutive <p>Change in patient management studies excluded if:</p> <ul style="list-style-type: none"> change in therapeutic impact is not determined by comparison to a clearly defined non-CE or pre-CE management plan reported outcomes are a subjective rating of physician's perceived usefulness of the test without actual changes in management plan <p>Prognostic studies of outcomes included if:</p> <ul style="list-style-type: none"> all patients receive the same treatment following CE, regardless of whether CE+ (for confirmation of suspected small bowel Crohn's disease) or CE- (for no small bowel Crohn's disease). all patients receive a specific therapy selected with versus without CE <p>Prognostic studies of outcomes excluded if:</p> <ul style="list-style-type: none"> the original treatment plan of patients was altered based on a CE result
Patients	<p>≥ 70% of patients with suspected small bowel Crohn's disease undiagnosed by standard tests:</p> <ul style="list-style-type: none"> ≥10 years of age (in line with TGA requirements) No clinical or radiographic evidence of bowel obstruction or pseudo-obstruction <p>Studies with <20 patients undergoing CE for the indication of interest excluded (unless there are none).¹</p>
Intervention/test	<p>Capsule endoscopy (CE) Plus prior tests</p>
Comparator	<p>Abdomen CT +/- enterography MR +/- enterography Empirical treatment</p>
Outcome	<p>Studies must report on at least one of the following outcomes:</p> <ul style="list-style-type: none"> diagnostic accuracy: sensitivity and specificity (or data enabling calculation); diagnostic odds ratio or ROC curves; Q*, additional TP and FP yield (may be used when accuracy cannot be calculated) impact of CE results on clinical management (definitive treatment avoided, investigations avoided, definitive treatment instigated, overall change, type of change occurring in ≥10% patients) patient outcomes (Crohn's disease progression, treatment morbidity, adverse events, quality of life) prognostic value of CE results (patient outcomes following specific therapy selected with CE versus without CE; patient outcomes in CE+ or CE- undergoing same treatment, no change of original treatment plan of patients was altered based on a CE result)
Language	<p>Non-English language articles will be excluded.</p>

Abbreviations: CE = capsule endoscopy, FP = false-positive, TP = true-positive, ROC = receiver operating characteristic, Q* = Cochran's Q test

1. For studies reporting diagnostic accuracy outcomes, the size criterion was lowered from <20 to <15 owing to the paucity of studies meeting the inclusion criteria.

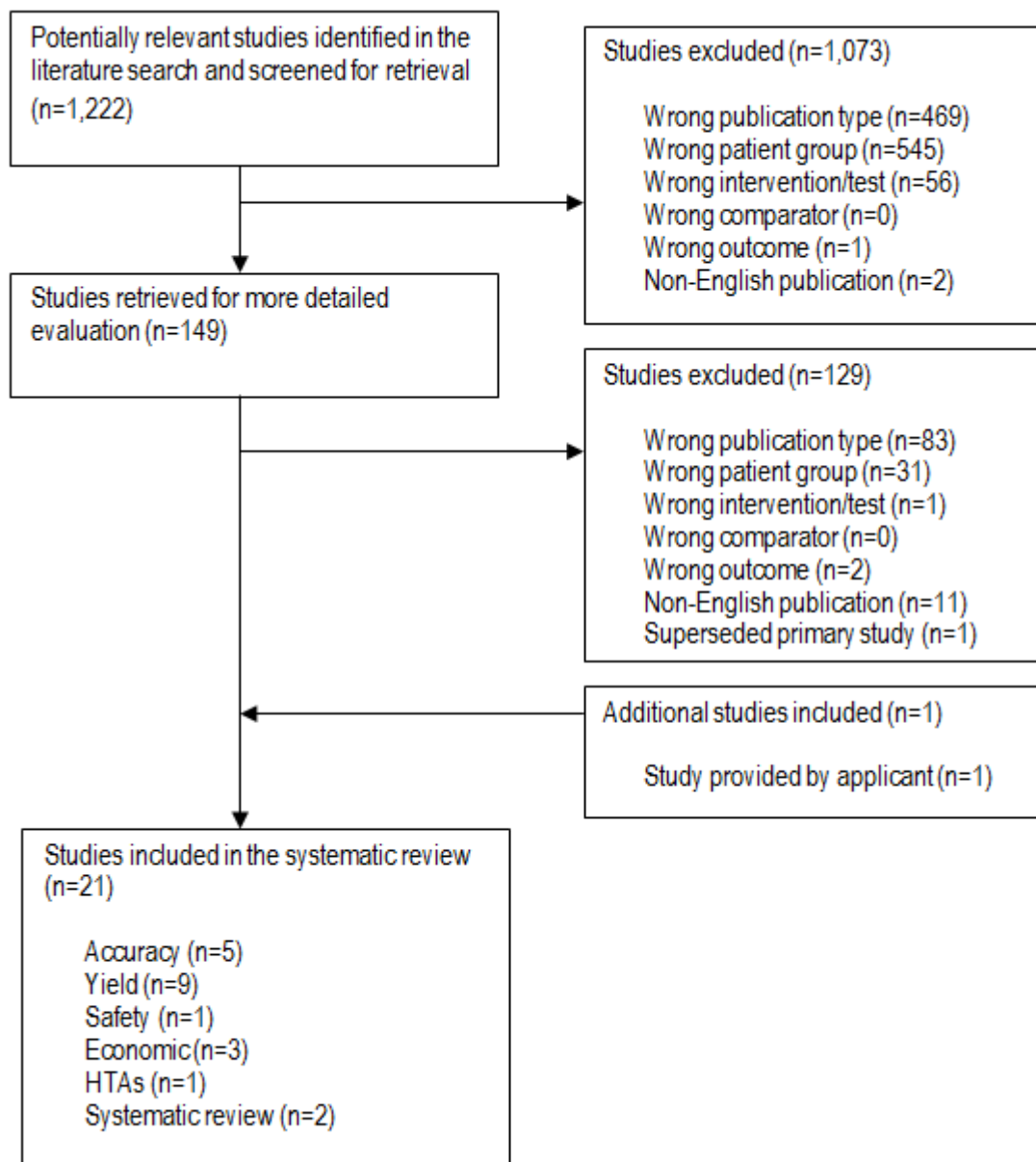
Search results

The search strategy retrieved a total of 1,222 non-duplicate citations. The citations were evaluated by two independent reviewers who determined whether the studies met the selection criteria outlined in Table 12. Discrepancies in the results of the screening process were resolved by discussion.

On the basis of the criteria, 1,202 citations were excluded from the review (Appendix E). The QUOROM (Quality of Reporting of Meta-analyses) flow chart (Figure 3) summarises the results of the literature search and the application of the study inclusion and exclusion criteria. The 21 studies meeting the criteria for inclusion in the review were 5 studies of diagnostic accuracy, 9 studies of diagnostic yield, 1 study with safety data only, 3 economic studies, 1 HTA and 2 systematic reviews.

QUOROM flow chart

Figure 3 Summary of the process used to identify and select studies for the review



Adapted from Moher et al (1999).

Data extraction and analysis

Data were extracted using a standardised instrument designed for this review. Items extracted included characteristics of the study objective and design, study population, type of diagnostic test, reference standard, comparator, study quality and relevant endpoints. Data were extracted by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion and by the involvement of a third reviewer if necessary. The data extraction tables are provided in Appendix D.

Where possible, two-by-two tables were reconstructed from study data to estimate measures of diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value and LRs) and associated 95% CIs for each test. Where study data were not available, the 95% CIs reported by the authors were presented.

Measurement of test accuracy

The accuracy of a test is determined by its ability to identify the target condition compared with a reference standard test that is used as a proxy for true disease status. Subjects who test positive using the reference standard are classified as having the disease; those who test negative are classified as disease-free.

Results of the index test and reference standard for a group of tested subjects were summarised in a two-by-two table where appropriate (see Figure 4).

Figure 4 Two-by-two table of data used to determine test accuracy

		Reference standard	
		disease +	disease -
Index test	+ result	true-positive (TP)	false-positive (FP)
	- result	false-negative (FN)	true-negative (TN)
		TP + FN	TN + FP

Total number of subjects tested = TP + TN + FP + FN
Number of subjects with disease = TP + FN
Number of subjects without disease = TN + FP

As shown, subjects who test positive for the disease of interest by both the index test and the reference standard were recorded as true-positive (TP). Subjects without the target condition who test negative by both tests were recorded as true-negative (TN). The index test result was recorded as a false-positive (FP) if it detected the target condition and the reference standard did not. A false-negative (FN) was recorded if the reference standard confirmed the target condition and the index test did not.

Sensitivity and specificity

The sensitivity of a test is the probability of a positive test in subjects with the disease of interest. The specificity of a test is the probability of a negative result in subjects without the disease. The sensitivity and specificity of a test are always considered together and vary according to the threshold used to define a positive test. Sensitivity and specificity vary according to the spectrum of disease (eg variation in disease severity) in the patient group tested. High sensitivity is particularly important if the penalty for missing a disease is high. However, high specificity is particularly important if a false-positive result can harm the patient.

Calculation

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{TN} + \text{FP})$$

Positive and negative predictive values

In studies reporting the additional value of a test, only patients testing positive may receive follow-up with the reference standard. In this case the proportion of positive test results that were correct (positive predictive value (PPV)) was calculated. Where patients with discordant negative results also receive the reference standard, the proportion of negative test results that were correct (negative predictive value (NPV)) was calculated. PPV and NPV vary according to the prevalence of disease in the population.

Calculation

$$\text{Positive predictive value} = \text{TP}/(\text{TP} + \text{FP})$$

$$\text{Negative predictive value} = \text{TN}/(\text{TN} + \text{FN})$$

Likelihood ratio (LR)

The LR measures the probability of the test result in patients with the disease compared with those without the disease.

Calculation

Positive LR (LR+): the odds that a positive test result would be found in a patient with, versus without, a disease.

$$\text{LR}(+) = [\text{TP} / (\text{TP} + \text{FN})] / [\text{FP} / (\text{FP} + \text{TN})]$$

Negative LR (LR-): the odds that a negative test result would be found in a patient with, versus without, a disease.

$$\text{LR}(-) = [\text{FN} / (\text{TP} + \text{FN})] / [\text{TN} / (\text{FP} + \text{TN})]$$

Interpretation

- An LR of 1 indicates that the test does not provide any useful diagnostic information.
- Positive LRs >10 and negative LRs <0.1 can provide convincing evidence of diagnostic effectiveness.
- Positive LRs >5 and LRs <0.2 can provide strong evidence of diagnostic effectiveness.

However, the interpretation depends on the context in which the test is used.

Diagnostic yield

The diagnostic yield measures the proportion of capsule endoscopy tests in which an (apparent) positive result or diagnosis occurred. The number of positive results and negative results are not compared against a reference standard and hence the extent of false-positives and false-negatives is unknown.

Calculation

Diagnostic yield = Number of diagnoses/Number of tests performed.

Appraisal of the evidence

Appraisal of the evidence was conducted at three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the NHMRC (NHMRC 2000b; NHMRC 2009). These dimensions (see Table 13) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 13 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

* See Table 14.

Strength of the evidence

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (see Table 14).

Table 14 Designations of levels of evidence according to type of research question (including table notes) from NHMRC (2008; 2009).

Level	Intervention	Diagnostic accuracy
I	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A pseudo randomised controlled trial (ie alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none">• Non-randomised, experimental trial• Cohort study• Case-control study• Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none">• Historical control study• Two or more single arm study• Interrupted time series without a parallel control group	Diagnostic case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)

Table notes can be found in NHMRC (2008; 2009).

Quality

The quality of a study refers to the extent to which it has been designed and conducted to reduce bias in the estimation of the outcome. The potential sources of bias vary according to whether the study is designed to estimate the impact of the test on health outcomes (where the ideal is a randomised trial of alternative tests) or to estimate the diagnostic accuracy of the test (for which the ideal is cross-sectional analytic studies of consecutive patients tested using both the test of interest and a valid reference standard).

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC 2005), as shown in Table 15. The quality and applicability of all individual studies included in the review are appraised and the results presented in a table in the results section of the assessment report.

This appraisal included an assessment of:

- the availability of evidence from a direct comparison of the index test strategy and the existing test strategy
- the applicability of the evidence to the intended use of the index test
- the quality of the evidence.

Table 15 Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed and to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium Q3 poor reference standard/poor quality or insufficient information

Source: MSAC (2005)

A structured appraisal was performed to assess the quality of all included studies. The quality of studies of diagnostic accuracy was assessed against a checklist of 11 items adapted from the QUADAS (Quality Assessment of Studies of Diagnostic Accuracy Included in Meta-Analyses) tool developed by Whiting et al (2003) (see Table 16). This tool was developed by experts in the field following a systematic review of the evidence relating to sources of bias and variation relevant to studies of diagnostic test accuracy. Studies were required to meet all 11 criteria to be assessed as high quality (see details in footnote to Table 16). Only prospective diagnostic test accuracy studies were assessed as high quality. Studies that did not use a valid reference standard in all patients were classified as low quality. Studies that did not clearly define the suspected small bowel Crohn's disease patient population were rated as 'No' for Item 3 even if some inclusion and exclusion criteria were explicitly described.

Table 16 Criteria used to assess the quality of diagnostic accuracy studies – the QUADAS tool (Adapted from Whiting et al 2003)).

Item	Criteria
1	Were patients prospectively recruited?
2	Were patients consecutively recruited (ie a consecutive group of patients presenting with a defined clinical presentation)?
3	Were selection criteria explicitly described (ie in enough detail to clearly define eligibility of patients and to be reproducible)?
4	Is the reference standard likely to correctly classify the target condition (valid/invalid/optimal)?
5	Did all patients receive verification using a reference standard?
6	Is the time period between reference standard, comparator and index test short enough to be reasonably sure that the target condition did not change between the tests?
7	Were CE/comparator results interpreted blind to reference standard?
8	Were reference standard results interpreted blind to CE/comparator results?
9	Were the same clinical data, including conventional imaging, available when test results were interpreted as would be available when the test is used in practice?
10	Were uninterpretable/intermediate test results reported?
11	Were withdrawals from the study explained?

CE = capsule endoscopy

High quality: Yes to 1, 3, 4, 5, 9, 10; other items required to be either Yes or Unclear.

Poor quality: No/Unclear for 4, 5 or 6.

Other studies are assessed as fair quality.

Seven criteria were used to assess the quality of systematic reviews, as outlined in Table 17. For the criterion addressing heterogeneity, systematic reviews that did not undertake a meta-analysis were rated ‘not applicable’ (N/A), unless heterogeneity was specifically mentioned. Studies were required to meet all seven criteria to be assessed as high quality. A study with four or fewer ‘Yes’ or ‘N/A’ ratings was considered to be of low quality. Seven criteria were used to assess the quality of case series, as outlined in Table 17.

Table 17 Criteria used to assess the quality of effectiveness studies (adapted from NHMRC (2000a) and CRD (2009))

Study design	Quality checklist
Systematic review	<p>Was the research question specified?</p> <p>Was the search strategy explicit and comprehensive?</p> <p>Were the eligibility criteria explicit and appropriate?</p> <p>Was a quality assessment of included studies undertaken?</p> <p>Were the methods of the study appraisal reproducible?</p> <p>Were sources of heterogeneity explored?</p> <p>Was a summary of the main results clear and appropriate?</p>
Case series	<p>Was the study based on a representative sample selected from a relevant population?</p> <p>Were the criteria for inclusion and exclusion explicit?</p> <p>Did all subjects enter the survey at a similar point in their disease progression?</p> <p>Was follow-up long enough for important events to occur?</p> <p>Were the techniques used adequately described?</p> <p>Were outcomes assessed using objective criteria or was blinding used?</p> <p>If comparisons of subseries were made, was there sufficient description of the series and the distribution of prognostic factors?</p>

Criteria for appraising the quality of therapeutic impact studies were not available. Therefore a checklist was developed based on criteria discussed by Guyatt et al (1986) (see Table 18).

Potential sources of bias in therapeutic impact studies are described in Guyatt et al (1986). To minimise bias and maximise applicability of the results, studies should be conducted prospectively in a routine clinical setting using patient eligibility criteria that reflect the intended use of the test in practice and the target test population; document what proportion of consecutive eligible patients were included in the study and reasons for exclusion of eligible patients; include all patients enrolled in data analysis; include independent assessment of the influence of test results on reported treatment decisions; document actual treatment received for comparison with clinician-recorded planned treatment; and include an assessment of test accuracy per patient and adequate follow-up of included subjects to capture potential false-negatives.

Table 18 Criteria used to assess the quality of therapeutic impact studies (Adapted from Guyatt et al 1986)

Item	Criteria
1	Was the study designed and conducted prospectively?
2	Explicit eligibility criteria reflecting specific presentation or clinical problem?
3	Consecutive recruitment of all patients eligible for testing?
4	Referring clinician determining management plan?
5	Test accuracy documented concomitantly?
6	Pretest plan independently assessed?
7	Blinding to study test results at pretest measurement?
8	Association between management change and study test result independently assessed?
9	Management changes reported for specific test use and patient presentation?
10	Management changes reported in adequate detail (eg surgery avoided, additional investigations)?
11	Descriptive information about patient outcomes reported?
12	Physician experience reported?

Statistical precision

Statistical precision was determined using statistical principles. Small CIs and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000b). Studies need to be appropriately powered to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

It is important to assess whether statistically significant differences between the new test and its comparator(s) are also clinically important. The size of the effect needs to be determined, as well as whether the 95% CI includes only clinically important effects.

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000b).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2008; 2009). Five components are considered essential by the NHMRC when judging the body of evidence:

- the evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients;
- the consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction, ie homogenous or heterogenous findings;
- the potential clinical impact – appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
- the generalisability of the evidence to the target population; and
- the applicability of the evidence – integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 19) (NHMRC 2008; NHMRC 2009).

Table 19 Body of evidence assessment matrix

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base¹	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency²	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population ³	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

SR = systematic review; several = more than two studies

1 Level of evidence determined from the NHMRC evidence hierarchy – Table 14.

2 If there is only one study, rank this component as 'not applicable'.

3 For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

Source: NHMRC (2009)

Expert advice

An advisory panel with expertise in gastroenterology was established to provide guidance to the health technology assessors to ensure that the assessment is clinically relevant and takes into account consumer interests. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Capsule endoscopy

After applying the selection criteria outlined in Table 12 to the 1,222 non-duplicate citations retrieved from the search strategy, a total of 21 studies were identified for the review. These 21 studies consisted of 1 HTA, 2 systematic reviews, 15 primary studies and 3 economic studies. The included primary studies are listed in Table 20. In total, 5 of these studies were included in the assessment of diagnostic accuracy, 14 in the assessment of diagnostic yield and 14 in the safety assessment (see Figure 3).

Table 20 Relevant studies of capsule endoscopy included in the review

Study	Study design	Reviewed for assessment of		
		Efficacy (accuracy)	Efficacy (yield)	Safety
Albert et al (2005)	Prospective, consecutive diagnostic accuracy	✓	✓	✓
Casciani et al (2011)	Prospective, consecutive diagnostic accuracy	✓	✓	✓
Figueiredo et al (2010)	Retrospective diagnostic accuracy	✓	✓	✓
Girelli et al (2007)	Prospective, consecutive diagnostic accuracy	✓	✓	✓
Tukey et al (2009)	Retrospective diagnostic accuracy	✓	✓	✓
Chong et al (2005)	Prospective, non-consecutive blinded diagnostic yield		✓	✓
De Bona et al (2006)	Prospective, consecutive diagnostic yield		✓	✓
Efthymiou et al (2009)	Prospective, blinded diagnostic yield		✓	✓
Eliakim et al (2004)	Prospective, consecutive, blinded diagnostic yield		✓	✓
Ge et al (2004)	Prospective diagnostic yield		✓	✓
Guilhon de Araujo Sant'Anna et al (2005)	Prospective, non-consecutive diagnostic yield		✓	
Herrerias et al (2003)	Prospective diagnostic yield		✓	✓
Selby et al (2008) ¹	Prospective diagnostic yield		✓	✓
Valle et al (2006)	Prospective diagnostic yield		✓	✓
Cheifetz et al (2006)	Retrospective case series			✓

1. This unpublished study was supplied by the applicant and was sponsored by Given Imaging Pty Ltd.

Is it safe?

Studies that met the selection criteria in Table 12 were included in the safety assessment. Safety data for patients with suspected small bowel Crohn's disease were reported in 14 studies and these data are summarised in Table 21. All were non-comparative.

Table 21 Adverse events from capsule endoscopy for small bowel Crohn's disease

Study	Adverse events				Excluded strictures on prior radiology
	Adverse events %	Retention %	Surgery following retention %	Incomplete CE %	
Albert et al (2005)	nr	4.2% (1/24)	0.0% (0/1)	nr	✓
Casciani et al (2011)	nr	nr	nr	13.5% (5/37)	✓
Cheifetz et al (2006)	nr	1.6% (1/64)	100% (1/1)	nr	no
Chong et al (2005)	nr	0.0% (0/21)	N/A	19.0% (4/21)	✓
De Bona et al (2006)	0.0% (0/38)	2.6% (1/38)	100% (1/1)	2.6% (1/38)	no
Efthymiou et al (2009)	0.0% (0/26)	0.0% (0/26)	N/A	3.8% (1/26)	✓
Eliakim et al (2004)	0.0% (0/35)	0.0% (0/35)	N/A	nr	✓
Figueiredo et al (2010)	0.0% (0/78)	5.1% (4/78)	50.0% (2/4)	17.9% (14/78)	✓
Ge et al (2004)	0.0% (0/20)	15.0% (3/20)	nr	10.0% (2/20)	✓ Strictures on x-ray or history of obstruction
Girelli et al (2007)	0.0% (0/27)	11.1% (3/27)	66.7% (2/3)	14.8% (4/27)	Excl patients with intestinal obstruction
Herrerias et al (2003)	0.0% (0/21)	0.0% (0/21)	N/A	0.0% (0/21)	no
Selby et al (2008)	1.7% (2/120)	0.8% (1/120)	nr	12.5% (15/120)	✓
Tukey et al (2009)	nr	0.0% (0/102)	N/A	nr	no
Valle et al (2006)	nr	8.7% (2/23)	50.0% (1/2)	nr	Not a criterion, but reported that no patients had strictures revealed by SBFT

CE = capsule endoscopy, nr = not reported

1. Details of population characteristics, quality and applicability are found in Appendix D.
2. All of the safety results listed above apply to patients with suspected Crohn's disease, either because the entire study population consisted of patients with suspected Crohn's disease or because the results for the suspected Crohn's disease subgroup were reported separately.

Adverse events

Eight studies reported adverse events with seven of these reporting that no adverse events or complications occurred during or after the procedure. Six of these studies included less than 40 patients. In the unpublished study by Selby et al (2008), two moderate to severe adverse events were reported (2/120, 1.7%) – one patient had severe nausea with vomiting that was treated with anti-nausea medication, the other suffered from moderate pain. Both events were resolved within 24 hours (Selby et al 2008).

Adverse event reporting in the published literature was generally of a poor standard, with most studies reporting that no complications were observed during or after the

procedure without indicating what counted as a potential 'adverse event'. However the available data suggest that the use of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease has a similar adverse event profile to the use of this technology for the evaluation of OGIB in adult patients: adverse events are infrequent (1-2%), typically mild, and may include nausea, vomiting and pain (MSAC 2003).

Delayed passage

Delayed passage or non-passage of the capsule, usually associated with gastrointestinal strictures, are the most commonly reported and acknowledged risks of the procedure. These are not usually classified as adverse events because capsule retention involves a balance of possible harms (surgery, nausea, vomiting, pain), technical failures (incomplete visualisation of the small bowel) and benefits (the retention and/or the subsequent surgery may facilitate the diagnosis and/or treatment of pathological stenoses or other conditions).

Data concerning delayed passage or retention of the capsule were reported in 13 of the 14 studies included in the safety assessment. The rate of capsule retention reported in the included studies ranged from 0% to 15%.

Of the six included studies with data on capsule retention and surgical removal, 7 of 12 subjects with a retained capsule later had surgery at which the capsule was surgically removed.

The included studies did not always explicitly report whether such patients underwent surgery for the removal of the retained capsule, or instead had the capsule removed during surgery that was indicated for Crohn's disease or other conditions. However, it appears that of the 7 subjects in whom retained capsules were surgically removed, 5 underwent surgery for capsule removal and 2 had the retained capsule removed during surgery for other conditions (resection of a Crohn's disease stricture following recurrent small bowel obstructions which were suspected even before the capsule endoscopy was performed; and removal of a carcinoid tumour detected on capsule endoscopy).

Overall, there did not tend to be higher retentions in studies which failed to explicitly exclude patients with strictures on radiology, compared with studies that did. Small sample sizes and the possibility that studies excluded such subjects without reporting so explicitly may explain this result. However, the reported rates of capsule retention were highest in studies that excluded patients on the basis of known intestinal obstruction (current or prior) and/or strictures revealed by x-ray (15% [3/20] in Ge et al (2004) and 11% [3/27] in Girelli et al (2007)) as opposed to strictures revealed by other forms of small bowel radiology.

In comparison with the use of capsule endoscopy for the evaluation of OGIB in adult patients, the use of capsule endoscopy for the present indication appears to have a greater range of rates of capsule retention and a higher rate of surgical removal of retained capsules (MSAC 2003).

Comparative safety

Owing to the lack of identified comparative studies with safety data, an assessment of the safety of capsule endoscopy in comparison to empirical treatment, MR and/or CT was not undertaken. An overview of these safety considerations is presented in the discussion section 'Is it safe?' (page 73).

Summary of safety – Is capsule endoscopy safe?

No studies reported comparative safety data of capsule endoscopy against MR, CT or empirical treatment. Safety data for capsule endoscopy for patients with suspected small bowel Crohn's disease were reported in 14 studies.

Two moderate to severe adverse events associated with the use of capsule endoscopy were reported in one study. One patient had severe nausea with vomiting that was treated with anti-nausea medication (1/120, <1%), the other suffered from moderate pain (1/120, <1%). Both events were resolved within 24 hours. Seven other studies reported no adverse events associated with the use of capsule endoscopy for the diagnosis of patients with suspected small bowel Crohn's disease. Adverse events are likely to be similar, and occur at similar rates, as those reported for other indications (MSAC 2003).

Data concerning delayed passage or retention of the capsule were reported in 13 of the 14 studies included in the safety assessment. The rate of capsule retention reported in the included studies ranged from 0% to 15%. Most subjects who retained the capsule did not experience any symptoms as a result of the retention. In included studies where the rate of capsule retention and the rate of surgical removal were reported, 7 of 12 subjects who retained a capsule later had surgery at which the capsule was removed.

Capsule endoscopy for the diagnosis of small bowel Crohn's disease has a potentially higher rate of retention compared with other indications. It appears that this can be partially mitigated with prior screening for strictures but that excluding patients on the basis of known intestinal obstruction (or a history of obstruction) is insufficient.

Is it effective?

Studies that met the selection criteria in Table 12 were included in the effectiveness assessment. Effectiveness data were reported in 14 primary studies and these data are summarised in Appendix D.

Existing systematic reviews and HTA reports

A search for existing HTA reports and published systematic reviews on the use of capsule endoscopy for the diagnosis of small bowel Crohn's disease yielded one HTA report, one meta-analysis and one systematic review (Dionisio et al 2010; Poelmans et al 2006; Varela-Lema & Ruano-Ravina 2008). Five further HTAs were identified but excluded because their findings were superseded by Poelmans et al (2006) (MAS 2003; Mundy & Merlin 2003; NICE 2004) or because the full text English publication was unavailable (Hayes Inc 2008; Mueller et al 2004). Three further meta-analyses were identified but excluded because their findings were superseded by Dionisio et al (2010) (Leighton et al 2006; Marmo et al 2005; Triester et al 2006).

The characteristics and quality assessment of the included HTAs and systematic reviews are summarised in Table 22.

Dionisio (2010)

The objective of this meta-analysis was to evaluate the diagnostic yield of capsule endoscopy compared with other diagnostic modalities – small bowel barium radiography, CT enterography or enteroclysis, colonoscopy with ileoscopy, push enteroscopy and MRE – in patients with suspected or established Crohn's disease. The review did not provide data on the comparative diagnostic accuracy of capsule endoscopy and comparator modalities due to the absence of a reference standard. This meta-analysis is of limited applicability to the research question addressed by this report, primarily because the subjects were not required to have undergone the prior tests specified in the PPICO criteria for the present report. Only studies in adult patients were included. The meta-analysis by Dionisio et al (2010) was rated of fair quality due to the quality of included studies not being assessed or ranked explicitly, and because the summary of the main results was based on inappropriately pooled estimates of diagnostic yield (see below).

The meta-analysis was based on a systematic review of studies published up until May 2009; no language restrictions were applied and 19 eligible studies were included. The authors reported that most primary studies did not have a reference standard but that one used consensus-based clinical diagnosis. Capsule endoscopy was found to have a significantly higher weighted incremental diagnostic yield than CT (enterography or enteroclysis) (3 trials, n=53) (47% [95% CI = 31-63%], $P < 0.00001$). The weighted incremental yield of capsule endoscopy compared with MRE (3 trials, n=31) was 10% (95% CI = -14-34%) and non-significant ($P = 0.43$).

The report concluded that capsule endoscopy is superior to the comparators; however, the meta-analysis reports only on diagnostic yield and therefore cannot differentiate true-positives from false-positives; a higher diagnostic yield may not reflect greater accuracy. Furthermore, threshold variation due to the absence of an explicit test threshold was not explored across the studies and should have been a consideration prior to statistical

pooling. For these reasons, the pooled estimates of diagnostic yield are considered inappropriate measures of effect.

Varela-Lema and Ruano-Ravina (2008)

Varela-Lema and Ruano-Ravina (2008) summarise a systematic review undertaken for a HTA report available only in Spanish (Varela-Lema & Ruano-Ravina 2005). The objective was to assess the effectiveness, safety and clinical use of capsule endoscopy in the diagnosis of small bowel diseases, including suspected and established Crohn's disease. The applicability of this systematic review to the research question addressed by this report may be limited because suspected and established Crohn's disease were considered together and many studies used colonoscopy and ileoscopy as a comparator rather than, or as well as, a prior test. The systematic review by Varela-Lema and Ruano-Ravina (2008) was rated of fair quality due to the clinical question for review not being explicitly defined.

The review was based on a systematic search of studies published in English, Spanish, French, Italian and Portuguese between January 2003 and December 2005. Nine primary studies containing subjects with suspected and established Crohn's disease were included. Of these, the authors reported that three studies were of patients with 'primary suspicion of Crohn's disease'; however, the patient group in one of these studies consisted of patients with newly diagnosed Crohn's disease (Marmo et al 2005). Study quality was assessed using a purpose-built quality scale that measured validity and applicability (Varela-Lema & Ruano-Ravina 2006).

The authors reported data on comparative diagnostic accuracy from two studies; both of existing, rather than suspected, Crohn's disease. For patients with suspected Crohn's disease, the yield of suggestive findings ranged from 19% to 71% versus 0% to 37% for radiological techniques. The authors concluded that existing studies suggest that capsule endoscopy may occupy a preferential place in the diagnosis of Crohn's disease, but that there is insufficient evidence to establish if it should be used as a first line diagnostic test. In addition, they stated that capsule endoscopy is contraindicated in patients with stenosis (a particular limitation in established Crohn's disease) and does not allow precise localisation of the lesion. It was judged that existing studies that evaluate changes in patient management following capsule endoscopy report different results, and that additional studies are needed in order to assess changes to management as well as the clinical consequences of changes in management.

Poelmans et al (2006) (KCE)

The objective of the health technology assessment report by Federaal Kenniscentrum voor de Gezondheidszorg (Belgium Health Care Knowledge Centre – KCE) was to assess the clinical efficacy and economic effectiveness of capsule endoscopy compared with competing diagnostic modalities in small bowel diseases. Potential limitations to applicability include the fact that only one of the included primary studies pertained exclusively to subjects with suspected Crohn's disease and the fact that an explicit population, comparator and prior tests were not defined within the research question. Due to the breadth of the report's scope (small bowel diseases) and the inherent characteristics of the body of evidence included, issues regarding the sequence of tests, patient spectrum and absence of defined test thresholds may limit the applicability of the results to the indication considered in this review. The review was rated of fair quality due to the lack of explicit clinical questions and quality appraisals.

The report was based on a systematic review of studies up to October 2005 in English. Seven eligible studies using subjects with suspected and established Crohn's disease were included, including five primary studies, one systematic review and one HTA report. The authors reported that one of the included studies on the diagnosis of suspected Crohn's disease used the final diagnosis at 12 months follow-up as the reference standard but commented that the extent to which the final diagnosis was blinded to the results of previous tests, including capsule endoscopy, was unclear. The quality of studies was discussed qualitatively. The authors noted a number of issues that may have affected the quality of the included studies. These include small and heterogeneous populations, the possibility of false-positives which arises when diagnostic yield is used as the outcome measure, apparent absence of blinding, and the use of different timing between tests.

The authors reported comparative diagnostic accuracy data from one study but the majority of results concerned diagnostic yield, changes in patient management and adverse events. Against a reference standard of final diagnosis at 12 months, the sensitivity of capsule endoscopy was 92% (12/13 patients) and the specificity was 100% (10/10 patients). It was noted that these results may overestimate the diagnostic accuracy of capsule endoscopy due to the small patient numbers and the fact that it is unclear whether the reference test was blindly assessed. Based on five primary studies that included subjects with suspected and established Crohn's disease, capsule endoscopy was found to have a higher diagnostic yield than comparators in four of the studies and a similar diagnostic yield to SBFT in one study. The comparators included SBFT, push enteroscopy and enteroclysis, CT enteroclysis, and MRI and enteroclysis.

Poelmans et al (2006) concluded that the available evidence is of insufficient quality and quantity to determine the relative diagnostic performance of capsule endoscopy compared with conventional diagnostic tests for Crohn's disease and that no conclusions could be made regarding whether capsule endoscopy is an effective alternative to other tests.

Table 22 Characteristics and appraisal of included HTA reports and systematic reviews

Author (year) Country	Objective and methods	Included studies	Quality assessment of review
Dionisio et al (2010) USA Updates Triester et al (2006)	Objective: To evaluate the diagnostic yield of CE compared with other modalities in patients with suspected and established Crohn's disease (CD) Method: meta-analysis <i>Time period:</i> until May 2009 <i>Inclusion criteria:</i> adult patients, prospective trial comparing yield of CE with ≥1 comparator <i>Exclusion criteria:</i> duplicates, articles included in Triester et al (2006), reviews, retrospective studies, alternate indications, no comparative modality, case reports, letters <i>Outcomes:</i> weighted incremental diagnostic yield <i>Language:</i> All	Suspected and established Crohn's disease: 19 prospective studies.	Quality: FAIR Explicit review questions: yes Explicit & appropriate eligibility criteria: yes Explicit & comprehensive search strategy: yes Quality of included studies appraised: no Methods of study appraisal reproducible: N/A Heterogeneity between studies assessed: yes Summary of main results clear and appropriate: no
Varela-Lema & Ruano-Ravina (2008) Spain GAHTA	Objective: Assess the effectiveness, safety and clinical use of CE in the diagnosis of small bowel diseases. Method: systematic review. <i>Time period:</i> January 2003-December 2005 <i>Inclusion/exclusion criteria:</i> Inclusion: Original, published, peer-reviewed; prospective or retrospective diagnostic studies, SRs or meta-analyses; ≥20 patients for CD studies; ≥1 comparator; comparison test performed within 6 months of CE; reports on yield, accuracy, safety, reliability or clinical management <i>Outcomes:</i> diagnostic accuracy (sn, sp, PPV, NPV) diagnostic yield, change in management., adverse events <i>Language:</i> English, Spanish, French, Italian, Portuguese	Suspected and established Crohn's disease: 9 studies Small bowel diseases in general: 9 systematic reviews	Quality: FAIR Explicit review questions: no Explicit & appropriate eligibility criteria: yes Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: yes
Poelmans et al (2006) Belgium KCE	Objective: To assess the clinical efficacy and economic effectiveness of CE compared with competing diagnostic modalities in small bowel diseases. Method: HTA and SR <i>Time period:</i> to June 2005 (CRD) and to October 2005 (MEDLINE) <i>Inclusion/exclusion criteria:</i> <u>Primary studies</u> Inclusion: prospective and comparative studies reporting on the diagnostic performance of CE and not in existing HTAs and SRs; intervention is CE report on at least one of the following outcomes – diagnostic yield, diagnostic accuracy, impact on patient management or patient outcome in terms of morbidity or mortality, homogeneous patient populations, English language, published full papers Exclusion: abstracts, editorials, proceedings <u>Systematic reviews</u> Inclusion: relevant to the indication Exclusion: paper which include all studies and findings present in a previous HTA report or systematic review <i>Outcomes:</i> diagnostic yield, diagnostic accuracy, therapeutic impact, adverse events <i>Language:</i> English, full papers	Suspected and established Crohn's disease: 7 studies (5 prospective and comparative primary studies, 1 systematic review, 1 HTA).	Quality: FAIR Explicit review questions: no Explicit & appropriate eligibility criteria: yes Explicit & comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: no Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: yes

Abbreviations: CE= capsule endoscopy, CD = Crohn's disease, SR = systematic review, HTA = health technology assessment, sn = sensitivity, sp = specificity, PPV = positive predictive value, NPV = negative predictive value

Direct evidence

The current review did not identify any studies comparing the health outcomes of symptomatic patients with suspected but unconfirmed small bowel Crohn's disease, assessed with and without capsule endoscopy. In the absence of direct evidence for the effectiveness of capsule endoscopy, evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes is presented in order to draw conclusions about the effectiveness of capsule endoscopy using a linked evidence approach.

Indirect evidence

Technical issues affecting test performance

Incomplete capsule endoscopy

Incomplete visualisation of the small bowel may occur for a number of reasons such as failure of the capsule to reach the caecum during the battery life; failure to transmit images due to workstation malfunction; footage that is missing or obscured due to bowel contents; and battery malfunction (Schnoll-Sussman & Kulkarni 2008). Incomplete capsule endoscopy can sometimes be diagnostic despite being incomplete, and is not always caused by a retained capsule.

Data concerning rates of incomplete capsule endoscopy due to failure to reach the caecum during the battery life were reported in 9 of the 14 studies included in the safety assessment (see Table 21, page 47). The rate of incomplete capsule endoscopies reported in the included studies ranged from 0% (0/21) to 19% (4/21). Eight of the nine studies that reported rates of incomplete capsule endoscopy defined this as failure to reach the caecum during the battery life whereas the rate from Selby et al (2008) includes workstation malfunctions (4/120) as well as failure to reach the caecum (11/120).

Is it accurate?

Study characteristics and appraisal

The systematic review identified five primary studies that investigated the diagnostic accuracy of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease (Albert et al 2005; Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007; Tukey et al 2009). The characteristics and the appraisal of the quality and applicability of the included accuracy studies are summarised in Table 23; full detail of all included studies is presented in the data extraction tables in Appendix D.

All of the included diagnostic accuracy studies provided level III-2 evidence and were of either poor or fair quality. All included studies had limited applicability (P2) owing to differences in prior tests and in the selection criteria for patients with suspected small bowel Crohn's disease. Two studies presented results on the comparative accuracy of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease relative to MR with (Casciani et al 2011) or without (Albert et al 2005) enterography. The remaining studies presented results on the accuracy of capsule endoscopy without any comparators and therefore provided the basis for a comparison of capsule endoscopy and empirical treatment (capsule endoscopy as an incremental test over prior tests). All included studies used the diagnosis obtained at long-term follow-up (>12 months) as the reference

standard. Histology was at least partially incorporated into the reference standards used by three studies (Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007).

All diagnostic accuracy studies enrolled a predominantly adult patient with the exception of Casciani et al (2011) which enrolled a younger population (average age 14 years, range 6 to 18 years). All studies enrolled patients with suspected small bowel Crohn's disease. Prior tests varied across the five included studies (see Table 23 and Table 24). Only one study explicitly reported that all enrolled patients had negative or equivocal prior colonoscopy with ileoscopy and small bowel radiology (Tukey et al 2009), as required by the clinical flow chart (page 1). The patients in the other four included studies did not: in two studies, patients underwent prior small bowel radiology and colonoscopy with ileoscopy but patients who tested positive for Crohn's disease on these prior tests were not explicitly excluded (Albert et al 2005; Casciani et al 2011); in one study most patients had prior negative or equivocal tests (Figueiredo et al 2010); and in one study patients had prior negative or equivocal small bowel radiology and colonoscopy, but the colonoscopy was only performed up to the caecum (Girelli et al 2007). Two studies excluded patients on the basis of previous intake of nonsteroidal anti-inflammatory drugs (NSAIDs) (Figueiredo et al 2010; Girelli et al 2007) whereas this was not a reported exclusion criteria for the other studies. Four of the five studies excluded patients who had suspected or known strictures or stenosis (defined in various ways) whereas one study (Tukey et al 2009) did not report whether patients of this type had been excluded. Three studies explicitly reported the number of lesions required for a diagnosis of Crohn's disease (Casciani et al 2011; Girelli et al 2007; Tukey et al 2009).

Table 23 Characteristics and appraisal of included accuracy studies

Author (year) Setting Time period	N	Test comparison	Population	Study design	Quality and applicability
Figueiredo et al (2010) Portugal Single centre 1/01-12/07	78	CE	<ul style="list-style-type: none"> Patients with clinically suspected CD Mean age 37 years, 68% female Prior tests: C+IL (either negative for CD or failed ileoscopy), blood tests, some patients had SBFT, CT or enteroclysis 	Study design: Retrospective Reference standard: Diagnosis at follow-up. Outcomes: Accuracy, diagnostic yield, safety	NHMRC level of evidence: III-2 Comparison: CX: ET Applicability: P2 Quality: POOR
Albert et al (2005) Germany Single centre 5/02-12/03	25	CE compared with MRI and SBE	<ul style="list-style-type: none"> Patients with newly suspected CD in which the work-up did not establish a diagnosis other than CD Mean age 37 years (m) or 40 years (f), 75% female Prior tests: AU, E, C+IL, MS, UE (not necessarily negative for CD) 	Study design: Prospective, consecutive Reference standard: Combined diagnostic endpoint of all imaging methods and diagnosis at follow-up Outcomes: Accuracy, diagnostic yield, safety	NHMRC level of evidence: III-2 Comparison: C1: MRI, CX: ET Applicability: P2 Quality: POOR
Casciani et al (2011) Italy Single centre 1/09-12/09	60	CE compared with MRE	<ul style="list-style-type: none"> Paediatric patients with suspected CD (≥ 1 symptom and one biochemical sign of systemic inflammation) Mean age 14 years, 40% female Prior tests: C+IL (not necessarily negative for CD), EGD, +ve blood tests or inflammatory markers 	Study design: Prospective, consecutive Reference standard: Diagnosis at follow-up Outcomes: Accuracy, diagnostic yield, complete CE/capsule reached the caecum, capsule reached the distal ileum.	NHMRC level of evidence: III-2 Comparison: C1: MRE, CX: ET Applicability: P2 Quality: FAIR
Girelli et al (2007) Italy Single centre 4/02-3/05	27	CE	<ul style="list-style-type: none"> Patients with suspected small bowel CD referred for symptoms (continuous or recurrent abdominal pain, diarrhoea ≥ 3 months plus extra symptom/s) Mean age 40 years, 48% female Prior tests: Colonoscopy up to the caecum, stool cultures, blood tests, SBS/AU/CT (diagnosis of CD either unconfirmed or equivocal for all tests) 	Study design: Prospective, consecutive Reference standard: Final diagnosis at LTFU Outcomes: Accuracy, diagnostic yield, failure to reach caecum, surgical retention/therapy following capsule retention	NHMRC level of evidence: III-2 Comparison: CX: ET Applicability: P2 Quality: FAIR
Tukey et al (2009) USA Single centre Up to 5/07	105	CE	<ul style="list-style-type: none"> Adult patients evaluated by CE for suspected CD with normal or equivocal prior investigations Mean age 50 years, 66% female Prior tests: C+IL, SBFT or CT (all tests negative or equivocal for CD) 	Study design: Retrospective Reference standard: Diagnosis at follow-up Outcomes: Accuracy, diagnostic yield incomplete CE	NHMRC level of evidence: III-2 Comparison: CX: ET Applicability: P2 Quality: FAIR

Abbreviations: AU = abdominal ultrasound, CE = capsule endoscopy, CD = Crohn's disease, C+IL = colonoscopy with attempted ileoscopy, CT = computed tomography, E= endoscopy, EGD = oesophagogastroduodenoscopy, ET = empirical treatment, LTFU= long-term follow-up, MS = microbiological stool tests, MRE = magnetic resonance imaging with enterography, MRI = magnetic resonance imaging, SBE = small bowel enteroclysis (double contrast small bowel fluoroscopy), SBFT = small bowel follow-through, SBS = small bowel series, UE = upper endoscopy

Diagnostic accuracy results

The results of studies reporting the accuracy of capsule endoscopy for suspected small bowel Crohn's disease are presented in Table 24.

Capsule endoscopy versus ET

The five included studies that reported on the diagnostic accuracy of capsule endoscopy provided the basis for a comparison of capsule endoscopy and empirical treatment (Albert et al 2005; Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007; Tukey et al 2009).

In the four studies reporting results using a threshold of at least ≥ 2 ulcers or Crohn's disease specific lesions, the sensitivity of capsule endoscopy ranged from 47% (95% CI 22-73%) to 92% (95% CI 62-100%) and the specificity ranged from 89% (95% CI 81-94%) to 100% (95% CI 72-100%). The TN:FN ratio ranged from 1.4:1 to 26.3:1 (Albert et al 2005; Casciani et al 2011; Girelli et al 2007; Tukey et al 2009). Two of the studies reported negative LRs which are considered convincing evidence for excluding disease (0.08 and 0.09) and two reported a negative LR which is considered as providing little evidence for excluding disease (0.26 and 0.58).

For the less stringent threshold of any small bowel ulcers, reported in four studies, the sensitivity of capsule endoscopy ranged from 85% (95% CI 58-96%) to 100% (95% CI 72-100%) and the specificity ranged from 74% (95% CI 64-82%) to 92% (95% CI 73-99%). The TN:FN ratio was between 10:1 and 33:1. The negative LR was considered convincing in three studies (0, 0.08, 0.08) and borderline strong evidence in another (0.21).

Capsule endoscopy versus MRI and MRE

Two included studies provided head-to-head comparisons of capsule endoscopy and MR – with (Casciani et al 2011) and without (Albert et al 2005) enterography. The study by Casciani et al (2011) reported diagnostic accuracy results for two different capsule endoscopy test thresholds: >3 small bowel ulcers and 'any small bowel ulcers'. For the threshold of >3 small bowel ulcers sensitivity for capsule endoscopy versus MRE was 91% (95% CI 57-100%) versus 100% (95% CI 82-100%) and specificity was 100% (95% CI 87-100%) versus 98% (87-100%). For the threshold of any small bowel ulcers sensitivity for capsule endoscopy versus MRE was 100% (95% CI 72-100%) versus 100% (95% CI 82-100%) and specificity was 92% (95% CI 73-99%) versus 98% (95% CI 87-100%) (Casciani et al 2011). In the study by Albert et al (2005), sensitivity for capsule endoscopy versus MRI was 92% (95% CI 62-100%) versus 71% (95% CI 42-90%). Specificity for capsule endoscopy versus MRI was 100% (95% CI 72-100%) versus 80% (95% CI 44-96%).

The patients in the study by Casciani et al (2011) were aged between 6 and 18 and the reported accuracy of MRE in their study is high compared with previous studies. The superior accuracy of MRE reported by Casciani (2011) compared with Albert et al (2005) may be partially attributed to the use of enterography in the former study.

Capsule endoscopy versus CT

This review did not identify any studies comparing the diagnostic accuracy of capsule endoscopy and CT (with or without enterography) for suspected but unconfirmed small bowel Crohn's disease.

Summary

Five included studies provided evidence for a comparison of capsule endoscopy and empirical treatment (Albert et al 2005; Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007; Tukey et al 2009). In studies using a threshold of at least ≥ 2 ulcers or Crohn's disease specific lesions, the sensitivity of capsule endoscopy ranged from 47% (95% CI 22-73%) to 92% (95% CI 62-100%) and the specificity ranged from 89% (95% CI 8-94%) to 100% (95% CI 72-100%). The negative LR ranged from 0.08 to 0.58 (Albert et al 2005; Casciani et al 2011; Girelli et al 2007; Tukey et al 2009). For the threshold of any small bowel ulcers, the sensitivity of capsule endoscopy ranged from 85% (95% CI 58-96%) to 100% (95% CI 72-100%) and the specificity ranged from 74% (95% CI 64-82%) to 92% (95% CI 73-99%). The negative LR ranged from 0 to 0.21 (Casciani et al 2011; Figueiredo et al 2010; Girelli et al 2007; Tukey et al 2009). Overall, most studies had negative LRs < 0.10 , the threshold for providing convincing evidence to exclude disease; however, two studies had negative LRs which were above the negative LR threshold for providing strong evidence for excluding disease < 0.20 . This included the largest and most applicable study which had a negative LR > 0.20 at both thresholds.

Two included studies comparing capsule endoscopy and MRI or MRE (Albert et al 2005; Casciani et al 2011) found that capsule endoscopy and MRE have similar comparative accuracy and that capsule endoscopy is more accurate than MRI without enterography. Using a threshold of > 3 small bowel ulcers, the sensitivity of capsule endoscopy versus MRE was 91% (95% CI 57-100%) versus 100% (95% CI 82-100%) and the specificity was 100% (95% CI 87-100%) versus 98% (95% CI 87-100%). Using a threshold of any small bowel ulcers, capsule endoscopy and MRE had similar sensitivity (100% [95% CI 72-100%] versus 100% [95% CI 82-100%]) and specificity (92% [95% CI 73-99%] versus 98% [95% CI 87-100%]). On this basis, capsule endoscopy is considered likely to have at least comparable accuracy to MR.

No studies were included that compared the diagnostic accuracy of capsule endoscopy and CT (with or without enterography).

Table 24 Diagnostic accuracy of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease

Author (year)	N/pts [§]	-ve C+IL [°]	-ve SBR [°]	Sensitivity % (95% CI)		Specificity % (95% CI)		LR+		LR-		TP:FP		TN:FN	
				CE	Comparator	CE	Comparator	CE	Comparator	CE	Comparator	CE	Comparator	CE	Comparator
CE versus MR															
<i>>3 small bowel ulcers</i>															
Casciani et al 2010 – MRE	37 (60)	Unclear		91(57-100)	100(82-100)	100(87-100)	98(87-100)	nd	41.00	0.09	0.00	10:0	19:1	26:1	40:0
<i>≥2 ulcers or Crohn's specific lesions</i>															
Albert et al 2005 [†] – MRI	24 (24)	×	×	92(62-100)	71(42-90)	100(72-100)	80(44-96)	nd	3.57	0.08	0.36	12:0	5:1	11:1	2:1
<i>Any small bowel ulcers</i>															
Casciani et al 2010 – MRE	37 (60)	Unclear		100(72-100)	100(82-100)	92(73-99)	98(87-100)	13.00	41.00	0.00	0.00	5.5:1	19:1	24:0	40:0
				Sensitivity%	Specificity%	Prevalence	CE additional								
				(95% CI)	(95% CI)	CD %	Negatives	TN	FN	TN:FN	LR-				
CE															
<i>≥2 ulcers or Crohn's specific lesions</i>															
Albert et al 2005 [†]	24	×	×	92(62-100)	100(72-100)	54	12	11	1	11:1	0.08				
Casciani et al 2010	37	Unclear		91(57-100)	100(87-100)	30	27	26	1	26:1	0.09				
Girelli et al 2007	27	×	✓	47(22-73)	92(60-100)	56	19	11	8	1.4:1	0.58				
Tukey et al 2009	102	✓	✓	77(50-92)	89(81-94)	13	82	79	3	26.3:1	0.26				
<i>Any small bowel lesions/ulcers</i>															
Casciani et al 2010	37	Unclear		100(72-100)	92(73-99)	30	24	24	0	24:0	0.00				
Figueiredo et al 2010	72	✓	Unclear	94(79-98)	80(66-90)	43	35	33	2	16.5:1	0.08				
Figueiredo et al 2010 [‡]	43	✓	Unclear	96(77-100)	86(63-96)	51	19	18	1	18:1	0.05				
Girelli et al 2007	27	×	✓	93(66-100)	83(51-97)	56	11	10	1	10:1	0.08				
Tukey et al 2009	102	✓	✓	85(58-96)	74(64-82)	13	68	66	2	33:1	0.21				

[†] Patients did have prior tests (including C+IL) but those receiving a diagnosis of Crohn's disease on prior tests were not excluded. [‡] In patients for whom retrograde ileoscopy was achieved and negative.

[§] N(N) = total patients included in 2x2 table for CE (total patients in 2x2 table for comparator). [°]Diagnosis of Crohn's disease unconfirmed by colonoscopy and attempted ileoscopy (C+IL) or small bowel radiology (SBR). A rating of × indicates patients did not receive a negative result on the test listed in the column (C+IL or SBR) (test was not performed or the test was performed but patients with a positive result were not necessarily excluded). A rating of ✓ indicates that patients received a negative result on the test listed. A rating of unclear indicates that the reporting was insufficient to determine whether patients received a negative result on the prior tests.

Abbreviations: nd=not defined, CE = capsule endoscopy, MR = magnetic resonance imaging or magnetic resonance enterography, MRI = magnetic resonance imaging without enterography, MRE = magnetic resonance imaging with enterography, C+IL = colonoscopy plus attempted ileoscopy, SBR = small bowel radiology, CD = Crohn's disease, CI = confidence interval, TN = true-negative, FN = false-negative, TP = true-positive, FP = false-positive

Diagnostic yield

Fourteen studies were identified that assessed the diagnostic yield of capsule endoscopy. Most of the 14 studies that reported diagnostic yield of capsule endoscopy were of poor quality (11 poor, 3 fair) and of limited applicability (11 limited, 3 applicable). Eleven of 14 included studies reported the diagnostic yield of capsule endoscopy for <40 subjects with suspected Crohn's disease; 8 of 14 reported it for <30 subjects with suspected Crohn's disease.

Full details of all included studies are presented in the data extraction tables in Appendix D. As no accuracy studies were identified which directly compared capsule endoscopy with CT, Table 25 summarises the results of all included diagnostic yield studies that provided a direct comparison of the yield of capsule endoscopy with CT (with or without enterography).

Table 25 Comparative diagnostic yield of CE for the diagnosis of suspected small bowel Crohn's disease

Author (year)	n pts [§]	-ve	-ve	Yield% (95% CI)		Quality	Applicability	Level
		C+IL [°]	SBR [°]	CE	Comparator			
CE versus CT								
<i>Any CD small bowel lesions/ulcers</i>								
Figueiredo et al 2010 [‡] – CT	78(37)	✓	Unclear	47(37-58)	38(23-55)	POOR	Limited	III-2
<i>Explained referral</i>								
Eliakim et al 2004 – CTE	35(35)	✓	✓	77(59-89)	20(raw data nr)	POOR	No/Limited	IV

[‡] CT was not a comparator in this study however yield data were provided for 37 patients who underwent CT. Threshold for a positive CT result is unknown.

[§] n = number of patients who underwent CE; (n) = number of patients who underwent CT.

[°] A rating of ✓ indicates that a diagnosis of Crohn's disease unconfirmed by colonoscopy and attempted ileoscopy (C+IL) or small bowel radiology (SBR). A rating of unclear indicates that this was not clearly reported in the study.

Abbreviations: CE = capsule endoscopy, CT = computed tomography with or without enterography, CTE = computed tomography with enterography, C+IL = colonoscopy plus attempted ileoscopy, SBR = small bowel radiology, CD = Crohn's disease, CI = confidence interval

Capsule endoscopy versus CT

One included study provided a direct comparison of the diagnostic yield of capsule endoscopy with CT enterography (Eliakim et al 2004). One study, in which CT was not an explicit comparator, provided data on the yield of CT in 37 of the 78 patients enrolled in the study (Figueiredo et al 2010). Both of these studies reported that capsule endoscopy had a higher diagnostic yield than CT (see Table 25) although Figueiredo (2010) reported similar yields for each test.

Does it change patient management?

No studies reporting on changes in patient management were identified in the systematic literature review.

Does change in management improve patient outcomes?

Capsule endoscopy versus empirical treatment

In patients who are treated empirically, all patients undergo drug treatment for Crohn's disease. In this subgroup of patients, the main role of capsule endoscopy is to exclude those patients who do not have Crohn's disease so that they are not treated unnecessarily. Therefore, a change in management is only expected in those patients who test negative on capsule endoscopy. In the assessment of capsule endoscopy as an

incremental test over prior tests, a case for improved patient outcomes using a linked evidence approach depends on three pieces of evidence: evidence that capsule endoscopy accurately excludes disease; that this test result leads to an avoidance of treatment; and that this change in management results in improved patient outcomes.

A case for improved management could not be established due to the uncertainty that affected each of the three constituents of a potential linked evidence case. Firstly, the discriminatory ability of capsule endoscopy to exclude Crohn's disease remains uncertain because the accuracy data in the present review were variable, and were derived from studies of poor to fair quality and of limited applicability. Although in several smaller studies, the negative LRs provided convincing evidence of the ability of capsule endoscopy to exclude Crohn's disease, in the largest and most applicable study, the negative LR failed to meet this threshold.

Secondly, the extent to which excluding Crohn's disease by using capsule endoscopy as an incremental test over prior tests would affect patient management is uncertain. No studies were identified which demonstrated changes in patient management (including the avoidance of planned treatment) due to capsule endoscopy results. The proportion of patients who would receive empirical treatment despite a negative capsule endoscopy result is therefore uncertain. Thirdly, it is uncertain whether a change in management would result in improved patient outcomes due to uncertainty regarding the balance of trade-offs between the benefits (avoiding side-effects) and harms (avoiding potential symptom alleviation) of avoiding empirical treatment on the basis of a negative capsule endoscopy result.

With variable accuracy data on the discriminatory ability of capsule endoscopy to exclude disease, no studies identified on change in management, and uncertainties about the nature of the empirical treatment patient pathway and its harms and benefits, a linked evidence case for improved patient outcomes when capsule endoscopy is used as an incremental test over prior tests cannot be made.

Capsule endoscopy versus MRI/MRE

When patients are treated with either MRI/MRE or CE, the main role of each test is to provide the best discrimination of true disease status. Only two small studies, of poor and fair quality respectively, were identified in the systematic review and confidence intervals for sensitivity and specificity between the two tests were wide and overlapping. In the absence of evidence of either improved accuracy or change in management, a linked evidence case for improved patient outcomes cannot be made.

Summary

Accuracy

Capsule endoscopy versus ET

- Three fair quality studies and two poor quality studies provided evidence for a comparison of the accuracy of CE and empirical treatment (CE as incremental over prior tests).
- In four studies with a threshold of at least ≥ 2 ulcers or Crohn's specific lesions, the sensitivity of CE ranged from 47% (95% CI 22-73%) to 92% (95% CI 62-100%) and the specificity ranged from 89% (95% CI 81-94%) to 100% (95% CI 72-100%). The negative LR ranged from 0.08 to 0.58.
- In four studies that used the threshold of any small bowel ulcers, the sensitivity of CE ranged from 85% (95% CI 58-96%) to 100% (95% CI 72-100%) and the specificity ranged from 74% (95% CI 64-82%) to 92% (95% CI 73-99%). The negative LR ranged from 0 to 0.21. Overall, most studies had negative LRs < 0.10 , the threshold for providing convincing evidence to exclude disease; however, two studies had negative LRs which were above the negative LR threshold for providing strong evidence for excluding disease < 0.20 . This included the largest and most applicable study which had a negative LR > 0.20 at both thresholds.

Capsule endoscopy versus MRI and MRE

- One fair quality and one poor quality study comparing CE versus MRE or MRI found that CE has similar accuracy to MRE and greater accuracy than MRI. On this basis, CE is likely to have at least comparable accuracy to MR.
- Using a threshold of > 3 small bowel ulcers, the sensitivity of CE versus MRE was 91% (95% CI 57-100%) versus 100% (95% CI 82-100%) and the specificity was 100% (95% CI 87-100%) versus 98% (87-100%).
- Using a threshold of any small bowel ulcers, CE and MRE had similar sensitivity (100% [95% CI 72-100%] versus 100% [95% CI 82-100%]) and specificity (92% [95% CI 73-99%] versus 98% [95% CI 87-100%]).

Capsule endoscopy versus CT and CTE

The systematic review did not yield any studies comparing the accuracy of CE and CT (or CTE) for diagnosing suspected small bowel Crohn's disease.

Change in management

No studies investigating the therapeutic impact of CE in patients with suspected small bowel Crohn's disease were identified.

Patient outcomes

A linked evidence case for an improvement of patient outcomes due to CE in this indication cannot be made.

Abbreviations: CE = capsule endoscopy, CI = confidence interval, CT = computed tomography, CTE = computed tomography enterography, ET = empirical treatment, LR = likelihood ratio, MRE = magnetic resonance enterography, MRI = magnetic resonance imaging without enterography,

Other relevant considerations

Ongoing clinical trials

A search of the clinical trials registries identified one clinical trial in Denmark which evaluates the comparative accuracy of three diagnostic methods – MRE, CTE and capsule endoscopy – for assessing small bowel disease in patients with suspected or known Crohn’s disease against the reference standard of ileoscopy and/or surgery. This trial is summarised in Appendix F. A forthcoming publication from this trial (Jensen et al 2011), identified after completion of the systematic literature review described previously, reports that this study includes 93 patients with suspected or newly diagnosed Crohn’s disease who underwent MRE, CTE, and, if no stenosis was detected, capsule endoscopy. The sensitivity and specificity for the diagnosis of Crohn’s disease of the terminal ileum only was 100% (95% CI = 79-100%) and 91% (95% CI = 79-97%) for capsule endoscopy (n=69), 81% (58-95%) and 86% (74-94%) for MRE (n=72) and 76% (95% CI = 53-92%) and 85% (95% CI = 72-93%) for CTE (n=73). In 80 patients who underwent all modalities, capsule endoscopy detected 18 positive Crohn’s disease results in the proximal small bowel, compared with 2 and 6 diagnoses detected by MRE or CTE (P<0.05). It is unknown whether these were true- or false-positives. The applicability of these results to the present review is limited because the patient population was not restricted to those that tested negative on prior colonoscopy with ileoscopy and small bowel radiology and because it included newly diagnosed Crohn’s disease patients. The use of a less highly selected population is expected to result in higher diagnostic accuracy for all tests than would be found in a setting where the use of the test is restricted to patients with suspected Crohn’s disease that are undiagnosed on prior tests.

Expert opinion

It is the opinion of the majority of members of the Advisory Panel that capsule endoscopy for the diagnosis of small bowel Crohn’s disease may lead to benefits that are not evident from the limited available data. Expert opinion suggested that in clinical practice there are a small number of patients for whom it is very difficult to reach a diagnosis of Crohn’s disease. It is the view of the Advisory Panel that approximately half of such patients can be diagnosed with Crohn’s disease via other capsule endoscopy indications already funded through the MBS (such as OGIB). However, this is not the case for some of these patients in whom the use of capsule endoscopy for the indication of suspected small bowel Crohn’s disease may be the only way to confirm the diagnosis.

Expert opinion also suggested that around half of new diagnoses of Crohn’s disease currently made via capsule endoscopy occur in patients who are being evaluated for OGIB. Based on available data, the utilisation of capsule endoscopy for the diagnosis of small bowel Crohn’s disease that was unconfirmed on prior tests was estimated to lie between 664 and 1,431 per year (see page 23).

What are the economic considerations?

The economic considerations appropriate to this application are twofold:

1. Assessment of the value for money associated with the introduction of capsule endoscopy (economic evaluation).
2. Estimation of the financial implications of the introduction of capsule endoscopy for the MBS and society (including costs to MBS and patient copayments).

Economic evaluation

Economic evaluation is important in order to understand both the costs and consequences of introducing a new diagnostic test for the diagnosis of suspected small bowel Crohn's disease. The introduction of a new diagnostic test may be costly, and it is important to ensure that where public funds are limited, those tests which represent the best value for money are identified (Drummond et al 2005). In an economic evaluation, alternative options (ie diagnostic tests or patient pathways) are compared in terms of their costs and consequences. The most widely used type of economic evaluation is the cost-effectiveness analysis (CEA). In a CEA, consequences are measured in natural or physical units, for example detected cases of Crohn's disease or life years gained. A cost-utility analysis (CUA) is a specific form of CEA in which the effect of healthcare technologies on life expectancy and health-related quality of life (HRQoL) are combined. The most common outcome measure for a CUA is the quality-adjusted life year (QALY). A CUA is considered the gold standard for economic evaluations because it allows the direct comparison of the relative health benefits of healthcare technologies across different disease areas and populations and therefore facilitates resource allocation decisions (Drummond et al 2005; Gold et al 1996).

To the extent that data allow, a decision-analytic model can be used to synthesise data on costs and consequences obtained from various sources, such as the literature, primary data collected and expert opinion, to estimate the cost-effectiveness or cost per QALY of the new diagnostic test compared to conventional approaches (Briggs et al 2006). In the context of economic evaluation, a decision-analytic model uses mathematical relationships to define a series of possible consequences that would follow from a set of alternative options being evaluated. A key purpose of decision-analytic modelling is to allow for the variability and uncertainty associated with all decisions. Nevertheless, the quality of the model is highly dependent on the quality of information used to populate the model. A comparison of costs and an array of health outcomes or consequences of the new diagnostic test and its comparators may be the preferable approach when accuracy data or data on health outcomes are inadequate to populate the decision model.

Published economic literature

Three economic analyses in the international literature were identified as part of the current review. All three studies used decision-analytic modelling techniques to explore either the costs or cost-effectiveness of imaging strategies for diagnosing Crohn's disease in the United States.

Goldfarb et al (2004) constructed decision models to explore the costs of diagnosing Crohn's disease using capsule endoscopy compared to other diagnostic methods (eg SBFT, enteroclysis, colonoscopy, computed tomography, MRI). A payer perspective was adopted, only including direct medical costs for diagnostic testing. The model estimated that the net saving of using capsule endoscopy was US\$291 per case initially presenting for work-up. As long as the diagnostic yield for capsule endoscopy was 64% or greater, capsule endoscopy was the lower cost diagnostic option regardless of the diagnostic yield of SBFT and colonoscopy. The study arms in Goldfarb's study do not reflect the clinical flow chart (page 1) that a radiologic study needs to rule out the presence of a stricture prior to the use of capsule endoscopy. Hence, their conclusions that capsule endoscopy produces a cost saving in the diagnostic work-up should be regarded with caution since it does not reflect the Australian real-life clinical situation.

A more recent cost-effectiveness study by Levesque et al (2010) took these issues into account and studied capsule endoscopy as a third line test (after the failure of ileocolonoscopy followed by CTE or SBFT to establish a diagnosis). They developed a decision-analytic model to compare the lifetime costs and benefits of CTE versus SBFT and to test whether adding capsule endoscopy as a third test in patients in whom a high suspicion of disease remains after a negative ileocolonoscopy and follow-up SBFT is cost-effective. Effectiveness was measured in QALYs gained. The addition of capsule endoscopy after ileocolonoscopy and negative CTE or SBFT was estimated to cost more than \$500,000 per QALY gained in all tested scenarios. Capsule endoscopy was deemed too expensive even in patients with a high pretest probability (75%) of having Crohn's disease, due to the poor accuracy of capsule endoscopy. Of note, the lifetime radiation risk with CTE and SBFT was not modelled in this analysis.

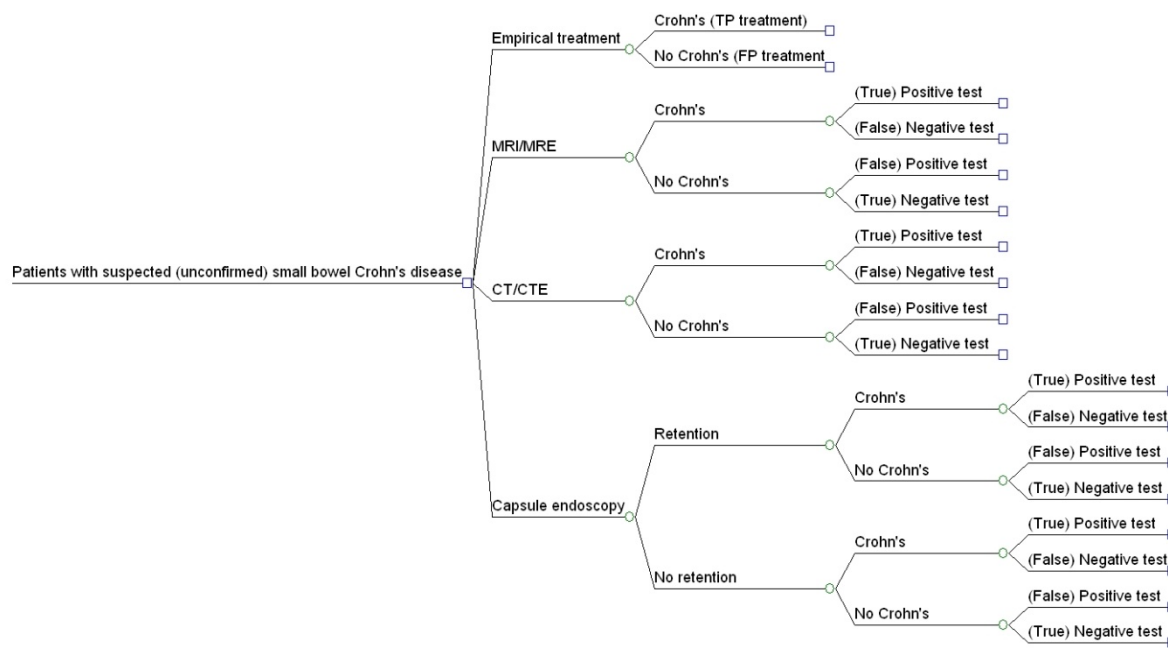
Leighton et al (2009) modelled the clinical and economic benefits of capsule endoscopy compared to SBFT as a second line investigation after a non-diagnostic ileocolonoscopy. The decision-analytic model incorporated total and yearly costs of diagnostic work-up for suspected Crohn's disease, including procedure-related adverse events, hospitalisations, office visits and medications. The model compared capsule endoscopy to SBFT following ileocolonoscopy and secondarily compared capsule endoscopy to SBFT for initial evaluation. At sensitivity >98.7% and specificity >86.4%, capsule endoscopy was estimated to be less costly than SBFT. They concluded that capsule endoscopy for the diagnostic evaluation of suspected Crohn's disease is comparable in cost to SBFT, and may be used immediately following ileocolonoscopy. However, their model assumed 'no obstruction' was present though it is unclear how one would reach that conclusion in a real-time scenario without prior radiologic imaging. The authors report that including retention in the model did not change the results though the assumptions used to reach this conclusion are not provided.

Economic evaluation of capsule endoscopy for small bowel Crohn's disease in Australia

The three economic studies identified for this report could not be used as evidence of cost-effectiveness for the use of capsule endoscopy in Australia since they did not reflect the patient population or clinical pathway under consideration in this report. In addition, none of the studies were conducted in Australia and the substantial differences between health systems limit transferability of economic studies. A decision-analytic model can synthesise effectiveness data from this report, cost data from other sources and expert opinion to estimate the cost-effectiveness of capsule endoscopy compared to conventional approaches. A simple decision-analytic model representing the possible

patient pathways is provided in Figure 5. It must be noted that MRI and MRE are currently not funded on the MBS as a diagnostic test for small bowel Crohn's disease in Australia. However, expert advice suggests that MRI and MRE are used in some Australian clinical settings for the diagnosis of small bowel Crohn's disease that is unconfirmed on prior tests.

Figure 5 Simplified decision tree for the diagnosis of small bowel Crohn's disease



Cost consequence analysis

High-level evidence on the comparative accuracy of capsule endoscopy, CT/CTE and MRI/MRE is unavailable and is essential information for a decision-analytic model. Due to the lack of comparative effectiveness data it is therefore not warranted to use a decision-analytic model to estimate cost-effectiveness.

The preferable approach to assess the value for money of using capsule endoscopy is a presentation of the costs and possible consequences of capsule endoscopy and its comparators. The estimation of costs takes a limited societal perspective, which includes patient copayments. Only costs of the diagnostic tests under evaluation are considered. Other costs such as downstream costs of treatment or costs of lost productivity are excluded as there is no evidence that suggests these cost components differ among the testing strategies.

Estimate of costs

The costs of performing the three diagnostic tests under evaluation were derived from a number of sources. These include the MBS (Commonwealth of Australia 2011a), the national hospital cost data collection AR-DRG version 5.1 round 13 (2008-09) – private sector (Commonwealth of Australia 2010), the PBS (Commonwealth of Australia 2011b) and expert advice.

MBS items

The MBS item fees for capsule endoscopy and CT/CTE, which represent the Australian Government contribution for each procedure, were obtained from MBS Online (Commonwealth of Australia 2011a). The patient usually receives a reimbursement of 75 per cent of the schedule fee for inpatient services and 85 per cent for outpatient services. Consequently, the benefit amount and not the full MBS fee were used in the calculations that follow, as using the full fee would double count some of the copayment contribution.

Average copayments

Average copayments for MBS items were provided by the Department of Health and Ageing. The copayment component is calculated as the fee charged minus the MBS benefit paid plus any additional specialist fees. The copayment may not be the exact patient contribution, since it may also include some insurance contribution (up to 25 per cent of the MBS fee). To avoid double counting, the 25 per cent insurance contribution is not included as a separate cost. The copayments are calculated as averages of all procedures claimed under the item number. Consequently, there may be a degree of heterogeneity in services claimed under each item. Therefore the accuracy of the copayment is dependent on the other procedures that are also claimed under the same item number.

The average copayments for PBS items were estimated from the maximum price patients are likely to be charged by a pharmacist, which was obtained from the PBS. Given that copayments for PBS items vary depending on both the item and the patient category (ie ordinary general beneficiaries, safety net general beneficiaries, ordinary concessional and free safety net concessional), the estimation of the average copayments was also based on an assumption about the distribution across these patient categories of patients with Crohn's disease (see notes to Table 26).

The cost of capsule endoscopy

The current MBS fee for capsule endoscopy (performed for MBS items 11820 and 11823) is \$1,961.95. The listed 85% reimbursement fee for capsule endoscopy is \$1890.75.

The average copayment for capsule endoscopy performed in an outpatient setting is \$32.95, which is the average aggregated copayment for MBS items 11820 and 11823 based on their respective number of services. It is assumed in this report that all capsule endoscopies for the diagnosis of small bowel Crohn's disease are performed in an outpatient setting.

Capsule endoscopy carries the risk of capsule retention, which may introduce additional costs to society. Based on expert advice, the following assumptions were made to estimate the cost of capsule retention (Table 26):

- The rate of capsule retention ranges between 0% and 15% across the studies identified in the systematic review (see Table 21).
- All patients with capsule retention are treated with corticosteroids (on average 25mg per day over a course of six weeks).

- In many patients the capsule will pass after medical therapy. However in the others, further intervention may be required for persistent capsule retention after medical therapy:
 - In up to 50% of these patients, double balloon enteroscopy via the oral or anal route is used (with extraction of the capsule and possibly balloon dilatation of a stricture).
 - In up to 50% of these patients, surgery is performed either:
 - primarily for Crohn’s disease where the capsule can be removed at that time, or
 - if the patient develops clinical obstruction or the capsule requires removal and cannot be retrieved by double balloon enteroscopy (this is usually a bowel resection).

Double balloon enteroscopy is an inpatient procedure and will involve costs for day hospital facility services.

Table 26 Estimated cost of capsule retention

Cost component	PBS item #	Dispensed price for max. qty	Max qty & pack size	Max price to consumer	Total tablets	Duration	Cost per patient	% of patients	Weighted cost per patient	Weighted average cost to Government	Weighted average cost to patient	Source of estimate
<i>Concession card holders or general beneficiaries who have exceeded the safety net threshold</i>												
Prednisone 25 mg	1936X	\$11.41	30	\$5.60	42	6 weeks	\$22.82 ¹	50%	\$11.41 ²	\$5.81 ³	\$5.60 ³	PBS
<i>General beneficiaries</i>												
Prednisone 25 mg	1936X	\$11.41	30	\$16.40	42	6 weeks	\$22.82 ¹	50%	\$11.41 ²	\$0 ³	\$16.40 ³	PBS
Subtotal – Estimated average cost of Prednisone							\$22.82 ¹	100%	\$22.82 ²	\$5.81 ³	\$22.00 ³	PBS
Cost component	MBS item #	MBS fee/ DRG cost	ALOS*	Cost to MBS	Patient copayment	Duration	Cost per patient	% of patients	Weighted cost per patient	Weighted cost to Government	Weighted patient copayment	
Double balloon enteroscopy (DBE)	30682	\$1,125.70	-	\$844.30 ⁴	\$540.03 ⁵	-	\$1,384.33	50	\$692.17	\$422.15	\$270.02	MBS / DoHA
Day hospital facilities - DBE	DRG G44C	\$713.00	1			1 day	\$713.00	50	\$356.50	\$356.50	\$0	National hospital cost data collection
Surgery (bowel resection)	DRG G05B	\$4,730.00	4.71			4.71 days	\$4,730.00	50	\$2,365.00	\$2,365.00	\$0	National hospital cost data collection
Subtotal – Estimated average cost of medical procedures and facilities									\$3,413.67	\$3,143.65	\$270.02	
Total – Estimated average cost of capsule retention									\$3,436.49	\$3,149.46	\$292.02	

¹ The quantity dispensed is a multiple of the pack size; hence 2 packs of 30 tablets (\$11.41) are needed to supply the required number of tablets (42).

² Due to patient copayments and patient categories within the PBS, the weighted cost per patient does not equal the weighted average cost to government plus the weighted average cost to patient.

³ The cost to government and patient is based on the distribution of patients across patient categories within the PBS and the associated maximum amount a pharmacist can charge a patient for a pack of 30 tablets of Prednisone 25 mg. It is assumed that in the patient population of this report, 50% of patients are general beneficiaries (\$0 cost to government and \$32.80 to patient (2 packs multiplied by the maximum price to patients of \$16.40) and 50% are either general beneficiaries who have reached the safety net threshold or are concession card holders (\$11.62 cost to government and \$11.20 to patient (2 packs multiplied by the maximum price to patients of \$5.60) in both cases).

⁴ MBS benefit, 75% of MBS fee.

⁵ Average patient copayment for inpatient procedure.

* ALOS = average length of stay (in days).

Capsule retention will incur costs for society. If a high estimate for the capsule retention rate of 15% is applied the average cost of a capsule endoscopy is \$2,439. This is the cost of capsule endoscopy for the MBS (\$1,890.75) plus the average patient copayment (\$32.95) plus 15% of the average cost of capsule retention ($0.15 * [\$3,149.46 + \$292.02]$). However, it is important to note that surgery is not always performed merely to remove the capsule but rather patients may have the capsule removed during surgery that was otherwise indicated. When the cost of surgery is not ascribed to capsule retention, the average cost of a capsule endoscopy is \$2,085 ($\$1,890.75 + \$32.95 + 0.15 * [\$784.46 + \$292.02]$) (see Table 27).

Table 27 Estimated average cost of capsule endoscopy

Scenario	Cost to MBS	Patient copayments	Total cost to society
No retention	\$1,890.75	\$32.95	\$1,923.70
15% retention, costs of surgery excluded	\$2,008.42	\$76.75	\$2,085.17
15% retention, costs of surgery included	\$2,363.17	\$76.75	\$2,439.92

The cost of MRI and MRE

MRI and MRE are currently not funded on the MBS for the purpose of diagnosing small bowel Crohn's disease. Expert advice suggests that MRE is likely to cost more than MRI, due to the longer duration and special expertise required to perform the procedure, but no cost price is available for this economic analysis.

The cost of CT

The current MBS fee for CT with intravenous contrast medium is \$480.05 (MBS item 56507). The listed 85% reimbursement fee is \$408.85. This cost is used for both CT and CTE.

The average copayment for CT performed in an outpatient setting is \$25.32. Hence, the average cost of CT/CTE is \$434.17 (\$408.85 to the government and \$25.32 to the patient).

Estimate of consequences (health outcomes)

Capsule endoscopy is considered to be a safe procedure and has a low risk of adverse events, such as nausea, vomiting and pain. It may, however, lead to capsule retention in up to 15% of cases, approximately half of which may be removed during surgery. Most subjects who retain the capsule do not experience any symptoms as a result of the retention. Unlike CT, capsule endoscopy involves no exposure to ionising radiation, and provides a potential clinical pathway that minimises the repetition of ionising radiation exposure, as prior small bowel radiology is still required.

The main potential consequence of adding capsule endoscopy to the conventional diagnostic pathway is an increase in timely diagnoses of Crohn's disease. This may lead to changes in patient management, and may ultimately result in improved patient outcomes. These potential benefits were endorsed by the Advisory Panel (see page 63). Based on evidence from this report, capsule endoscopy is likely to have at least comparable accuracy to MR. The comparative accuracy of capsule endoscopy and CT could not be

assessed. In addition, studies documenting changes in patient management due to capsule endoscopy were not identified. The impact of capsule endoscopy findings on patient management is therefore unknown and the resultant impact on health outcomes is uncertain.

Summary of the costs and consequences of capsule endoscopy versus MR and CT

In summary, the average cost of capsule endoscopy to society ranges between \$1,924 per test (\$1890.74 to the government and \$32.95 to the patient) when the costs of capsule retention are not taken into account to \$2,085 per test (\$2,008.42 to the government and \$76.75 to the patient) when a 15% capsule retention rate is assumed but the costs of surgery to remove the retained capsule are not attributed to capsule endoscopy. The average cost of CT/CTE is \$434 per test (\$408.85 to the government and \$25.32 to the patient). MRI/MRE as a diagnostic test for Crohn's disease is currently not funded through the MBS.

The consequences of introducing capsule endoscopy for patient management, compared to a repeat CT/CTE or MR/MRI, are unknown and the resultant impact on health outcomes is uncertain.

Estimation of the financial implications of the introduction of capsule endoscopy

The estimated utilisation of capsule endoscopy for the diagnosis of small bowel Crohn's disease unconfirmed on prior tests lies between 664 and 1,431 per year (see page 23 for detailed calculations). The estimated utilisation refers to the number of patients per year, not the number of tests. In this analysis, it is assumed that each patient will undergo one capsule endoscopy per year in an outpatient setting and no capsules are retained. The zero retention assumption was adopted on the basis that the most applicable studies had a capsule retention rate of 0-1% (Selby et al 2008; Tukey et al 2009). While the range of retention rates from the assessment was 0-15% (Table 21), expert opinion suggested that the capsule rate was likely to be closer to 0-1%. The potential cost of capsule endoscopy to society was estimated based on the potential utilisation of capsule endoscopy.

If publicly funded, capsule endoscopy will replace repeat CT/CTE or MRI/MRE tests currently performed in the patient population to diagnose Crohn's disease. Therefore, some of the costs of capsule endoscopy will be offset by a reduction in reimbursement costs for repeat CT/CTEs. For MRI/MRE an estimate of the financial implications cannot be provided, since MRI/MRE is currently not publicly funded through the MBS for the diagnosis of Crohn's disease.

Implication for the extended safety net

Capsule endoscopy is undertaken in the outpatient setting and therefore the copayment will contribute to the Extended Medicare Safety Net (EMSN). Out-of-pocket contributions for capsule endoscopy are only slightly higher than for CTs performed in outpatient setting (\$32.95 versus \$25.32). Hence, the introduction of capsule endoscopy, replacing CT/CTE, is unlikely to have a significant impact upon the EMSN.

Financial implications

The estimated costs of capsule endoscopy and CT/CTE for diagnosing small bowel Crohn's disease are presented in Table 28. This estimation used the MBS benefits for capsule endoscopy and CT/CTE, which are \$1,890.75 and \$408.85 respectively, and average patient copayments, which are \$32.95 and \$25.32 respectively.

Table 28 Estimated total annual cost of CE and CT as a second line test for diagnosing small bowel Crohn's disease

	CE	CT
Minimum utilisation (n=664)		
Total MBS benefits	\$1,255,458	\$271,476
Total patient out-of-pocket ¹	\$21,879	\$16,812
Total cost	\$1,277,337	\$288,288
<i>Incremental cost (CE vs CT)</i>		\$989,049
<i>Incremental cost MBS (CE vs CT)</i>		\$983,982
Maximum utilisation (n=1431)		
Total MBS benefits	\$2,705,663	\$585,064
Total patient out-of-pocket ¹	\$47,151	\$36,233
Total cost	\$2,752,814	\$621,297
<i>Incremental cost (CE vs CT)</i>		\$2,131,517
<i>Incremental cost MBS (CE vs CT)</i>		\$2,120,599

¹ Patient out-of-pocket cost are based on average patient copayments for CE and CT performed in an outpatient setting, which were provided by the Department of Health and Ageing

CE = capsule endoscopy, CT = Computed tomography (with or without enterography)

If repeat CT/CTEs are replaced by a capsule endoscopy, the financial implication for the MBS is estimated to be between \$983,982 and \$2,120,599 per year. The incremental cost to society (ie including patient copayments) is estimated to be between \$989,049 and \$2,131,517 per year.

The cost impact is sensitive to the rate of capsule retention and whether costs of surgery to remove a retained capsule are classified as a cost of capsule endoscopy. Additionally, the implementation of public funding for capsule endoscopy may lead to a change in the utilisation rate. It may lead to a modest increase in use; however, it could also lead to a modest decline in claims for MBS item 11820, capsule endoscopy for OGIB. The extent to which this will occur, and its implications for the MBS and patients, is unknown.

Discussion

Is it safe?

Capsule endoscopy is considered to be a relatively safe procedure with a low risk of adverse events such as nausea, vomiting and pain. Adverse events in patients with suspected small bowel Crohn's disease are likely to be similar, and occur at similar rates, as those reported for other indications (MSAC 2003; MSAC 2007).

Capsule endoscopy for the diagnosis of small bowel Crohn's disease has a potentially higher rate of capsule retention compared with other indications due to Crohn's disease causing bowel strictures. In 13 included studies, the rate of capsule retention ranged from 0% to 15% and in studies where the rates of capsule retention and surgical removal were reported, 7 of 12 subjects with retained capsules later had surgery at which the capsule was removed. Some of these surgeries are likely to have been otherwise avoidable. It appears that capsule retention can be partially mitigated, but not eliminated, with prior screening for strictures on small bowel radiology but that excluding patients on the basis of known intestinal obstruction (or a history of obstruction) is insufficient.

Compared to capsule endoscopy, the performance of CT is associated with radiation exposure, which has small risks, such as a small increased lifetime risk of cancer. This is especially relevant in younger people. Although patients are required to undergo small bowel radiology prior to capsule endoscopy and hence, unless MR is used, will not avoid ionising radiation exposure, repeated exposure would be expected to increase risk. MR does not involve exposure to ionising radiation (Markova et al 2010) and has a lower risk of nephrotoxicity (kidney damage) from contrast agents.

Is it effective?

The body of evidence included in this assessment was appraised according to the NHMRC guidelines (NHMRC 2008; 2009), which are summarised under 'Assessment of the body of evidence' on page 44.

This assessment did not identify any studies comparing the health outcomes of patient populations with suspected small bowel Crohn's disease assessed with and without capsule endoscopy. Evidence for accuracy, change in management and the expected benefit of changes in treatment on health outcomes was appraised using a linked evidence approach.

A summary of the body of evidence for the accuracy of capsule endoscopy is presented in Table 29.

The evidence base was considered poor on the basis of the level of evidence and the risk of bias in the included studies. Five level III-2 accuracy studies were identified. Three were rated of fair quality but had a moderate to high risk of measurement and/or selection bias due to lack of explicit patient selection criteria and test thresholds. The use of long-term follow-up as a reference standard without blinding from the results of capsule endoscopy in all five level III-2 studies placed these studies at moderate risk of bias in the measurement of outcomes.

Table 29 Body of evidence assessment matrix: linked evidence for CE for small bowel Crohn's disease

Rating \ Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base				Five level III-2 studies with a moderate to high risk of bias
Consistency			Some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact				Unknown ¹
Generalisability				Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability		Applicable to Australian healthcare context with few caveats		

CE = capsule endoscopy. Adapted from (NHMRC 2009). For table notes see (NHMRC 2009).

¹ Relates to the impact of capsule endoscopy on patient outcomes.

There were some inconsistencies in the results of these studies, some of which could be explained. Capsule endoscopy was found to have similar diagnostic accuracy to MRE in one study (Casciani et al 2011) and improved accuracy relative to MRI in another (Albert et al 2005). This may be partially explained by the use of MR with enterography in Casciani et al (2011). However, variations in the prior tests and patient populations may have affected the results, and the extent to which this occurred could not always be resolved on the basis of reported study characteristics. For instance, Casciani et al (2011) noted that the accuracy of MRE found in their study was higher than had been previously reported; their study enrolled a predominantly paediatric population; and the proportion of patients that tested negative or equivocal on prior tests in this study was not reported.

The negative LRs found in the studies also differed and the reason for this is unknown. Of the four studies that reported the negative LR for the threshold of at least ≥ 2 ulcers or Crohn's specific lesions, two studies reported negative LRs which are considered convincing evidence for excluding disease (0.08 and 0.09) and two reported a negative LR which is considered to provide little evidence for excluding disease (0.26 and 0.58). In three studies where the negative LR was reported for the less stringent threshold of any small bowel ulcers, it provided convincing evidence for excluding disease in two studies (0, 0.08, 0.08) and borderline strong evidence in another (0.21). Overall, most studies had negative LRs < 0.10 , the threshold for providing convincing evidence to exclude disease; however, two studies had negative LRs which were > 0.20 , including the largest study which had a negative LR > 0.20 at both thresholds (Tukey et al 2009). Overall, in studies which employed more than one threshold of capsule endoscopy positivity, the lower threshold tended to yield lower negative LRs (ie were more predictive of absence of Crohn's disease when capsule endoscopy was negative) than studies using higher thresholds.

The populations studied in the body of evidence differ to the target population with respect to the use of prior tests and the selection criteria for patients with suspected small bowel Crohn's disease. In all five studies, patients had fewer prior tests and/or were a less highly selected group compared to the population addressed in this assessment. Two of the five included accuracy studies enrolled patients with clinically suspected Crohn's disease without explicitly requiring particular symptoms or biochemical evidence of inflammation (Figueiredo et al 2010; Tukey et al 2009). In most studies, not all enrolled subjects were required to undergo small bowel radiology (or underwent different types of radiology), and one study did not require prior colonoscopy with ileoscopy (Girelli et al 2007). Fewer prior tests may mean that the accuracy of capsule endoscopy found in this body of evidence may be higher than that which would occur in practice for the population considered in this assessment. Studies reporting more complete prior radiology or colonoscopy with ileoscopy which was negative or non-diagnostic for Crohn's disease tended to show higher negative LRs (ie were less predictive of the absence of Crohn's disease when capsule endoscopy was negative) than studies with less rigorous (or less well reported) prior testing.

The body of evidence was considered applicable to the Australian healthcare context with the caveat that the many of the studies were conducted in healthcare systems in which a different mix of prior tests are reimbursed.

In the absence of studies quantifying change in management due to capsule endoscopy in Crohn's disease patients, a linked evidence case for improved patient outcomes due to capsule endoscopy cannot be made. Hence, the potential clinical effect of capsule endoscopy on patient outcomes is unknown.

What are the economic considerations?

Due to the lack of comparative effectiveness data a cost-effectiveness analysis was not performed. The financial implications of public funding of capsule endoscopy were estimated as the potential incremental costs to the MBS and patients compared with the costs of using repeat CT/CTE. The analysis should be interpreted cautiously given the limited epidemiological data.

Assuming an estimated range of 664 to 1,431 capsule endoscopies per year, the incremental cost of testing was estimated to be between \$989,049 and \$2,131,517 per year for society, when capsule endoscopy replaces repeat CT/CTE. This estimate is based on the assumption that the total cost of capsule endoscopy will be borne by the Australian Government and patients.

The cost impact to society is sensitive to the rate of capsule retention and whether costs of surgery to remove a retained capsule are classified as costs of capsule endoscopy. Additionally, the implementation of public funding for capsule endoscopy may lead to a change in utilisation rate. Public funding may lead to a modest increase in use; however, it could also lead to a modest decline in claims for MBS item 11820, capsule endoscopy for OGIB.

Conclusions

The use of capsule endoscopy for the diagnosis of small bowel Crohn's disease is considered:

- safe
- to lead to capsule retention in up to 15% of cases; this risk can be partially, but not completely, mitigated by screening for strictures on small bowel radiology
- less likely to be predictive of the absence of Crohn's disease, when the capsule endoscopy is negative, in patient populations with negative or equivocal prior endoscopic and radiological tests
- more likely to be predictive of the absence of Crohn's disease, when the capsule endoscopy result is negative, when a lower threshold is used to define a positive test
- not to be highly predictive of the absence of Crohn's disease in the largest and most applicable study
- likely to have at least comparable accuracy to MR
- to lead to a cost increase to the Australian Government and patients between \$989,049 and \$2,131,517 per year if public funding is approved.

There were no included studies that provided evidence on the comparative accuracy of capsule endoscopy and CT. The impact of capsule endoscopy findings on patient management is unknown and the resultant impact on health outcomes is uncertain.

Appendix A MSAC terms of reference and membership

MSAC is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian healthcare system.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services including those that involve new or emerging technologies and procedures, in relation to:
 - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
 - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
 - the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
 - the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period; and
 - other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

The membership of MSAC at the July 2011 meeting comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, health administration and planning:

Member	Expertise or affiliation
Professor Robyn Ward (Chair)	Medical oncology
Dr Frederick Khafagi (Deputy Chair)	Nuclear medicine
Professor Jim Butler (Chair, Evaluation Sub-committee)	Health economics
Associate Professor John Atherton	Cardiology
Associate Professor Michael Bilous	Anatomical pathology
Professor Chris Baggoley	Interim Commonwealth Chief Medical Officer (<i>ex officio member</i>)
Associate Professor Kirsty Douglas	General practice/research
Professor Kwun Fong	Thoracic medicine
Professor Paul Glasziou	Evidence-based healthcare
Dr Scott Jansson	Pathology
Professor David Little	Orthopaedics
Mr Russell McGowan	Consumer health representative
Professor David Roder	Health medicine / epidemiology
Associate Professor Bev Rowbotham	Haematology
Dr Graeme Suthers	Genetics/pathology
Professor Ken Thomson	Radiology
Dr Christine Tippet	Obstetrics/gynaecology
Associate Professor David Winlaw	Paediatric cardiothoracic surgery
Dr Caroline Wright	Colorectal cancer / surgery
Vacant	AHMAC representative (<i>ex officio member</i>)

Appendix B Advisory Panel and Evaluators

Advisory Panel – Capsule endoscopy for suspected small bowel Crohn’s disease No. 1146

Member	Nomination / expertise or affiliation
Dr Kwun Fong (Chair)	Member of MSAC Thoracic medicine
Associate Professor David Winlaw (Deputy Chair)	Member of MSAC Paediatric cardiothoracic surgery
Associate Professor Paul Desmond	Gastroenterology
Dr Justin Evans	Colorectal surgery
Associate Professor Graham Radford-Smith	Gastroenterology
Ms Anita Reilly	Consumer health representative Crohn’s and Colitis Australia
Associate Professor Warwick Selby	The Gastroenterological Society of Australia (GESA) nominee Gastroenterology

Evaluation Sub-committee input

Professor Helen Lapsley (until February 20110)	Member of MSAC Evaluation Sub-Committee Health economics
Professor Justin Bielby (from March 2011)	Member of MSAC Evaluation Sub-Committee Health Science and General Practice

Evaluators

Name	Organisation
Ms Heather Gilbert	NHMRC Clinical Trials Centre
Dr Merel Kimman	NHMRC Clinical Trials Centre
Dr Samara Lewis	NHMRC Clinical Trials Centre

Appendix C Electronic databases

Table 30 Websites of health technology assessment agencies

1. International electronic databases	Website
NHS Centre for Reviews and Dissemination databases Economic evaluation database (NHS EED) Database of abstracts of reviews of effectiveness (DARE) Health Technology Assessment (HTA)	http://www.york.ac.uk/inst/crd/
Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register	http://www.cochrane.org
International Network of Agencies for Health Technology Assessment (INAHTA)	http://www.inahta.org/
2. Individual HTA Agencies	
ARGENTINA	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar/
AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/racs/research-and-audit/asernip-s
Centre for Clinical Effectiveness, Monash University	http://www.southernhealth.org.au/page/Health_Professionals/CCE/
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
Medical Services Advisory Committee (MSAC)	http://www.msac.gov.au
Adelaide Health Technology Assessment (AHTA)	http://www.adelaide.edu.au/ahta/
AUSTRIA	
Gesundheit Österreich GmbH (GÖG)	http://www.goeg.at/
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita/e1-3.htm
BELGIUM	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
BRAZIL	
Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia (DECIT-CGATS)	http://portal.saude.gov.br/portal/saude/area.cfm?id_area=1026
CANADA	
Agence d'évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) Québec	http://www.aetmis.gouv.qc.ca/site/home.phtml
Institute of Health Economics, Alberta	http://www.ihe.ca/
Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/home
Canadian Health Services Research Foundation (CHSRF)	http://www.chsrf.ca/home_e.php
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Institute for Clinical Evaluative Sciences (ICES)	http://www.ices.on.ca
Ontario Health Technology Advisory Committee (OHTAC) and Medical Advisory Secretariat (MAS)	http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html

CHILE	
Department of Quality and Patient Safety of the Ministry Health of Chile (Non-English) (ETESA)	http://www.redsalud.gov.cl
DENMARK	
Danish Centre for Health Technology Assessment (DACEHTA)	http://www.sst.dk/English/DACEHTA.aspx
Danish Institute for Health Services Research (DSI)	http://dsi.dk/english/
FINLAND	
Finnish Office for Health Technology Assessment FINOHTA	http://finohta.stakes.fi/EN/index.htm
FRANCE	
Haute Autorité de Santé (HAS) – or French National Authority for Health	http://www.has-sante.fr
Comité d’Evaluation et de Diffusion des Innovations Technologiques (CEDIT)	http://cedit.aphp.fr
GERMANY	
German Institute of Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/dynamic/en/hta/db/index.htm
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	http://www.iqwig.de
IRELAND	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie/
ISRAEL	
Israeli Center for Technology Assessment in Health Care (ICTAHC)	http://www.gertnerinst.org.il/e/health_policy_e/technology/
ITALY	
HTA Unit in A. Gemelli Teaching Hospital (UVT)	http://www.policlinicogemelli.it/area/?s=206
The Agency for Regional Healthcare	http://www.agenas.it/
KOREA	
Committee for New Health Technology Assessment (CNHTA)	No website
LITHUANIA	
State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania (VASPVT)	http://www.vaspvt.gov.lt/
MALAYSIA	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my/health_assesments [sic]
MEXICO	
Centro Nacional de Excelencia Tecnológica en Salud (CENETEC)	http://www.cenetec.gob.mx
NETHERLANDS	
Health Council of the Netherlands (Gezondheidsraad)	http://www.gezondheidsraad.nl/en
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
College voor Zorgverzekeringen (CVZ)	http://www.cvz.nl
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
Health Services Assessment Collaboration (HSAC)	http://www.healthsac.net
NORWAY	
Norwegian Knowledge Centre for the Health Services (NOKK)	http://www.kunnskapssenteret.no/home

POLAND	
Agency for Health Technology Assessment in Poland (AHTAPol)	http://aotm.eu/index.php?tpl=pl/wot/pake_zako
SPAIN	
Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud "Carlos III"/Health Technology Assessment Agency (AETS)	http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Catalan Agency for Health Technology Assessment and Research (CAHTA)	http://www.gencat.net/salut/depsan/units/aatrm/html/en/dir394/index.html
Unidad de Evaluación de Tecnologías Sanitarias (UETS)	http://www.madrid.org/lainentralgo
Basque Office for Health Technology Assessment (OSTEBA)	http://www.osanet.euskadi.net/osteba/es
Andalusian Agency for Health Technology Assessment (AETSA)	http://www.juntadeandalucia.es/salud/aetsa
Galician Agency for Health Technology Assessment (AVALIA-T)	http://avalia-t.sergas.es
SWEDEN	
Swedish Council on Health Technology Assessment (SBU)	http://www.sbu.se/en/
Center for Medical Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
SWITZERLAND	
Swiss Network for Health Technology Assessment (SNHTA)	http://www.snhta.ch/
TAIWAN, REPUBLIC OF CHINA	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
THAILAND	
Health Intervention and Technology Assessment Program (HITAP)	http://www.hitap.net/index_en.php
UNITED KINGDOM	
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/nhsqis/CCC_FirstPage.jsp
National Institute for Health Research Health Technology Assessment Programme	http://www.hta.ac.uk/
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/
Institute of Applied Health Sciences (IAHS)	http://www.abdn.ac.uk/iahs/
National Horizon Scanning Centre (NHSC)	http://www.haps.bham.ac.uk/publichealth/horizon/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Effectiveness Analysis Registry	https://research.tufts-nemc.org/cear4/default.aspx
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC)	http://www.bcbs.com/consumertec/index.html
U.S. Department of Health & Human Services, Effective Health Care Program	http://effectivehealthcare.ahrq.gov/index.cfm
VA Technology Assessment Program (VATAP)	http://www.va.gov/vatap

Table 31 Specialty websites

Organisation	Website
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov
American College of Gastroenterology	http://www.gi.org
American Gastroenterological Association	http://www.gastro.org
American Society of Colon and Rectal Surgeons (ASCRS)	http://www.fascrs.org
American Society for Gastrointestinal Endoscopy (ASGE)	http://www.askasge.org

Organisation	Website
Association of Coloproctology of Great Britain and Ireland	http://www.acpgbi.org.uk
British Society of Gastroenterology (BSG)	http://www.bsg.org.uk
Canadian Medical Association	http://www.cma.ca
Canadian Task Force on Preventive Health Care	http://www.ctfphc.org
Centers for Disease Control and Prevention	http://www.cdc.gov
Clinical Practice Guidelines and Protocols in British Columbia	http://www.health.gov.bc.ca/gpac
Cochrane Library/ Wiley	http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME
CORI: Clinical Outcomes Research Initiative	http://www.cori.org
Crohn's and Colitis Association of America	http://www.cafa.org
Crohn's and Colitis Australia	http://www.acca.net.au
Deutsche Gesellschaft für Verdauungs und Stoffwechselkrankheiten e.V.	http://www.dgvs.de
European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE I)	http://www.epage.ch
European Crohn's and Colitis Organization	http://www.ecco-ibd.org
Fondation canadienne des maladies inflammatoires de l'intestin (Crohn's and Colitis Foundation of Canada)	http://www.cfcf.ca
Gastroenterological Society of Australia	http://www.gesa.org.au
Guidelines Advisory Committee (GAC)	http://www.gacguidelines.ca
Guidelines International Network (G-I-N)	http://www.g-i-n.net
Haute Autorité de Santé (France)	http://www.has-sante.fr
Health On the Net Foundation	http://www.hon.ch
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
National Digestive Diseases Information Clearinghouse (NDDIC). A service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH	http://digestive.niddk.nih.gov
National Guideline Clearinghouse	http://www.guideline.gov
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au
National Health Service – UK (NHS)	http://www.nhs.uk
New Zealand Guidelines Group	http://www.nzgg.org.nz
Ontario Association of Gastroenterology	http://www.gastro.on.ca
Pubmed	http://www.pubmed.org
Royal College of Surgeons in Ireland	http://www.rcsi.ie
Santé Canada/ Health Canada	http://www.hc-sc.gc.ca
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk
Site Suisse pour les Maladies Inflammatoires de l'Intestin	http://www.ibd-net.ch
Société Française d'Endoscopie Digestive	http://www.sfed.org
Société Nationale Française de Gastro-Entérologie	http://www.snfge.asso.fr
Société Suisse de Gastroentérologie	http://www.sggsg.ch
US Department of Veterans Affairs (VA)	http://www.healthquality.va.gov/
World Endoscopy Organization	http://www.worldendo.org/
World Gastroenterology Organisation	http://www.worldgastroenterology.org

Appendix D Studies included in the review

Systematic reviews and HTA reports

HTA and systematic reviews					
Author/Year	Objective of report	Number and publication dates of included studies	Population considered in included studies Test comparison	Conclusions/ recommendation	Quality assessment
Dionisio et al (2010) USA This meta-analysis updates Triester et al 2006.	To evaluate the diagnostic yield of capsule endoscopy compared with other modalities in patients with suspected and established Crohn's disease. Indication: Suspected and established Crohn's disease where tests are used for findings outside the range of normal oesophagogastroduodenoscopy (EGD). Study design: A meta-analysis based on 'per protocol' results (rather than 'intention to treat'), including subgroup analyses of those with suspected and established Crohn's disease.	19 prospective trials were included. These related to patients with suspected and established Crohn's disease. Search method and date range: These consisted of 18 trials published up until May 2009 identified via a search of MEDLINE, EMBASE and the Cochrane Central Trials database and 1 trial identified by a manual search of conference proceedings published through 2008. The capsule manufacturer was consulted to provide additional trials from its database covering up until February 2009. The search was not limited to English language publications.	Population: Adult patients with suspected or established Crohn's disease. The suspicion of Crohn's disease was determined by biomarkers or patient symptoms. In 8 trials, patients with prior stricturing were excluded. Prior tests: nr Test comparison: <ul style="list-style-type: none"> • Small bowel barium radiography • Push enteroscopy • Colonoscopy with ileoscopy • CTE/enteroclysis • MRE Outcome: Weighted incremental diagnostic yield Reference standard/threshold: No reference standard. Positive test threshold defined within each study.	Overall conclusion: Capsule endoscopy is superior to small bowel barium radiography, CT enterography/enteroclysis, and colonoscopy with ileoscopy in the diagnosis of adult patients with suspected non-stricturing Crohn's disease, in virtue of its significantly higher weighted incremental diagnostic yield. It is not superior to MRE or push enteroscopy. Capsule endoscopy is an important first line diagnostic tool, especially when colonoscopy with ileoscopy is unsuccessful or undiagnostic.	Quality: FAIR Explicit review questions: yes Explicit and appropriate eligibility criteria: yes Explicit and comprehensive search strategy: yes Quality of included studies appraised: no Methods of study appraisal reproducible: N/A Heterogeneity between studies assessed: yes Summary of main results clear and appropriate: no
Results					

Diagnostic performance:

In patients with suspected Crohn's disease:

Weighted incremental yield of capsule endoscopy over:

Small bowel barium radiography (8 trials, n=155):

32% (95% CI = 16-48%; $p < 0.0001$), REM.

CT enterography/enteroclysis (3 trials, n=53):

47% (95% CI = 31-63%, $P < 0.00001$), REM.

Colonoscopy with ileoscopy (4 trials, n=59):

22% (95% CI = 5-39%, $P = 0.009$), FEM.

Push enteroscopy (2 trials, n=46):

18% (95% CI = -23-59%, $P = 0.39$), FEM.

MRE (3 trials, n=31):

10% (95% CI = -14-34%, $P = 0.43$), FEM.

FEM = fixed effects model, REM = random effects model

A sensitivity analysis was conducted using the highest quality trials that compared capsule endoscopy with small bowel barium radiography in patients with suspected Crohn's disease (8 trials, n=126). Suitability for the sensitivity analysis was based on studies being blinded and published as full manuscripts. Using the DerSimonian-Laird random effects model due to the presence of heterogeneity, it was found that in patients with suspected Crohn's disease, capsule endoscopy has a non-statistically significant weighted incremental diagnostic yield of 22% (95% CI = -1.44%; $p = 0.06$) compared with small bowel barium radiography.

Change in management: nr

Health outcomes: nr

Adverse effects: nr

HTA and systematic reviews					
Author/Year	Objective of report	Number and publication dates of included studies	Population considered in included studies	Conclusions/recommendation	Quality assessment
Varela-Lema et al (2008) Spain GAHTA	<p>To assess the effectiveness, safety and clinical use of capsule endoscopy in the diagnosis of small bowel diseases.</p> <p>Indications:</p> <ul style="list-style-type: none"> • OGIB • Crohn's disease - suspected and established • Hereditary polyposis syndromes • Celiac disease • Chronic abdominal pain and other disorders <p>Study design: Systematic review using qualitative data synthesis.</p>	<p>9 primary studies were included for the indications of suspected and/or established Crohn's disease. 9 systematic reviews were included that addressed small bowel diseases in general (see indications section).</p> <p>Search method and date range: Studies published between January 2003 until December 2005 were identified via a search of MEDLINE, EMBASE, the Cochrane Collaboration, the Centre for Reviews and Dissemination, IBECS, IME, LILACS and ISI Web of Knowledge. Additionally, the references of identified papers were manually searched.</p>	<p>Population: Patients with suspected and established Crohn's disease. Adult and paediatric patients (mostly adult) from Europe, the United States and Israel.</p> <p>Prior tests: nr</p> <p>Test comparison:</p> <ul style="list-style-type: none"> • SBFT • Enteroclysis • CT enteroclysis • CT enteroscopy • Push enteroscopy <p>Outcome: Diagnostic accuracy (sensitivity, specificity, positive predictive value and negative predictive value), diagnostic yield, change in management., adverse events.</p> <p>Reference standard/threshold: In 2 studies, ileoscopy with biopsy was the reference standard. Threshold for positive results not reported.</p>	<p>Overall conclusion: Existing studies suggest that capsule endoscopy might occupy a preferential place in the diagnosis of suspected Crohn's disease. However, the evidence is insufficient to establish if it should be used as a first line diagnostic test.</p> <p>Capsule endoscopy is contraindicated in patients with stenosis and does not allow precise localisation of the lesion.</p> <p>Additional studies are required to verify the usefulness of capsule endoscopy in incident Crohn's disease patients and assess the clinical consequences of changes in therapeutic management. Existing studies that evaluate changes to therapeutic management of Crohn's disease following capsule endoscopy report different results.</p> <p>In addition, clear criteria for a positive result needs to be established.</p>	<p>Quality: FAIR Explicit review questions: no Explicit and appropriate eligibility criteria: yes Explicit and comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: yes Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: yes</p>

Results

Diagnostic performance

Diagnostic yield:

In patients with suspected Crohn's disease

Suggestive findings found in capsule endoscopy compared with radiological techniques (4 studies)

19-71% for capsule endoscopy compared with 0-37% for radiologic techniques.

In paediatric patients with suspected Crohn's disease

Diagnostic yield of capsule endoscopy compared with comparator modalities (SBFT and endoscopies) (2 studies)

58-60% for capsule endoscopy compared with 0-20% for comparator modalities.

Diagnostic accuracy:

In patients with suspected Crohn's disease

Sensitivity and specificity of capsule endoscopy compared with ileoscopy with biopsy (1 study)

Sensitivity: 87%

Specificity: 100%

In patients with suspected and established Crohn's disease compared with radiological techniques (1 study):

Sensitivity: 89.6%

Specificity: 100%

Positive predictive value: 100%

Negative predictive value: 76.9%

Change in management: Therapeutic management changed in 67% of patients with suspected Crohn's disease, 38% of whom improved (1 study). The use of capsule endoscopy in suspected and established Crohn's disease changed therapeutic management in 24-73% of subjects in 2 studies, but in another study no change in diagnosis following capsule endoscopy was reported.

Health outcomes: nr

Adverse events: Despite previous performance of SBFT or other radiological techniques, most studies reported temporary capsule retention or delays in the capsule which led to incomplete visualisation of the small bowel. The rates reported are variable across studies, and range between 4.7-80% of patients.

The most severe adverse event reported was the permanent retention of the capsule (due to stenosis or fissures), leading to laparotomy.

HTA and systematic reviews					
Author/Year	Objective of report	Number and publication dates of included studies	Population considered in included studies Test comparison	Conclusions/ recommendation	Quality assessment
Poelmans et al (2006) Belgium KCE	<p>To assess the clinical efficacy and economic effectiveness of capsule endoscopy compared with competing diagnostic modalities in small bowel diseases.</p> <p>Indications:</p> <ul style="list-style-type: none"> Established and suspected Crohn's disease OGIB Celiac disease Polyposis Paediatric studies <p>Study design: Health technology assessment and systematic review.</p>	<p>7 publications included on suspected and established Crohn's disease. This includes 5 prospective and comparative primary studies (n=176), 1 systematic review and 1 HTA report.</p> <p>Search method and date range: Databases searched included the CRD database (All databases-DARE, NHS EED, HTA) to June 2005 and MEDLINE to October 2005.</p> <p>The search was restricted to full text English language publications.</p>	<p>Population: Patients with suspected and established Crohn's disease.</p> <p>Prior tests: Varies by study SBFT in some studies Most underwent prior radiological investigation of the small bowel.</p> <p>Test comparison: Alternate diagnostic modalities.</p> <ul style="list-style-type: none"> SBFT Push enteroscopy and enteroclysis CT enteroclysis MRI and enteroclysis <p>Outcome: Diagnostic yield or diagnostic accuracy, therapeutic impact and adverse events.</p> <p>Reference standard/threshold: Reference standard in 1 study (12 month follow-up). Threshold for positive result varies by study.</p>	<p>Overall conclusion: The available evidence is not of sufficient quantity and quality to determine the relative diagnostic performance of capsule endoscopy compared with conventional tests used to diagnose Crohn's disease. No conclusions can be made as to whether capsule endoscopy is an effective alternative to other tests.</p> <p>The existing body of evidence has limited generalisability because existing studies have small and heterogeneous patient populations.</p>	<p>Quality: FAIR</p> <p>Explicit review questions: no Explicit and appropriate eligibility criteria: yes Explicit and comprehensive search strategy: yes Quality of included studies appraised: yes Methods of study appraisal reproducible: no Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: yes</p>

Results

Diagnostic performance

Diagnostic accuracy of capsule endoscopy in patients with suspected Crohn's disease (Reference standard: final diagnosis at 12 months) (1 study, n=13)

Capsule endoscopy sensitivity: 92% (12/13 patients)

Capsule endoscopy specificity: 100% (10/10 patients)

Sensitivity and specificity may be overestimated as it was unclear if the reference test was blindly assessed.

Diagnostic yield (5 studies, n=176)

In 4 of the studies, capsule endoscopy had a higher diagnostic yield than the comparator and similar to SBFT in 1 study.

Change in management: 2 studies reported changes in patient management. A management change was reported in 67% (14/21) of patients with suspected Crohn's disease. A therapeutic impact was reported in 18% (10/56) of patients diagnosed with capsule endoscopy, 5 of whom had new diagnoses.

Health outcomes: nr

Adverse events: Adverse events were reported in 4.5% of patients (8/176). Capsule retention occurred in 2.8% of patients (5/176), requiring surgical removal in 2 patients, endoscopic removal in 1 patient and corticosteroid therapy in 1 patient. Other adverse events reported include painful passage of the capsule through the ileocaecal region in 2 patients, inability to swallow the capsule in 1 patient requiring endoscopy placement of the capsule in the duodenum, repeat capsule endoscopy in 1 patient due to prolonged stay in the stomach.

3 studies (n=114) reported on whether the capsule failed to reach the caecum within the battery life time, resulting in incomplete visualisation. This occurred in 17.5% (20/114) of patients.

Primary studies

All included studies on accuracy and diagnostic yield provided safety data except for Guilhon de Araujo Sant'Anna et al (2005). All included studies on accuracy provided diagnostic yield data.

Study profiles of included studies on accuracy

Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment																																														
<p>Albert et al (2005)</p> <p>Germany Single centre (hospital) 1 May 2002-15 December 2003</p> <p>n=52 patients (25 newly suspected of Crohn's disease, 27 with established non-small bowel Crohn's disease)</p> <p>Follow-up: Mean follow-up 14.5 months (SD 6.5 months).</p>	<p>Objective: To evaluate the efficacy and safety of capsule endoscopy in diagnosing small bowel Crohn's disease in comparison with MRI and double contrast small bowel fluoroscopy (enteroclysis).</p> <p>Study design: Prospective, consecutive diagnostic accuracy study</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator tests:</i></p> <ul style="list-style-type: none"> • MRI • Double contrast small bowel fluoroscopy (enteroclysis) <p><i>Reference test:</i> Combined diagnostic endpoint composed of all imaging methods including ileocolonoscopy, clinical and laboratory data and the evolution of diagnosis during follow-up >12 months.</p>	<p>Inclusion/exclusion criteria (for suspected CD group): <i>Inclusion:</i> Patients admitted for the evaluation of suspected or previously diagnosed but worsening Crohn's disease. Crohn's disease was suspected in the presence of suggestive clinical symptoms (diarrhoea, abdominal pain, anorexia, weight loss, rectal bleeding) and biochemical signs of systemic inflammation.</p> <p><i>Exclusion:</i> Dysphagia, gastrointestinal obstruction and/or ileus, pregnancy, presence of an implanted electromedical device (cardiac pacemaker or defibrillator). Patients <18 years. Significant bowel stricture detected on prior imaging. Detection of small bowel involvement did not potentially affect treatment strategies. For the suspected Crohn's disease subgroup: the diagnostic work-up (see prior tests) did not establish a diagnosis other than Crohn's disease.</p> <p>Patient characteristics: Age 18-72 years 39 female/13 male Male – Mean age 36.6 years SD 12.41 years</p>	<p>Test accuracy:</p> <table border="1" data-bbox="1189 440 1485 722"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">CE</th> <th>+</th> <td>12</td> <td>0</td> <td>12</td> </tr> <tr> <th>-</th> <td>1</td> <td>11</td> <td>12</td> </tr> <tr> <th>Total</th> <td>13</td> <td>11</td> <td>24</td> </tr> </tbody> </table> <p>CE: Sensitivity: 0.92 (95% CI = 0.62-1.00) Specificity: 1.00 (95% CI = 0.72-1.00) PPV: 1.00 (95% CI = 0.74-1.00) NPV: 0.92 (95% CI = 0.60-1.00) LR+: Undefined LR-: 0.08 Assumption: 1 drop out</p> <table border="1" data-bbox="1189 1054 1485 1342"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">MRI</th> <th>+</th> <td>10</td> <td>2</td> <td>12</td> </tr> <tr> <th>-</th> <td>4</td> <td>8</td> <td>12</td> </tr> <tr> <th>Total</th> <td>14</td> <td>10</td> <td>24</td> </tr> </tbody> </table> <p>MRI:</p>			Reference standard – Follow-up					CD	No CD	Total	CE	+	12	0	12	-	1	11	12	Total	13	11	24			Reference standard – Follow-up					CD	No CD	Total	MRI	+	10	2	12	-	4	8	12	Total	14	10	24	<p>Level III-2 Quality POOR Q3 Comparison: C1: for MRI CX: for empirical treatment Patient selection: Prospective: yes Consecutive: yes Explicit selection criteria: yes <i>Reference standard:</i> Diagnosis at follow-up Valid: yes Applied to all participants: no <i>Test interval in days/weeks:</i> Comparator: All investigations occurred within 10 days except for 1 patient (6 weeks). Ref std: Mean follow-up 14.5 months. Tests reported blinded to ref std: partially Ref std reported blinded to tests: no Routine clinical data available: yes <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: yes Sufficient data for 2x2 table: yes</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> yes <i>Applicable intervention:</i> yes</p>
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		<p>Female – Mean age 39.7 years, SD 16.0 years</p> <p><i>Prior tests:</i> Abdominal ultrasound, upper endoscopy, ileocolonoscopy, microbiological stool tests, endoscopy.</p> <p><i>Clinical characteristics:</i> Not reported by subgroup.</p> <p>Abdominal pain 51.9% (27/52) Diarrhoea 36.5% (19/52) Weight loss 5.8% (3/52) Perineal fistula 5.8% (3/52)</p> <p>Interpretation/threshold: CE: Aphthous mucosal lesions, irregularly shaped or fissural ulcers (occasionally associated with bleeding), cobblestone appearance, luminal narrowing due to oedema and/or fibrous scarring, and granularity with attenuated or lost vascular pattern resulted in the diagnosis of Crohn's disease. Patchy mucosal erythema, oedema or a single regular ulceration were considered inconclusive findings.</p> <p>MRI: Thickening of the bowel wall (≥4mm) and enhancement of the bowel wall after application of intravenous contrast medium were considered indicative of CD. Weak enhancement of bowel loops without bowel wall thickening was interpreted as non-specific.</p>	<p>Sensitivity: 0.71 (95% CI = 0.42-0.90) Specificity: 0.80 (95% CI = 0.44-0.96) PPV: 0.83 (95% CI = 0.51-0.97) NPV: 0.67 (95% CI = 0.35-0.89) LR+: 3.57 LR-: 0.36 Assumption: 1 drop-out</p> <p>Diagnostic yield: Capsule endoscopy: 50% (12/24) (95% CI = 30-70%) MRI: 50% (12/24) (95% CI = 30-70%)</p> <p>Adverse events: Capsule retention: 4.2% (1/24) 1 patient retained the capsule proximal to a bowel stricture (not detected by abdominal ultrasound and enteroclysis) but this did not cause complete obstruction or ileus. Steroids were started and the capsule was excreted 72 hours later.</p>	
Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment

<p>Casciani et al (2010)</p> <p>Italy Single centre (hospital) January-December 2009 n=60 patients with suspected Crohn's disease, CE performed in 37</p>	<p>Objective: To compare the diagnostic yield and efficacy of MRE with small bowel capsule endoscopy in diagnosing small bowel Crohn's disease in paediatric patients with suspected Crohn's disease.</p> <p>Study design: Prospective, consecutive diagnostic accuracy study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> MRE</p> <p><i>Reference test:</i> Combination of clinical evaluation, endoscopic, histological and/or biochemical investigations with a clinical follow-up of 12-14 months.</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> IBD was suspected if there was at least 1 suggestive clinical symptom (diarrhoea, abdominal pain, anorexia, weight loss, rectal bleeding) and 1 biochemical sign of systemic inflammation (high plasma levels of acute phase reactants (C-reactive protein, erythrocyte sedimentation rate) refractory anaemia and low serum albumin).</p> <p><i>Exclusion:</i> Age >18 years, dysphagia, gastrointestinal obstruction or ileus, inability to hold breath for 15-20 seconds apnoea, MRE showed stricture or excluded small bowel disease by revealing incidental findings outside the small bowel.</p> <p>Patient characteristics: Average age 14 years and range 6-18 years. 24 female/36 male</p> <p><i>Prior tests:</i> Ileocolonoscopy, oesophagogastroduodenoscopy under deep sedation.</p> <p><i>Clinical characteristics:</i> nr</p> <p>Interpretation/threshold: CE: Negative if no abnormalities were seen. Positive if clear abnormalities of the small bowel mucosa were observed. (ulcerations, erosions, polyps, vascular lesions, bleeding lesions). Features detected by CE were considered diagnostic</p>	<p>Test accuracy:</p> <p>Diagnostic (>3 ulcers):</p> <table border="1" data-bbox="1189 304 1482 587"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td rowspan="3">CE</td> <td>+</td> <td>10</td> <td>0</td> <td>10</td> </tr> <tr> <td>-</td> <td>1</td> <td>26</td> <td>27</td> </tr> <tr> <td>Total</td> <td>11</td> <td>26</td> <td>37</td> </tr> </tbody> </table> <p>Sensitivity: 0.91 (95% CI 0.57-1.00) Specificity: 1.00 (95% CI 0.87-1.00) PPV: 1.00 (95% CI 0.69-1.00) NPV: 0.96 (95% CI 0.81-1.00) LR+: Undefined LR-: 0.09</p> <p>Diagnostic (>3 ulcers) and suggestive (≤3 ulcers):</p> <table border="1" data-bbox="1189 959 1482 1241"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td rowspan="3">CE</td> <td>+</td> <td>11</td> <td>2</td> <td>13</td> </tr> <tr> <td>-</td> <td>0</td> <td>24</td> <td>24</td> </tr> <tr> <td>Total</td> <td>11</td> <td>26</td> <td>37</td> </tr> </tbody> </table> <p>Sensitivity: 1.00 (95% CI 0.72-1.00) Specificity: 0.92 (95% CI 0.73-</p>			Reference standard – Follow-up					CD	No CD	Total	CE	+	10	0	10	-	1	26	27	Total	11	26	37			Reference standard – Follow-up					CD	No CD	Total	CE	+	11	2	13	-	0	24	24	Total	11	26	37	<p>Level III-2 Quality FAIR Q2 Comparison: C1: for MRE CX: for empirical treatment</p> <p>Patient selection: Prospective: yes Consecutive: yes Explicit selection criteria: yes <i>Reference standard:</i> Diagnosis at follow-up Valid: yes Applied to all participants: yes <i>Test interval in days/weeks:</i> Comparator: MRE was conducted prior to CE. CE was conducted within 1 week of MRE. Ref std: diagnosis at follow-up 12-14 months. Tests reported blinded to ref std: partially Ref std reported blinded to tests: no Routine clinical data available: Partially <i>Analysis:</i> Uninterpretable/intermediate results reported: unclear Study withdrawals explained: yes Sufficient data for 2x2 table: yes</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> yes <i>Applicable intervention:</i> yes</p>
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		<p>of active Crohn's disease if >3 small bowel ulcerations were observed. Features of ≤3 ulcerations were considered suggestive but not diagnostic. Results with no abnormalities or non-specific findings (eg erythematous spots or mucosal breaks) were considered normal or non-specific.</p> <p>MRI: Positive if 1 of the following:</p> <ul style="list-style-type: none"> • Small bowel wall thickness >3 mm • Small bowel wall enhancement after contrast • Small bowel oedema • Stratified appearance 	<p>0.99) PPV: 0.85 (95% CI 0.54-0.97) NPV: 1.00 (95% CI 0.86-1.00) LR+: 13 LR-: 0</p> <p>Patients excluded from above due to parents' refusal (n=7), extraintestinal findings detected by MRE (n=11) or strictures (n=5).</p> <p>MRE:</p> <table border="1" data-bbox="1189 584 1482 871"> <thead> <tr> <th colspan="2" rowspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">MRE</th> <th>+</th> <td>19</td> <td>1</td> <td>20</td> </tr> <tr> <th>-</th> <td>0</td> <td>40</td> <td>40</td> </tr> <tr> <th>Total</th> <td>19</td> <td>41</td> <td>60</td> </tr> </tbody> </table> <p>Sensitivity: 1.00 (95% CI = 0.82-1.00) Specificity: 0.98 (95% CI = 0.87-1.00) PPV: 0.95 (95% CI = 0.75-1.00) NPV: 1.00 (95% CI = 0.91-1.00) LR+: 41.00 LR-: 0.00</p> <p>Diagnostic yield: CE: Diagnostic and suggestive: 35% (13/37) (95% CI 21-53%)</p>			Reference standard – Follow-up			CD	No CD	Total	MRE	+	19	1	20	-	0	40	40	Total	19	41	60	
		Reference standard – Follow-up																							
		CD	No CD	Total																					
MRE	+	19	1	20																					
	-	0	40	40																					
	Total	19	41	60																					

			<p>Diagnostic: 27% (10/37) (95% CI 14-44%) MRE: 33.3% (20/60) (95% CI = 23-46%)</p> <p>Adverse events: Complete CE (capsule reached caecum within the CE test time): 86% (32/37) Capsule reached distal ileum 14% (5/37) Capsule retention not reported</p>	
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment																							
<p>Figueiredo et al (2010)</p> <p>Portugal Single tertiary care centre January 2001-December 2007</p> <p>n=95 enrolled patients (78 for analysis: 14 excluded due to NSAID use in previous 30 days, 3 excluded due to inadequate follow up; of the 78 included in the analysis, 64 had complete capsule endoscopies, 72 had either complete capsule endoscopies or incomplete endoscopies in which lesions were nonetheless detected)</p> <p>Follow-up: Average 28.8 months ±13.3 (SD) (range 6-65)</p>	<p>Objective: To assess the value of capsule endoscopy in the diagnosis of patients with suspected Crohn's disease and the complications associated with this technique.</p> <p>Study design: Retrospective diagnostic accuracy study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> Diagnosis at follow-up (>6 months), based on contact with the referring physician.</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Patients undergoing capsule endoscopy for clinically suspected Crohn's disease.</p> <p><i>Exclusion:</i> Use of NSAIDs in the 30 days preceding the examination (as indicated by references in the medical file). Follow-up period <6 months after the date of the examination. Clinical or imaging study indicating stenosis of the small intestine.</p> <p>Patient characteristics (n=78): Mean age 37.2 years ±16.4 (SD) 53 female/25 male</p> <p><i>Prior tests:</i> (n=78)</p> <ul style="list-style-type: none"> • Colonoscopy 100% (78/78) • Retrograde ileoscopy with biopsy 60.3% (47/78), with slightly congested mucosa in 7 cases • Unsuccessful intubation of the terminal ileum 39.7% (31/78) • Small bowel series - Enteroclysis (19/78) • Lesions seen on enteroclysis (5/19) • SBFT (47/78) • Lesions seen on SBFT (5/47) • CT (37/78) • Lesions seen on CT (14/37). 	<p>Test accuracy: Excluding patients with an incomplete endoscopy where it was not possible to tell if they had findings suggestive of Crohn's disease (n=6):</p> <table border="1" data-bbox="1189 499 1458 786"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">CE</th> <th>+</th> <td>29</td> <td>8</td> <td>37</td> </tr> <tr> <th>-</th> <td>2</td> <td>33</td> <td>35</td> </tr> <tr> <th>Total</th> <td>31</td> <td>41</td> <td>72</td> </tr> </tbody> </table> <p>Sensitivity: 0.94 (95% CI = 0.79- 0.98) Specificity: 0.80 (95% CI = 0.66-0.90) PPV: 0.78 (95% CI = 0.63- 0.89) NPV: 0.94 (95% CI = 0.81- 0.98) LR+: 4.8 LR-: 0.08</p>			Reference standard – Follow-up					CD	No CD	Total	CE	+	29	8	37	-	2	33	35	Total	31	41	72	<p>Level III-2 Quality POOR Q3 Comparison: CX: for empirical treatment Patient selection: Prospective: no Consecutive: nr Explicit selection criteria: no <i>Reference standard:</i> Diagnosis at follow-up Valid: yes Applied to all participants: no <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: 28.8 months (mean) ±13.3 months (SD) after CE Tests reported blinded to ref std: nr Ref std reported blinded to tests: nr Routine clinical data available: nr <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: yes Sufficient data for 2x2 table: yes</p> <p>Applicability P2: <i>Relevant population:</i> limited (blood tests, radiology, MACCS criteria) <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> Yes</p>
		Reference standard – Follow-up																									
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	-	2	33	35																							
	Total	31	41	72																							

		<p><i>Clinical characteristics:</i> (n=78)</p> <ul style="list-style-type: none"> • Abdominal pain 79.5% (62/78) • Diarrhoea 60.3% (47/78) • Weight loss 34.6% (27/78) • Arthralgias 34.6% (27/78) • Fever 14.1% (11/78) • Duration of symptoms 22.3 ±26.2 months (mean ± SD) • Anaemia 53.8% (42/78) • Elevated C-reactive protein 35.9% (28/78) <p>Interpretation/threshold: Erosions, ulcers, ulcerated stenosis and villous atrophy were considered suggestive of Crohn's disease regardless of the number of lesions found.</p>	<p>In patients for whom retrograde ileoscopy was (i) achieved, and (ii) negative (n=43):</p> <table border="1" data-bbox="1189 304 1458 592"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">CE</th> <th>+</th> <td>21</td> <td>3</td> <td>24</td> </tr> <tr> <th>-</th> <td>1</td> <td>18</td> <td>19</td> </tr> <tr> <th>Total</th> <td>22</td> <td>21</td> <td>43</td> </tr> </tbody> </table> <p>Sensitivity: 0.96 (95% CI = 0.77-1.00) Specificity: 0.86 (95% CI = 0.63-0.96) PPV: 0.88 (95% CI = 0.67-0.97) NPV: 0.95 (95% CI = 0.74-1.00) LR+: 6.68 LR-: 0.05</p> <p>Diagnostic yield – CE: 47.4% (37/78) in all patients (95% CI = 37-58%) 56% (24/43) in patients with a negative ileoscopy (95% CI 40-71%)</p> <p>Diagnostic yield – CT: 38% (14/37) in patients who underwent CT (95% CI = 23-55%) CT was not a comparator in this study however yield data was provided for 37 patients who underwent CT.</p>			Reference standard – Follow-up					CD	No CD	Total	CE	+	21	3	24	-	1	18	19	Total	22	21	43	
		Reference standard – Follow-up																									
		CD	No CD	Total																							
CE	+	21	3	24																							
	-	1	18	19																							
	Total	22	21	43																							

			<p>Adverse events: Incomplete CE: 17.9% (14/78)</p> <p>Capsule retention: 5.1% (4/78). None developed signs or symptoms of intestinal occlusion. 2 underwent surgery and 2 expelled the capsule following medical treatment (note: the latter were twins).</p> <p>No other complications were reported.</p>	
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment																																														
<p>Girelli et al (2007)</p> <p>Italy Single centre April 2002-March 2005 n=27 patients with suspected Crohn's disease</p>	<p>Objective: To verify the accuracy and clinical impact of capsule endoscopy in a cohort of patients with suspected small bowel Crohn's disease, taking as the gold standard the final diagnosis made after a long follow-up. To check the safety of capsule endoscopy and seek clinical variables predictive of Crohn's disease.</p> <p>Study design: Prospective, consecutive diagnostic accuracy study</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> Final diagnosis after long-term follow-up (median 21 months, range 15-29 months), including histological confirmation of surgical and enteroscopic tissue samples when available. Follow-up comprised clinical evaluation and a complete chemistry panel every 3 months or less if red flag symptoms appeared.</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> All patients referred for continuous or recurrent abdominal pain and diarrhoea of at least 3 months and at least 1 additional symptom (either iron deficiency anaemia, weight loss more than 10% of usual body weight, fever or unexplained arthritis or other extra-intestinal manifestations of inflammatory bowel disease). Negative or inconclusive findings on stool cultures, colonoscopy up to the caecum, routine chemistry panel, blood tests, small bowel series and/or ultrasound and/or CT.</p> <p><i>Exclusion:</i> Age <18 years, history of NSAID intake, presence of pacemakers for patients enrolled before May 2004, intra-cardiac defibrillator, previous intestinal surgery of irradiation, intestinal obstruction, dysphagia, pregnancy or inability to fully understand the CE procedure.</p> <p>Patient characteristics: Mean age 40 years \pmSD 18 years 13 female/14 male</p>	<p>Test accuracy: Threshold group A/B:</p> <table border="1" data-bbox="1189 387 1482 624"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td rowspan="3">CE</td> <td>+</td> <td>7</td> <td>1</td> <td>8</td> </tr> <tr> <td>-</td> <td>8</td> <td>11</td> <td>19</td> </tr> <tr> <td>Total</td> <td>15</td> <td>12</td> <td>27</td> </tr> </tbody> </table> <p>Sensitivity: 0.47 (95% CI 0.22-0.73) Specificity: 0.92 (95% CI 0.60-1.00) PPV: 0.88 (95% CI 0.47-0.99) NPV: 0.58 (95% CI 0.34-0.79) LR+: 5.60 LR-: 0.58</p> <p>Any small bowel mucosal abnormalities:</p> <table border="1" data-bbox="1189 983 1482 1219"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td rowspan="3">CE</td> <td>+</td> <td>14</td> <td>2</td> <td>16</td> </tr> <tr> <td>-</td> <td>1</td> <td>10</td> <td>11</td> </tr> <tr> <td>Total</td> <td>15</td> <td>12</td> <td>27</td> </tr> </tbody> </table> <p>Sensitivity: 0.93 (95% CI = 0.66-1.00) Specificity 0.83 (95% CI = 0.51-0.97) PPV: 0.88 (95% CI = 0.60-0.98)</p>			Reference standard – Follow-up					CD	No CD	Total	CE	+	7	1	8	-	8	11	19	Total	15	12	27			Reference standard – Follow-up					CD	No CD	Total	CE	+	14	2	16	-	1	10	11	Total	15	12	27	<p>Level III-2 Quality: FAIR Q2 Comparison: CX: for empirical treatment Patient selection: Prospective: yes Consecutive: yes Explicit selection criteria: yes <i>Reference standard:</i> Final diagnosis after long-term follow-up Valid: yes Applied to all participants: yes <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: median 21 months, range 15-29 months. Tests reported blinded to ref std: nr Ref std reported blinded to tests: no Routine clinical data available: nr <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: no Sufficient data for 2x2 table: yes</p> <p>Applicability P2: <i>Relevant population:</i> limited (lack of prior tests esp. C+IL, age, small bowel radiology) <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>
		Reference standard – Follow-up																																																
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		<p><i>Prior tests:</i></p> <ul style="list-style-type: none"> • Previous small bowel follow-through 37% (10/27) • Previous CT 26% (7/27) • Previous ultrasound 67% (18/27). <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • Abdominal pain and diarrhoea mean duration 19 weeks \pmSD 6 weeks • Anaemia 33% (9/27) • Fever 18% (5/27) • Weight loss 33% (9/27) • Arthritis or extra-intestinal manifestations 22% (6/27) <p>Interpretation/threshold: Subjects were assigned to 1 of 3 groups based on capsule endoscopy findings: Group A involved capsule retention for severe stricturing disease necessitating surgery. Group B involved moderate inflammatory disease based on >2 ulcers or cobblestone or skip lesions without lumen narrowing, requiring further invasive investigations. Group C involved minimal change lesions (\leq2 ulcers, apthae, erosions, focal erythema, focal villi denudation) or normal CE findings or nodularity of terminal ileum interpreted as lymphoid hyperplasia.</p>	<p>NPV: 0.91 (95% CI = 0.57-1.00) LR+: 5.60 LR-: 0.08</p> <p>Diagnostic yield: Any small bowel mucosal abnormalities consistent with inflammatory changes: 59% (16/27) (95% CI = 39-77%)</p> <p>Yield for >2 ulcers or stricture: 30% (8/27) (95% CI = 15-50%)</p> <p>Adverse events: Failure to reach caecum: 15% (4/27). 1 was due to slow gastric emptying, 3 retained the capsule due to an impacted stricture (11%). Of the 3 retained capsules, 2 were surgically removed and 1 was excreted following 1 week of corticosteroids.</p> <p>No other adverse events were found during or after the procedure. No technical failures.</p>	
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment																																																			
<p>Tukey et al (2009)</p> <p>USA Single tertiary care centre Patients who underwent capsule endoscopy before May 2007</p> <p>n=102 patients with suspected CD (excluding 3 patients without 12 month follow-up data)</p>	<p>Objective: To determine the utility and test characteristics of capsule endoscopy for the subsequent diagnosis of Crohn's disease in a cohort of patients suspected of this condition.</p> <p>Study design: Retrospective diagnostic accuracy study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> Diagnosis at 12 months – radiological, histological or endoscopic abnormalities consistent with Crohn's disease or treated for Crohn's disease on the basis of symptoms and additional objective findings.</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Adult patients who underwent CE before May 2007 for the evaluation of suspected Crohn's disease and had undergone other investigations that were normal or equivocal.</p> <p><i>Exclusion:</i> Previous diagnosis of Crohn's disease, actively being treated for a malignancy.</p> <p>Patient characteristics (n=105): Mean age 49.5 years <30 years 12% (13/105) 69 female/36 male</p> <p><i>Prior tests:</i></p> <ul style="list-style-type: none"> • Colonoscopy 99% • Radiological small bowel imaging by SBFT or CT 95% • Successful ileal intubation 64% of colonoscopies. <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • NSAIDs user 27% • Abdominal pain only 41% • Diarrhoea only 14% • Pain and diarrhoea 41% • Met ICCE criteria for suspected CD 75% • Normal CT or SBFT 80% • Abnormal CT or SBFT 20% • Normal colonoscopy 87% • Abnormal colonoscopy 13% 	<p>Test accuracy:</p> <p>Any small bowel ulcers:</p> <table border="1" data-bbox="1189 416 1485 703"> <thead> <tr> <th colspan="2"></th> <th colspan="3">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>CD</th> <th>No CD</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">CE</th> <th>+</th> <td>11</td> <td>23</td> <td>34</td> </tr> <tr> <th>-</th> <td>2</td> <td>66</td> <td>68</td> </tr> <tr> <th>Total</th> <td>13</td> <td>89</td> <td>102</td> </tr> </tbody> </table> <p>Sensitivity: 0.85 (95% CI 0.58-0.96) Specificity: 0.74 (95% CI 0.64-0.82) PPV: 0.32 (95% CI 0.19-0.49) NPV: 0.97 (95% CI 0.90-0.99) LR+: 3.27 LR-: 0.21</p> <p>>3 ulcers:</p> <table border="1" data-bbox="1189 1038 1485 1294"> <thead> <tr> <th colspan="2"></th> <th colspan="4">Reference standard – Follow-up</th> </tr> <tr> <th colspan="2"></th> <th>Yes</th> <th>No</th> <th>?</th> <th>Total</th> </tr> </thead> <tbody> <tr> <th rowspan="3">CE</th> <th>+</th> <td>10</td> <td>10</td> <td>0</td> <td>20</td> </tr> <tr> <th>-</th> <td>3</td> <td>79</td> <td>3</td> <td>85</td> </tr> <tr> <th>Total</th> <td>13</td> <td>89</td> <td>3</td> <td>105</td> </tr> </tbody> </table> <p>? = 12 month FU data unavailable.</p>			Reference standard – Follow-up					CD	No CD	Total	CE	+	11	23	34	-	2	66	68	Total	13	89	102			Reference standard – Follow-up						Yes	No	?	Total	CE	+	10	10	0	20	-	3	79	3	85	Total	13	89	3	105	<p>Level III-2 Quality FAIR Q2 Comparison: CX: for empirical treatment</p> <p>Patient selection: Prospective: no Consecutive: nr Explicit selection criteria: yes <i>Reference standard:</i> Diagnosis at 12 months Valid: yes Applied to all participants: yes <i>Test interval in days/weeks:</i> Comparator: N/A Tests reported blinded to ref std: nr Ref std reported blinded to tests: no Routine clinical data available: nr <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: yes Sufficient data for 2x2 table: no</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>
		Reference standard – Follow-up																																																					
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		<p>Interpretation/threshold: Abnormal capsule endoscopy: Any ulcers in the small bowel detected by capsule endoscopy, classified as:</p> <ul style="list-style-type: none"> • grade A (>3 small bowel ulcers) • grade B (1-3 small bowel ulcers), or • grade C (small bowel inflammation without ulcers). 	<p>2x2 tables obtained via personal correspondence with authors.</p> <p>Sensitivity: 0.77 (95% CI 0.50-0.92) Specificity: 0.89 (95% CI 0.81-0.94) PPV: 0.50 (95% CI 0.30-0.70) NPV: 0.96 (95% CI 0.90-0.99) LR+: 6.85 LR-: 0.26</p> <p>Diagnostic yield: Any small bowel ulcers: 37% (39/105) (95% CI = 29-47%)</p> <p>>3 small bowel ulcers: 19% (20/105) (95% CI = 13-28%)</p> <p>Adverse events: No patients had an incomplete study because of the obstruction of the capsule in the small intestine. The study was repeated if the capsule failed to reach the caecum (number not reported).</p>	
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Study profiles of included studies on diagnostic yield

Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Chong et al (2005)</p> <p>Australia Single tertiary hospital May 2002-November 2003</p> <p>n=43 patients – 21 with suspected Crohn's disease, 22 with known (non-small bowel) Crohn's disease.</p> <p>Results presented for suspected Crohn's disease only.</p> <p>Follow-up (Group 2): Mean 8.4 months (range 3-15).</p>	<p>Objective: To evaluate the diagnostic yield of capsule endoscopy compared with push enteroscopy and enteroclysis in the detection of suspected small bowel Crohn's disease in patients with no prior diagnosis of Crohn's disease or with known Crohn's disease with suspected recurrence or more extensive small bowel disease than identified by other investigations. To determine the effect of capsule endoscopy on management and patient outcomes.</p> <p>Study design: Prospective, non-consecutive, blinded diagnostic yield study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> Push enteroscopy Enteroclysis (double contrast SBFT)</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria for the suspected Crohn's disease sub-group (n=21):</p> <p><i>Inclusion:</i> Patients without a prior diagnosis of Crohn's disease suspected to have small bowel Crohn's disease based on symptoms ± biochemical markers or radiography.</p> <p><i>Exclusion:</i> Age <14 years, pregnancy, dysphagia, NSAIDs, presence of a pacemaker. Patients did not undergo capsule endoscopy if strictures were identified via enteroclysis.</p> <p>Patient characteristics: Mean age 35 years, range 20-80 years 11 female/10 male</p> <p><i>Prior tests:</i> Prior tests deemed appropriate by the gastroenterologist, including endoscopy, barium contrast radiography of the small bowel, abdomen CT and nuclear scintigraphy (indium-labelled white cell). Abnormal radiology 14% (3/21) A complete blood count, erythrocyte sedimentation rate,</p>	<p>Test performance:</p> <p>Diagnostic yield: 24% (4/17) (95% CI 8-50%)</p> <p>2 TP/2 FP (on the basis of follow-up and prior tests)</p> <p>Assumptions: Patients for whom capsule endoscopy failed to reach the caecum were excluded (4 patients).</p> <p>Impact on management: 4 positive results: <ul style="list-style-type: none"> • 1 lost to FU (CD) • 1 corticosteroid (CD) • 1 mesalazine • 1 surgery • (pre-CE plan not stated). </p> <p>The impact on management related to the effect of all the investigations (capsule endoscopy, push enteroscopy, enteroclysis). The management plan was changed for 14/21 patients compared with the pre-CE plan.</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment Patient selection: Prospective: yes Consecutive: no Explicit selection criteria: no <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: Comparator not applicable for this report Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: no <i>Analysis:</i> Uninterpretable/intermediate results reported: no Study withdrawals explained: yes Sufficient data for 2x2 table: N/A</p> <p>Applicability P2: <i>Relevant population:</i> unknown <i>Applicable comparator:</i> no <i>Applicable intervention:</i> yes</p>

		<p>C-reactive protein and iron studies were obtained at enrolment.</p> <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • Pain 71% (15/21) • Diarrhoea 76% (16/21) • Raised ESR/CRP 33% (7/21) • Iron deficiency 24% (5/21) <p>Interpretation/threshold: Not explicitly defined, however it appears that yield was calculated based on the presence of any erosions or ulcers.</p>	<p>Patients with a normal CE result did not receive further evaluation for small bowel Crohn's disease and were treated expectantly or as having irritable bowel syndrome.</p> <p>Adverse events: Failure to reach caecum: 19% (4/21) No capsules were retained.</p>	
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment															
<p>De Bona et al (2006)</p> <p>Italy Clinical setting not reported Recruitment period not reported</p> <p>n=38 patients with suspected Crohn's disease</p>	<p>Objective: To assess the role of capsule endoscopy in the diagnosis of patients with suspected Crohn's disease.</p> <p>Study design: Prospective, consecutive, diagnostic yield study</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Clinical features suggestive of Crohn's disease.</p> <p>Patients were divided into 2 groups:</p> <p>Group 1. Those with ongoing symptoms (weight loss and/or abdominal pain and/or chronic diarrhoea and/or anaemia) (n=12)</p> <p>Group 2. Those with ongoing symptoms and biochemical inflammatory markers (CRP and/or ESR) (n=26)</p> <p><i>Exclusion:</i> Pregnancy, swallowing disorders, NSAIDs in the previous 4 weeks and the presence of a pacemaker.</p> <p>Patient characteristics: Mean age 46.2 years, range 17-76 years. 22 female/16 male</p> <p><i>Prior tests:</i> Negative on conventional imaging (Upper/lower endoscopy, retrograde ileoscopy and SBFT). Before capsule endoscopy, a complete blood count, erythrocyte sedimentation rate, C-reactive protein and iron studies were obtained.</p>	<p>Test performance:</p> <p>Diagnostic yield:</p> <table border="1" data-bbox="1189 416 1458 616"> <tr> <td>Diagnostic</td> <td>13</td> <td>34%</td> </tr> <tr> <td>Suspicious</td> <td>2</td> <td>5%</td> </tr> <tr> <td>Non-specific</td> <td>4</td> <td>11%</td> </tr> <tr> <td>Normal</td> <td>19</td> <td>50%</td> </tr> <tr> <td>Total</td> <td>38</td> <td>100%</td> </tr> </table> <p>Diagnostic: 34% (95% CI 20-51%)</p> <p>Diagnostic and suspicious: All: 39% (15/38) (95% CI 25-57%)</p> <p>Group 2: 46.2% (14/26) (95% CI 34-73%)</p> <p>Group 1: 8.3% (1/12) (95% CI 0.4-40%)</p> <p>(Group 1 versus Group 2: p = 0.022)¹</p> <p>1. Reported % for group 2 does not equal reported numerator/denominator. If Group 2 is 14/26 (53.8%) then p = 0.01 (Fisher's exact test).</p> <p>Adverse events: Capsule retention: 2.6% (1/38) Failure to reach colon: 2.6% (1/38) These occurred in 1 patient (due</p>	Diagnostic	13	34%	Suspicious	2	5%	Non-specific	4	11%	Normal	19	50%	Total	38	100%	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment</p> <p>Patient selection: Prospective: yes Consecutive: yes Explicit selection criteria: yes <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: nr <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: nr Sufficient data for 2x2 table: N/A</p> <p>Applicability P1: <i>Relevant population:</i> applicable <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>
Diagnostic	13	34%																	
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		<p><i>Clinical characteristics:</i></p> <table border="1"> <thead> <tr> <th></th> <th>Group 1</th> <th>Group 2</th> </tr> </thead> <tbody> <tr> <td>Abdominal pain %</td> <td>58.3% (7/12)</td> <td>88.5% (23/26)</td> </tr> <tr> <td>Diarrhoea %</td> <td>25% (3/12)</td> <td>42.3% (11/26)</td> </tr> <tr> <td>Iron deficiency %</td> <td>75% (9/12)</td> <td>80.8% (21/26)</td> </tr> <tr> <td>Weight loss %</td> <td>16.7% (4/12)*</td> <td>30.8% (8/26)</td> </tr> </tbody> </table> <p>*reported % does not equate with reported numerator / denominator</p> <p>Interpretation/threshold: Findings were classified as either:</p> <ul style="list-style-type: none"> • diagnostic (multiple erosions or ulcerations), or • suspicious (≤ 3 erosions or ulcerations and/or nodular mucosa pattern), or • non-specific (mucosal changes unrelated to Crohn's disease), or • normal (no changes). 		Group 1	Group 2	Abdominal pain %	58.3% (7/12)	88.5% (23/26)	Diarrhoea %	25% (3/12)	42.3% (11/26)	Iron deficiency %	75% (9/12)	80.8% (21/26)	Weight loss %	16.7% (4/12)*	30.8% (8/26)	<p>to unsuspected small bowel stenosis) leading to elective laparotomy for capsule retrieval.</p> <p>No other adverse events occurred during the procedure.</p>	
	Group 1	Group 2																	
Abdominal pain %	58.3% (7/12)	88.5% (23/26)																	
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Weight loss %	16.7% (4/12)*	30.8% (8/26)																	

Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Efthymiou et al (2009)</p> <p>Greece Single tertiary referral centre with patients referred from 3 general hospitals in Athens September 2003-May 2006</p> <p>n=55 (29 with known Crohn's disease, 26 with suspected Crohn's disease)</p>	<p>Objective: To prospectively compare the diagnostic yield of wireless capsule endoscopy and double contrast enteroclysis in the detection of small bowel Crohn's disease in a large cohort of patients.</p> <p>Study design: Prospective, blinded, diagnostic yield study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> Barium radiography (double contrast enteroclysis)</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria for patients with suspected Crohn's disease (n=26):</p> <p><i>Inclusion:</i> Patients suspected of Crohn's disease on the basis of symptoms, biochemical markers of inflammation or radiology. Patients had at least 1 of: constant or intermittent abdominal pain for more than 3 months, chronic diarrhoea (>1 month) of any severity, anaemia or weight loss.</p> <p><i>Exclusion:</i> Pregnancy, age <18 years, earlier use of NSAIDs, stenosing Crohn's disease, history of small bowel surgery, presence of a pacemaker, strictures found during enteroclysis.</p> <p>Patient characteristics: Mean age 33.9 years (range 19-55 years) 15 female/11 male</p> <p><i>Prior tests:</i> Evaluation by the treating physician prior to enrolment which may include clinical examination, inflammatory biochemical markers, colonoscopy, abdomen CT and SBFT. Clinical assessment, full blood count, electrolytes and C-reactive protein were obtained</p>	<p>Test performance:</p> <p>Diagnostic yield: 61.5% (16/26) (95% CI 41-79%)</p> <p>Adverse events: Failure to reach caecum: 3.8% (1/26)</p> <p>No capsule retention or other adverse effects were found (inability to swallow, dysphagia induced by the capsule, abdominal pain).</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment Patient selection: Prospective: yes Consecutive: no Explicit selection criteria: yes <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: Inapplicable comparator Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: no <i>Analysis:</i> Uninterpretable/intermediate results reported: no Study withdrawals explained: yes Sufficient data for 2x2 table: N/A</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> no <i>Applicable intervention:</i> yes</p>

		<p>at enrolment. All had colonoscopy. 37/55: attempted ileoscopy. 28/55: successful ileoscopy.</p> <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • Abdominal pain 77% (20/26) • Diarrhoea 73% (19/26) • Anaemia 30.7% (8/26) • Weight loss 11.5% (3/26) • Raised C-reactive protein 57.7% (15/26) • Abnormal radiology 11.5% (3/26) • Crohn's disease activity index 186 (range 114-290) <p>Interpretation/threshold:</p> <p>Positive findings: diffuse erythema, erosions, >3 aphthous ulcers, ulcers of different shape and strictures. Non-specific and classified as negative: <3 aphthous ulcers, isolated mucosal breaks and non-specific erythematous spots.</p>		
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Eliakim et al (2004)</p> <p>Final report of Eliakim et al (2003)</p> <p>Israel Single centre (outpatient clinic with patients referred by family practitioner or gastroenterologist) Recruitment period not reported</p> <p>n=35 patients with suspected Crohn's disease</p>	<p>Objective: To prospectively compare capsule endoscopy with barium follow through and entero computerised tomography in patients with suspected Crohn's disease.</p> <p>Study design: Prospective, consecutive, blinded diagnostic yield study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> Entero-CT Barium SBFT</p> <p><i>Reference test:</i> N/A but colonoscopy and ileoscopy were used in cases of discrepancy.</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Patients with chronic diarrhoea and/or recurrent abdominal pain and/or weight loss were referred by either family practitioners or gastroenterologists to the outpatient clinic.</p> <p><i>Exclusion:</i> History of bowel obstruction, major abdominal surgery, diabetes mellitus, cardiac pacemaker, mental condition precluding compliance, pregnancy, taking NSAIDs. Strictures discovered via barium follow through.</p> <p>Patient characteristics: Mean age 28.4 years (range 19-57 years) 13 female/22 male</p> <p><i>Prior tests:</i> Colonoscopies, gastroscopies, barium follow through, CT scans. Prior tests did not explain the patients' symptoms.</p> <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • Mean weight 67kg • Abdominal pain 89% • Diarrhoea 83% • Weight loss 69% • Significant weight loss 45% • No evidence of gastrointestinal bleeding 	<p>Test performance:</p> <p>Diagnostic yield:</p> <p>CE: 77% (27/35) (95% CI 59-89%)</p> <p>CE confirmed radiological findings in 9, extended involvement in 6 and ruled out radiological suspicion of CD in 10.</p> <p>CTE: 20% (raw data nr)</p> <p>Capsule endoscopy had a significantly higher diagnostic yield than CTE (p<0.0125).</p> <p>Capsule endoscopy detected all of the lesions diagnosed by CTE.</p> <p>Adverse events: No capsule retention occurred. No side-effects occurred during or after the procedure. There were no problems ingesting the capsule.</p>	<p>Level IV Quality POOR Q3 Comparison: C1: for CTE CX: for empirical treatment Patient selection: Prospective: yes Consecutive: yes Explicit selection criteria: yes <i>Reference standard:</i> Valid: N/A (ileoscopy was used to confirm controversial results for 17 patients) Applied to all participants: no <i>Test interval in days/weeks:</i> Comparator: Barium follow through followed by capsule endoscopy, then CTE. Completed within 3 months of each other Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: no <i>Analysis:</i> Uninterpretable/intermediate results reported: yes/partially Study withdrawals explained: no Sufficient data for 2x2 table: N/A</p> <p>Applicability P2: <i>Relevant population:</i> no/limited (ileoscopy, prior tests) <i>Applicable comparator:</i> yes (CTE) <i>Applicable intervention:</i> yes</p>

		<p>Interpretation/threshold: Capsule findings that were 'medically significant or explained the patient's reason for referral' were considered for the purposes of calculating diagnostic yield.</p>		
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Ge et al (2004)</p> <p>China Clinical setting not reported May 2002-April 2003 n=20 patients with suspected Crohn's disease</p>	<p>Objective: To evaluate the effectiveness of wireless capsule endoscopy in patients with suspected Crohn's disease of the small bowel undetected by conventional modalities and to determine the diagnostic yield of M2A Given capsule endoscopy.</p> <p>Study design: Prospective diagnostic yield study</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria:</p> <p><i>Inclusion:</i> Patients with suspected Crohn's disease of the small bowel undetected by conventional modalities based on symptoms such as abdominal pain, weight loss, positive faecal occult blood test, iron deficiency anaemia, diarrhoea and fever.</p> <p><i>Exclusion:</i> History of bowel obstruction, x-ray evidence of small bowel stricture, evidence of any pathological abnormalities of the small bowel, any use of NSAIDs in the past year.</p> <p>Patient characteristics: Mean age 45.2 years (range 16-78 years) 5 female/15 male</p> <p><i>Prior tests:</i> Normal results in small bowel series and upper and lower gastrointestinal endoscopy within 6 months preceding the examination. Total colonoscopy (16/20), successful ileoscopy (5/20) gastroscopy (20/20), abdomen CT (14/20), small bowel x-ray series (20/20).</p> <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> Anaemia 55% (10/20) Haemoglobin mean 8% SD 2% 	<p>Test performance:</p> <p>Diagnostic yield:</p> <p>CE: 65% (13/20) (95% CI 41-84%)</p> <p>Adverse events: Capsule retention 15% (3/20) due to small bowel stenosis caused by Crohn's disease. None showed symptoms of acute or subacute obstruction. Failure to reach colon: 10% (2/20).</p> <p>No complications were observed.</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment Patient selection: Prospective: yes Consecutive: nr Explicit selection criteria: no <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: nr <i>Analysis:</i> Uninterpretable/intermediate results reported: no Study withdrawals explained: no Sufficient data for 2x2 table: N/A</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>

		<ul style="list-style-type: none"> • Abdominal pain 70% (14/20) • Diarrhoea 20% (4/20) • Weight loss 15% (3/20) • Fever 10% (2/20) • Positive faecal occult blood test 65% (13/20) <p>Mean duration of symptoms before diagnosis was 6.5 years (SD 6.5)</p> <p>Interpretation/threshold: Not explicitly defined but it appears that a variety of findings other than normal small bowel mucosa were considered indicative of Crohn's disease, for example mucosal erosions, aphthas, nodularity, large ulcers and ulcerated stenosis.</p>		
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Guilhon de Araujo Sant'Anna et al (2005)</p> <p>Canada Single referral centre October 2001-November 2002 n=30 paediatric patients (10-18 years) including 20 paediatric patients with suspected Crohn's disease</p>	<p>Objective: To evaluate the diagnostic value of capsule endoscopy for identifying specific, obscure small bowel disorders in children and adolescents (Crohn's disease, polyposis, OGIB). To determine its safety and tolerance in this age group.</p> <p>Study design: Prospective, non-consecutive diagnostic yield study</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria for suspected CD: (n=20): <i>Inclusion:</i> Patients clinically suspected to have Crohn's disease that had undergone traditional investigations (see prior tests) that neither confirmed nor excluded a diagnosis of Crohn's disease.</p> <p><i>Exclusion:</i> NSAIDs in previous 3 weeks.</p> <p>Patient characteristics (n=30): Not reported by subgroup. Mean age 14.1 years (range 10-18 years) 13 female/17 male</p> <p><i>Prior tests:</i> Colonoscopy with biopsy SBFT Normal or non-diagnostic 20/20</p> <p><i>Clinical characteristics:</i> nr</p> <p>Interpretation/threshold: CE findings were classified as:</p> <ul style="list-style-type: none"> • positive – a diagnosis for any condition was established • suspicious – uncertain relationship between the observed lesion and the clinical presentation. • negative – no abnormalities 	<p>Test performance:</p> <p>Diagnostic yield:</p> <p>Findings positive for CD (excluding suspicious results):</p> <p>CE: 50% (10/20) (95% CI 28-72%)</p> <p>Findings positive for any diagnosis (excluding suspicious results):</p> <p>CE: 60% (12/20) (95% CI 36-80%)</p> <p>Adverse events: Not reported by subgroup.</p> <p>There was some difficulty convincing younger children to swallow the capsule due to its size.</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment Patient selection: Prospective: yes Consecutive: nr Explicit selection criteria: no <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Prior tests were performed within 4 weeks prior to the CE. Comparator: N/A Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: partially <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: nr Sufficient data for 2x2 table: N/A</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>

Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Herrerias et al (2003)</p> <p>Spain Clinical setting not reported Recruitment period not reported n=21 patients with suspected Crohn's disease</p>	<p>Objective: To assess the value of capsule endoscopy in the diagnostic work-up of patients in whom there is a clinical suspicion of incipient small bowel Crohn's disease not confirmed by conventional radiological and endoscopic findings.</p> <p>Study design: Prospective diagnostic yield study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Clinical and biochemical suspicion of Crohn's disease as indicated by symptoms (chronic diarrhoea (>6 months), diffuse abdominal pain, fever or weight loss). Crohn's disease not confirmed using traditional techniques.</p> <p><i>Exclusion:</i> Taking NSAIDs.</p> <p>Patient characteristics: Mean age 43 ± 8 years 7 female/14 male</p> <p><i>Prior tests:</i> Conventional imaging workup - including upper and lower endoscopy, SBFT. Antigliadin antibodies, stool culture, examinations for ova and parasites, thyroid hormones with normal results. Normal colonoscopy with biopsy with 1 exception. Attempted ileoscopy with biopsy (17/21) with no macroscopic abnormalities. Histological examination showed minimal changes (6/21) or normal mucosa (11/21).</p> <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • Diarrhoea 100% (21/21) • Abdominal pain 100% (21/21) • Weight loss 52.4% (11/21) • Fever 33.3% (7/21) 	<p>Test performance:</p> <p>Diagnostic yield:</p> <p>CE: 42.9% (9/21) (95% CI 23-66%)</p> <p>Adverse events: The capsule reached the colon and was excreted uneventfully in all patients No adverse events were observed.</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment Patient selection: Prospective: yes Consecutive: nr Explicit selection criteria: no <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: nr <i>Analysis:</i> Uninterpretable/intermediate results reported: no Study withdrawals explained :nr Sufficient data for 2x2 table :N/A</p> <p>Applicability P2: <i>Relevant population:</i> limited <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>

		<ul style="list-style-type: none">• Haemoglobin <10g/dl 42.9% (9/21)• Leukocytes >12000/μl 42.9% (9/21)• CRP >0.8 mg/dl 38.1% (8/21) <p>Interpretation/threshold: Not explicitly defined. Observation of lesions supporting the diagnosis of Crohn's disease.</p>		
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment																		
<p>Selby et al (2008)</p> <p>Australia Multicentre Recruitment period not reported n=120 enrolled patients with suspected Crohn's disease</p> <p>Funding: Given Imaging Pty Ltd</p>	<p>Objective: To evaluate the yield of capsule endoscopy for the diagnosis of small bowel Crohn's disease in symptomatic patients with non-diagnostic standard work-up. To assess the clinical impact of capsule endoscopy in these patients.</p> <p>Study design: Prospective diagnostic yield study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> ≥10 years old, abdominal pain and/or diarrhoea for the last 6 weeks and/or extra-intestinal manifestations of Crohn's disease, plus at least 1 additional sign over the preceding 6 months (eg positive inflammatory marker, unexplained anaemia, recurrent fever – see Selby et al (2008) for complete list), non-diagnostic standard evaluation within 6 months prior to enrolment (including colonoscopy, attempted ileoscopy and SBFT).</p> <p><i>Exclusion:</i> Known history of small bowel Crohn's disease, patients with indeterminate colitis where the purpose is only to make a definitive diagnosis and inclusion criteria are not met, suspected celiac disease or life threatening conditions, known intestinal obstruction or definite stricture seen on SBFT, suspected stricture and did not pass the patency capsule, pacemaker or other implanted electromedical device, on treatment for active inflammatory bowel disease, NSAIDs during the 3 months preceding enrolment or currently participating in another clinical study that may affect the study results, pregnant.</p>	<p>Test performance:</p> <p>Diagnostic yield:</p> <p>Definite Crohn's disease:</p> <p>24/120 = 20% (95% CI = 14-28%) Definite + possible Crohn's disease:</p> <p>33/120 = 28% (95% CI = 20-36%)</p> <p>Interobserver variability: ≥3 ulcers or aphthoid lesions K=0.793 ≥1 and <3 ulcers or aphthoid lesions K = 0.823</p> <table border="1" data-bbox="1189 858 1480 1182"> <thead> <tr> <th></th> <th>N</th> <th>Yield</th> </tr> </thead> <tbody> <tr> <td>Normal</td> <td>82</td> <td>683%</td> </tr> <tr> <td>Possible</td> <td>9</td> <td>7.7%</td> </tr> <tr> <td>Definite</td> <td>24</td> <td>20%</td> </tr> <tr> <td>Capsule technical failure or retention</td> <td>5</td> <td>4.2%</td> </tr> <tr> <td>Total</td> <td>120</td> <td>100%</td> </tr> </tbody> </table> <p>Adverse events: 2 moderate to severe adverse events were reported during the study – 1 patient had severe nausea with vomiting that were treated with anti-nausea</p>		N	Yield	Normal	82	683%	Possible	9	7.7%	Definite	24	20%	Capsule technical failure or retention	5	4.2%	Total	120	100%	<p>Level IV Quality POOR Comparison: CX: Empirical treatment Patient selection: Prospective: yes Consecutive: nr Explicit selection criteria: yes <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: no <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: yes Sufficient data for 2x2 table: N/A</p> <p>Applicability P1: <i>Relevant population:</i> yes <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>
	N	Yield																				
Normal	82	683%																				
Possible	9	7.7%																				
Definite	24	20%																				
Capsule technical failure or retention	5	4.2%																				
Total	120	100%																				

		<p>Patient characteristics (n=115, excludes patients with failed capsule endoscopy): Mean age 35 years, SD 12.96 years (range 11-73 years) 83 female/32 male</p> <p><i>Prior tests:</i> All patients underwent colonoscopy and radiological tests. 94 of 115 patients underwent upper endoscopy. There was an average of 4.6 procedures per patient (average 1.6 colonoscopies per patient, 1.8 radiological tests per patient and 1.5 upper endoscopies per patient).</p> <p><i>Clinical characteristics:</i></p> <ul style="list-style-type: none"> • Abdominal pain 93% (107/115) • Diarrhoea 78% (90/115) • Weight loss 51% (59/115) • Positive inflammatory markers 42% (48/115) • Constipation 24% (28/115) • Vomiting 17% (20/115) • Anaemia 6% (7/115) • Nausea 3% (4/115) • Fever 2% (2/115) <p>Interpretation/threshold: CE findings were categorised as definite Crohn's disease (>3 small bowel ulcerations), possible Crohn's disease (≤3 small bowel ulcerations) or normal or non-Crohn's disease (without ulcerations but non-specific findings).</p>	<p>medication, the other suffered from moderate pain. Both events were resolved within 24 hours.</p> <p>Incomplete capsule endoscopy due to either failure to reach the caecum or technical failure: 12.5% (15/120)</p> <p>Incomplete capsule endoscopy due to failure to reach the caecum: 9.2% (11/120)</p> <p>Incomplete capsule endoscopy due to technical failure of the RAPID® workstation: 3.3% (4/120)</p> <p>Capsule retention 0.8% (1/120)</p>	
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Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
Valle et al (2006) Spain Single centre May 2004-September 2005 n=23 patients with suspected Crohn's disease	<p>Objective: To determine which clinical features predict the diagnosis of Crohn's disease by capsule endoscopy in patients with suggestive symptoms but negative results from traditional diagnostic work-up.</p> <p>Study design: Prospective diagnostic yield study.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Patients with negative results from conventional imaging techniques but suspected of Crohn's disease based on long standing abdominal pain and/or diarrhoea and at least 1 symptom (anaemia, weight loss, long standing fever, perianal disease, extra-intestinal manifestations typical of inflammatory bowel disease, elevated inflammatory parameters (C-reactive protein, platelet count, fibrinogen, erythrocyte sedimentation rate), family history of inflammatory bowel disease).</p> <p><i>Exclusion:</i> NSAIDs taken for >1 week during the previous 6 months.</p> <p>Patient characteristics: Mean age 40 ± 15 years 16 female/7 male</p> <p><i>Prior tests:</i></p> <ul style="list-style-type: none"> • Colonoscopy 100% • Attempted ileoscopy (52% reached distal ileum) • SBFT 100% • Upper gastrointestinal endoscopy 61% (14/23) <p><i>Clinical characteristics:</i> No patients had strictures revealed by the SBFT.</p>	<p>Test performance:</p> <p>Diagnostic yield:</p> <p>Excluding patients with possible Crohn's disease (n=2)</p> <p>CE: 26.1% (6/23) (95% CI 11-49%)</p> <p>Definite or possible Crohn's disease:</p> <p>CE: 34.8% (8/23) (95% CI 17-57%)</p> <p>Diagnosis of any condition:</p> <p>CE: 57% (13/23) (95% CI 35-76%)</p> <p>Adverse events: Capsule retention: 8.7% (2/23), 1 in whom no strictures had been found on SBFT and who excreted the capsule 25 days later following oral steroid therapy, 1 who underwent surgical resection for a carcinoid tumour which included surgical removal of the capsule.</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment</p> <p>Patient selection: Prospective: yes Consecutive: no Explicit selection criteria: yes <i>Reference standard:</i> Valid: N/A Applied to all participants: N/A <i>Test interval in days/weeks:</i> Comparator: N/A Ref std: N/A Tests reported blinded to ref std: N/A Ref std reported blinded to tests: N/A Routine clinical data available: <i>Analysis:</i> Uninterpretable/intermediate results reported: yes Study withdrawals explained: nr Sufficient data for 2x2 table: N/A</p> <p>Applicability P1: <i>Relevant population:</i> yes <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>

		<p>Interpretation/threshold: Severe capsule endoscopy findings such as ≥ 2 irregular/fissural ulcers and/or strictures were considered to indicate Crohn's disease. Mild changes (eg aphthoid ulcerations, villous denudation, patchy erythema) were not considered sufficient for a diagnosis of Crohn's disease.</p>		
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Study profiles of included studies on safety

Author/Year Country Setting n	Study objective and design	Study population	Results	Quality assessment
<p>Cheifetz et al (2006)</p> <p>USA Multicentre (3 private gastroenterology practices) December 2000-December 2003 n=102 patients with suspected (n=64) or known (n=38) Crohn's disease.</p>	<p>Objective: To determine the risk of capsule retention in patients with suspected or known Crohn's disease and to describe their clinical outcomes.</p> <p>Study design: Retrospective case series.</p> <p><i>Index test:</i> Capsule endoscopy</p> <p><i>Comparator test:</i> N/A</p> <p><i>Reference test:</i> N/A</p>	<p>Inclusion/exclusion criteria: <i>Inclusion:</i> Patients with suspected Crohn's disease for whom capsule endoscopy was performed at the authors' private gastroenterology practices.</p> <p><i>Exclusion:</i> nr</p> <p>Patient characteristics: nr</p> <p><i>Prior tests:</i> nr</p> <p><i>Clinical characteristics:</i> nr</p> <p>Interpretation/threshold: nr</p>	<p>Test accuracy: N/A</p> <p>Adverse events: Capsule retention in patients with suspected Crohn's disease: 1.6% (1/64)</p> <p>1 patient with suspected Crohn's disease and a possible small bowel obstruction retained the capsule with no symptoms of acute small bowel obstruction. After 3 months, symptoms consistent with recurrent partial small bowel obstructions occurred and the capsule was removed via elective surgery, leading to the resolution of all symptoms.</p>	<p>Level IV Quality POOR Q3 Comparison: CX: for empirical treatment Representative sample: nr Explicit selection criteria: no Similar entry point: nr Adequate duration of FU: yes Were the techniques used adequately described? no Objective outcomes: no Blinding: no Comparison of sub-series: N/A</p> <p>Applicability P2: <i>Relevant population:</i> Unknown; probably limited <i>Applicable comparator:</i> N/A <i>Applicable intervention:</i> yes</p>

Appendix E Excluded studies

The following studies were assessed as ineligible against the inclusion criteria (see Table 12) after the full paper was retrieved for evaluation.

Excluded due to wrong publication type

Berry, PA, Srirajaskanthan, R et al 2010. An urgent call to the magnetic resonance scanner: Potential dangers of capsule endoscopy, *Clinical Gastroenterology and Hepatology*, 8 (5), A26.

Biko, DM, Anupindi, SA et al 2010. Does wireless capsule endoscopy (WCE) eliminate need for small bowel follow-through (SBFT) and/or CT in patients with inflammatory bowel disease (IBD)?, *Pediatric Radiology*, 40 (4), 582-583.

Cave, DR 2006. Technology insight: Current status of video capsule endoscopy, *Nature Clinical Practice Gastroenterology and Hepatology*, 3 (3), 158-164.

Ciorba, MA and Prakash, C 2003. Wireless capsule endoscopy in the diagnosis of small bowel Crohn's disease, *Inflammatory Bowel Diseases*, 9 (4), 276.

Coron, E, Cholet, F et al 2007. Capsule endoscopy at AGA (American Gastroenterology Association) 2007: A good year?, *Hepato-Gastro*, 14 (5), 411-421.

Costea, F and Seidman, EG 2010. Survey on the value of capsule endoscopy in clinical practice: The referring gastroenterologist's perspective, *Gastrointestinal Endoscopy*, 71 (5), AB245.

de Graaf, AP, Westerhof, J et al 2008. Correlation between predicted and actual consequences of capsule endoscopy on patient management, *Digestive and Liver Disease*, 40 (9), 761-766.

Doherty, GA, Moss, AC et al 2010. Capsule endoscopy in suspected Crohn's disease: Yield does not equal diagnosis, *American Journal of Gastroenterology*, 105 (9), 2111.

Eisen, G 2005. Capsule endoscopy for Crohn's disease: The test of choice?, *Evidence-Based Gastroenterology*, 6 (4), 112-113.

Eisen, GM 2006. The economics of PillCam, *Gastrointestinal Endoscopy Clinics of North America*, 16 (2), 337-345.

Eisen, GM and Schreiner, M 2007. Small-bowel endoscopy, *Endoscopy*, 39 (2), 113-117.

Eliakim, R 2007. The impact of capsule endoscopy on Crohn's disease, *Digestive and Liver Disease*, 39 (2), 154-155.

Erber, WF and Erber, JA 2006. Meta-analysis of the yield of capsule endoscopy in patients with Crohn's disease [8], *American Journal of Gastroenterology*, 101 (11), 2669.

Ersoy, O, Harmanci, O et al 2009. Capability of capsule endoscopy in detecting small bowel ulcers, *Digestive Diseases and Sciences*, 54 (1), 136-141.

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Appendix F Ongoing studies

Author/Year Setting n	Study objective and design	Study population	Results
<p>NCT01019460</p> <p>Jensen et al (2011)</p> <p>Denmark-based 5 sites Recruitment: From October 2007</p> <p>n=150</p> <p>Follow-up 12 months follow-up</p> <p>Sponsor/Collaborators: University of Southern Denmark, Odense Private Hospital Vejele Hospital</p>	<p>Objective: To evaluate three diagnostic methods for assessing small bowel disease in patients with suspected or known Crohn's disease (ileo-colonoscopy, MRI, CT of the small bowel and, if no stenosis was detected, capsule endoscopy). To establish the diagnostic validity and inter-observer agreement of MRI, CT and capsule endoscopy and establish the optimal diagnostic strategy in these 2 patient categories.</p> <p>Study design: Comparative, diagnostic accuracy study. Subject and caregiver are blinded.</p> <p>At inclusion all patients will have a standardised work-up including medical history, physical examination, blood and faeces samples and ileo-colonoscopy. Within 2 weeks MRI and CT scanning of the small intestine are performed (on the same day and in randomised order) and, if no stenosis is found, CE.</p> <p>All investigations are described in a similar pre-defined and standardised fashion and the radiologist and physician responsible for describing the findings at MRI, CT and CE are blinded to the findings at ileo-colonoscopy and other small bowel examinations. In follow-up, the treating physician receives a randomised result (MRI, CT or CE) and patients are followed up for 12 months to evaluate differences in clinical outcome.</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age >15 years • written informed consent. <p>Patients with established CD included if assessment of small bowel disease was necessary prior to expected surgery or a change in medical therapy.</p> <p>Patients with suspected CD included on either clinical, endoscopic or histological criteria or a combination of these.</p> <ul style="list-style-type: none"> • Clinical criteria: Diarrhoea and/or abdominal pain for more than 1 month (or repeated episodes) associated with at least 1 of: CRP >5 mg/l, thrombocytosis, anaemia, fever, weight loss, perianal abscess/fistula or a family history of inflammatory bowel disease. • Endoscopic criteria (≥1): Ulcerations and/or stenosis in the terminal ileum, inflammation in the colon not involving the rectum, and aphthous ulcerations in the colon. • Histological criteria (≥1): Epithelioid cell granulomas, chronic inflammation in the lamina muscularis mucosae or deeper and chronic inflammation in the colon not involving the rectum. <p>Exclusion criteria: Acute bowel obstruction, elevated serum-creatinine, severe claustrophobia, cardiac pacemaker, implanted magnetic foreign bodies, use of NSAIDs, pregnancy and lactation.</p>	<p>Outcomes:</p> <p><i>Primary end point</i> Sensitivity and specificity for CT, MRI and CE</p> <p><i>Secondary end points</i> Interobserver variation for CE, MRI and CT Patient-experienced discomfort</p>

Glossary and abbreviations

AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
ALOS	average length of stay
AR-DRG	Australian refined diagnosis related groups
AU	abdominal ultrasound
AUC	area under the curve
C+IL	colonoscopy with attempted ileoscopy
CD	Crohn's disease
CE	Capsule endoscopy
CEA	cost-effectiveness analysis
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CT	computed tomography
CTE	computed tomography with enterography
CUA	cost-utility analysis
DOR	diagnostic odds ratio
ED	emergency department
EGD	oesophagogastroduodenoscopy
ESR	erythrocyte sedimentation rate
ET	empirical treatment
FEM	fixed effects model
FN	false-negative
FP	false-positive
GP	general practitioner
HRQoL	health-related quality of life
HTA	health technology assessment
IBD	inflammatory bowel disease
ICD	international classification of disease
ICCE	International Conference on Capsule Endoscopy
IV	intravenous
KCE	Federaal Kenniscentrum voor de Gezondheidszorg (Belgium Health Care Knowledge Centre)
LFT	liver function test
LR	likelihood ratio
LR-	negative likelihood ratio
LR+	positive likelihood ratio

LTFU	long-term follow-up
MACCS	Multi Center Australian Capsule Endoscopy in Patients with Suspected Crohn's Disease Study
MAS	Medical Advisory Secretariat (Ontario, Canada)
MBS	Medicare Benefits Schedule
MR	magnetic resonance imaging with or without enterography
MRE	magnetic resonance imaging with enterography
MRI	magnetic resonance imaging without enterography
MS	microbiological stool tests
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence (UK)
NPV	negative predictive value
nr	not reported
NSAIDs	nonsteroidal anti-inflammatory drugs
OGIB	obscure gastrointestinal bleeding
p	p-value
PBS	Pharmaceutical Benefits Scheme
PJS	Peutz-Jeghers syndrome
PPICO	Population, Prior tests, Intervention, Comparator, Outcomes
PPV	positive predictive value
Q*	Cochran's Q* test
QALY	quality-adjusted life year
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy Included in Meta-Analyses
QUOROM	Quality of Reporting of Meta-analyses
ref std	reference standard
REM	random effects model
ROC	receiver operating characteristic
SBE	small bowel enteroclysis (barium imaging with enteroclysis)
SBFT	small bowel follow-through
SBR	small bowel radiology
SBS	small bowel series
SD	standard deviation
sn	sensitivity
sp	specificity
SR	systematic review
TGA	Therapeutic Goods Administration
TN	true-negative
TNF	tumour necrosis factor

TP	true-positive
U&E	urea, electrolytes and creatinine
UE	upper endoscopy
WHO	World Health Organization

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