Endoscopie par capsule

KCE reports vol. 25 B

Federaal Kenniscentrum voor de Gezondheidszorg
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Préface

Destinée à l'origine à des fins de renseignement, la technologie d'endoscopie par capsule a été récemment mise sur le marché pour des applications médicales. Le premier développement a porté sur l'aide au diagnostic d'affections de l'intestin grêle. Le patient avale une caméra vidéo (la capsule) qui retransmet des images à un mini-enregistreur porté à la ceinture. Ces images sont ensuite analysées sur écran.

Dans les méthodes classiques d'investigation endoscopique, le tube flexible qui est introduit permet l'examen détaillé des parties supérieures et inférieures du système gastro-intestinal.

Les segments intermédiaires de l'intestin grêle ne sont cependant pas accessibles par cette approche. Ceci est dû à la longueur importante, l'étroitesse et les sinuosités de l'intestin grêle. L'endoscopie capsulaire permet aujourd'hui l'exploration endoscopique de ces segments. Ceci revêt une importance décisive pour un diagnostic correct et un traitement ciblé lorsque s'observe dans ces zones un foyer actif de saignement. Il existe un risque faible mais pas inexistant de rétention de la capsule lors de l'examen par vidéo-capsule. Ceci mis à part, rien ne s'oppose à l'emploi de cette technologie impressionnante où une mini-caméra voyage dans l'intestin. Mais la réalité est différente. La lecture des images demande beaucoup de temps et exige une solide expertise. De plus, cette technologie n'a probablement sa plus-value que dans quelques rares indications.

Cette évaluation d'une technologie de la santé (HTA) examine pour quelles applications précises l'endoscopie capsulaire est actuellement utile et comment cette technologie peut être organisée d'une façon efficiente.

Ce rapport a vu le jour grâce à une collaboration fructueuse entre le KCE et des instances extérieures. Nous voulons ici exprimer notre gratitude pour leur contribution et leurs réponses aux experts belges, à l'Institut National d'Assurance-Maladie-Invalidité, ainsi qu'aux fabricants et distributeurs du matériel pour endoscopie capsulaire.

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Résumé

Introduction

Le diagnostic d'affections de l'intestin grêle n'est pas dénué de difficultés. Lors de l'examen endoscopique classique du système gastro-intestinal, un tube flexible est introduit par la bouche ou l'anus pour visualiser la muqueuse digestive. L'oesophago-gastro-duodénoscopie permet de mettre en évidence des hémorragies et anomalies du segment supérieur du tube digestif. L'iléocoloscopie explore le gros intestin et la partie terminale du grêle. Ces 2 examens endoscopiques classiques ne permettent pas de localiser l'origine du saignement chez 3 à 5 % des patients qui présentent un saignement gastro-intestinal. La radiologie et la médecine nucléaire ont ici aussi leurs limites. On parle alors de saignements gastro-intestinaux d'origine obscure (OGIB). Souvent, l'origine du saignement se trouve quelque part au milieu d'un intestin grêle qui fait 6 mètres de long et n'est pas accessible par l'endoscopie classique. La cause du saignement est souvent l'angiodysplasie ou anomalie vasculaire locale, et dans une moindre mesure, une ulcération ou une tumeur. D'autres affections peuvent également s'observer dans ce segment de l'intestin grêle comme des polypes (polypose), la maladie coeliaque, la maladie de Crohn, une forme d'inflammation chronique de la paroi intestinale avec ulcération et rétrécissement cicatriciel.

L'endoscopie par capsule (EC) est une technique endoscopique récente qui visualise la paroi interne de l'intestin grêle, y compris les segments qui ne sont pas accessibles par l'endoscopie classique. Le patient avale une caméra vidéo (la capsule) qui retransmet des images à un mini-enregistreur porté à la ceinture. Les batteries électriques permettent 8 heures d'enregistrement, temps suffisant chez 80% des patients, pour atteindre l'extrémité de l'intestin grêle (l'iléon). Ces images sont ensuite analysées sur écran.

Objectifs

Les objectifs de cette évaluation d'une technologie de la santé (HTA) sont triples :

- Evaluer l'efficacité clinique et l'efficience (rapport coût-efficacité) de l'EC dans différentes indications à partir de la littérature. ;
- Calculer le prix de revient et le volume attendu des EC dans le(s) indication(s) recommandée(s) en Belgique ;
- Formuler des recommandations pour l'organisation et le financement de l'EC en Belgique.

Méthode

Cette HTA suit la méthodologie usuelle pour les HTA réalisées par le Centre Fédéral d'Expertise (KCE). Une équipe d'experts externes a épluché la version provisoire du rapport, fait part de son expérience et formulé ses critiques. Les producteurs et distributeurs de la technologie

EC ont été contactés et ont fourni l'information sur leurs produits. Trois experts externes indépendants ont validé le rapport final.

Les rapports récents d'HTA, les revues systématiques de la littérature ainsi que les études cliniques à la fois prospectives et comparatives constituent le fondement pour l'évaluation de l'efficacité clinique de l'EC dans les différentes indications possibles.

Efficacité clinique et rapport coût-efficacité

On peut aujourd'hui considérer comme suffisantes les évidences concernant la valeur diagnostique de l'EC dans les saignements gastro-intestinaux obscurs (OGIB) à savoir la recherche d'une source possible de saignements dans l'intestin grêle. Pour d'autres indications possibles, les évidences actuelles concernant la valeur diagnostique de l'EC sont encore insuffisamment documentées ou trop sommaires (maladie de Crohn, maladie coeliaque, polypose).

Subsistent encore quelques problèmes importants à résoudre impérativement. La plupart des études traitent du rendement diagnostique (nombre de patients avec anomalies identifiées par rapport au nombre de patients explorés). Le seul rendement diagnostique ne permet pas de distinguer les résultats vraiment positifs des faux positifs et encore moins de distinguer l'absence réelle d'anomalies des résultats faussement négatifs. Pour cela, une définition de l'exactitude diagnostique (sensibilité et spécificité) est à tout le moins nécessaire. Lors d'OGIB, il demeure souvent délicat pour le clinicien d'apprécier si un petit angiome qui ne saigne pas est bien à l'origine d'un saignement. A ce jour, une seule étude auprès de patients souffrant d'OGIB sérieux a comparé l'exactitude diagnostique de l'EC par rapport à celle de l'entéroscopie peropératoire, méthode de référence. En cas d'implémentation de l'EC en Belgique, il faut être conscient que la précision diagnostique optimale de cet outil couvre les patients qui présentent une OGIB sévère comme ceux étudiés dans l'étude mentionnée ci-avant. Si l'EC était proposée à des patients qui présentent une OGIB modérée, la précision diagnostique serait inévitablement plus faible et le risque de résultats faussement positifs ou faussement négatifs plus important. Une telle situation peut conduire à un plus grand nombre de décisions malheureuses dans la conduite thérapeutique et à un risque accrû de traitement inadéquat. Puisque de discrètes perturbations de la muqueuse de l'intestin grêle, comme de petits angiomes et des érosions, s'observent aussi chez des volontaires sains, il est de la plus haute importance de dresser un inventaire des observations normales et anormales lors de l'EC. Ceci demandera nécessairement du temps et du travail.

Sur base de l'évidence clinique, le KCE recommande de considérer l'OGIB comme une bonne indication de l'EC. Les patients avec OGIB susceptibles de bénéficier de l'EC doivent être anémiques (hémoglobinémie seuil non précisée). Avant de proposer un examen par EC, les patients doivent au minimum avoir présenté une iléocoloscopie négative et une oesophago-gastro-duodénoscopie négative, cette dernière endéans les 6 mois qui précèdent l'EC. Il n'y a pas de critères

d'âge recommandés. La mise en œuvre d'une EC chez l'enfant est laissée à l'appréciation du clinicien.

Perspective pour le patient

Pour le patient, les avantages et inconvénients possibles de l'EC sont importants. Les avantages possibles de l'EC pour le patient sont notamment la valeur ajoutée au moment du diagnostic étiologique de l'OGIB et la meilleure tolérance par rapport à d'autres procédures diagnostiques. Le risque principal lié à l'EC est la rétention de la capsule dans l'intestin grêle. Ce risque doit être évoqué au préalable avec le patient. Une telle complication peut d'ailleurs conduire à une intervention chirurgicale imprévue pour extirper la capsule. Un autre risque lié à l'utilisation de l'EC est la visualisation incomplète de l'intestin grêle. L'accessibilité pour le patient à la technique d'EC est également un point important qui dépend de la distribution de cette technologie au sein du territoire belge et de son remboursement.

Organisation

Le KCE recommande l'introduction de la technique d'EC dans un nombre limité de centres. Une première raison pour cette limitation est le nombre restreint de patients porteurs d'OGIB chez qui l'examen par EC est indiqué (un maximum de 800 patients par an). Une seconde raison tient à l'expertise nécessaire pour l'exécution et l'interprétation de l'EC. Les experts externes proposent un minimum de 30 EC par an pour pouvoir garantir une qualité suffisante. Ces examens devraient être analysés et interprétés uniquement par un endoscopiste senior. Les experts externes désapprouvent l'interprétation en routine des images par un expert qui n'a pas vu au préalable le patient.

Parmi les conditions minimales à remplir pour être reconnus, les centres doivent disposer d'un cercle suffisamment étendu de patients investigués et traités pour OGIB. A côté de la situation géographique, un critère objectif de sélection pour la reconnaissance d'un hôpital peut aussi être le nombre de diagnostics primaires ou secondaires d'angiodysplasie lors de l'admission.

Afin de garantir l'accessibilité, les centres d'EC devraient être répartis harmonieusement sur le territoire belge. Il est possible qu'un nombre important de patients requièrent une hospitalisation de jour pour l'examen par EC en raison soit de la distance entre leur domicile et l'hôpital qui dispose de l'équipement pour EC, soit du mauvais état général consécutif à l'anémie sous-jacente.

Un total de 4 centres est suffisant pour l'indication recommandée d'OGIB puisque chaque appareil d'EC permet l'exécution de 200 examens par an. Le budget annuel estimé de 300 000 € (en 2006) à 600 000 € (en 2010) peut être réparti entre les centres dans le cadre, par exemple, d'une convention. Chaque centre d'EC rédigera annuellement un rapport d'activité qui comprend les données démographiques des patients investigués, l'indication clinique et le résultat de l'EC.

Messages clés

- Le KCE recommande l'endoscopie par capsule (EC) en cas de saignements gastro-intestinaux obscurs (OGIB) pour rechercher une source possible de saignement dans l'intestin grêle.
- Une EC en cas d'OGIB s'indique seulement si les résultats de l'iléo-coloscopie et de l'oesophago-gastroduodenoscopie préalables étaient négatifs.
- Le risque principal lié à l'utilisation de l'EC est la rétention de la capsule dans l'intestin grêle. Lors d'un essai clinique, cette élimination a nécessité une intervention endoscopique ou chirurgicale chez 0,7 à 5,0 % des patients avec OGIB.
- Chez 17 à 34 % des patients, la durée d'enregistrement est trop courte pour visualiser la partie terminale de l'iléon : ceci entraîne une perte d'information importante.
- Pour d'autres indications possibles, les évidences actuelles concernant la valeur diagnostique de l'EC sont encore insuffisamment documentées ou trop sommaires (maladie de Crohn, maladie coeliaque, polypose).
- Pour des raisons de qualité et de volume, l'implémentation de l'EC doit se limiter en Belgique à quelques centres.
- Le budget annuel à prévoir pour l'EC en Belgique dans l'indication OGIB est estimé à 600 000 € maximum après 5 ans.

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List of abbreviations

AGA American Gastroenterological Association

AUD Australian dollar

BCBS Blue Cross Blue Shield (US)

CCD charge coupled device

CD Crohn's disease

CE Capsule endoscopy

CEDIT Comité d'Evaluation et de Diffusion des Innovations Technologiques (France)

CI Confidence Interval

CMOS complementary metal oxide semiconductor

CRD Centre for Reviews and Dissemination University of York (UK)

CT Computer tomography

DARE Database of Abstracts of Reviews of Effects (UK)

DBE Double balloon enteroscopy

EGD Esophagogastroduodenoscopy

FAP Familial adenomatous polyposis

GI Gastrointestinal

HTA Health technology assessment

NHS EED National Health Service Economic Evaluation Database (UK)

MRI Magnetic resonance imaging

MSAC Medical Services Advisory Committee (Australia)

n number

NICE National Institute for Clinical Excellence (UK)

NSAID Non-steroid anti-inflammatory drugs

OGIB Obscure gastrointestinal bleeding

PE Push enteroscopy

PJS Peutz-Jeghers' syndrome

RD Rate difference

RIZIV/INAMI Rijksinstituut voor ziekte- en invaliditeitverzekering/Institut national d'insurance maladie et invalidité

SBFT Small bowel follow through

SBS Small bowel series

SR Systematic review

USD United States Dollar

1. BACKGROUND

1.1. CLINICAL PROBLEM

Diagnosing small bowel diseases may be difficult because examination of the small bowel is limited by its length and its complex configuration. The human small bowel has an average length of approximately 6 meters. Gastric contents (food, liquids, gastric acid, saliva, mucus) first pass through the duodenum and subsequently through the jejunum and ileum. Small bowel residues further pass into the colon through the ileocaecal valve.

Endoscopic evaluation of the small bowel may be required in the diagnosis of small bowel diseases such as causes of obscure gastrointestinal bleeding (OGIB) (e.g. angiodysplasia, tumour, ulceration) and Crohn's disease (CD).

In most patients with gastrointestinal (GI) bleeding, a bleeding source is found on classical endoscopic examinations. The upper and lower GI tract are visualised on esophagogastroduodenoscopy (EGD) and ileocolonoscopy, respectively. Up to 60 cm and on average 15 cm of the terminal ileum can be seen on ileocolonoscopy. Push enteroscopy (PE) allows visualisation of the initial 60-120 cm of the small bowel. In 3-5% of patients with GI bleeding, a bleeding source cannot be detected on classical upper and lower GI endoscopy. In these patients, bleeding is of obscure origin (OGIB) and most frequently caused by a bleeding lesion in the small bowel. According to the guidelines of the American Gastroenterological Association (AGA) [1] [2], obscure GI bleeding is defined as bleeding most likely originating from the gastrointestinal tract but with no bleeding source found on EGD and colonoscopy. Obscure GI bleeding is defined as obscure-overt in case of repeated episodes of visible blood loss (melena or much more rarely: hematemesis) and as obscure-occult in case of repeated or persistent severe iron deficiency anemia and/or a positive faecal occult blood test. Vascular lesions (angiodysplasia) are among the most frequent causes of OGIB. Less frequent causes include bleeding ulcerations in Crohn's disease (CD), small bowel tumours and coeliac disease. Bleeding caused by NSAID use or anticoagulant should have been excluded prior to evaluation of the small bowel in patients with OGIB (discontinuation of NSAIDs and monitoring of anticoagulant therapy). Diagnosis of OGIB may be difficult because bleeding can be intermittent or slow. Patients may experience repeated or prolonged blood loss leading to iron deficiency anemia, in some cases resulting in repeated hospital admissions and blood transfusions. Endoscopic evaluation of the entire small bowel is feasible using intraoperative endoscopy and double balloon enteroscopy (DBE) (sonde endoscopy has become obsolete). Unfortunately, these techniques are time consuming, poorly tolerated and/or limited by their invasive nature. Double balloon enteroscopy is a promising new method of endoscopic evaluation of the entire small bowel but additional studies are needed. Radiological evaluations of the small bowel include small bowel follow through (SBFT) using abdominal barium contrast

radiography at timed intervals, CT-enteroclysis, MRI-enteroclysis, angiography and scintigraphy. Due to a too low sensitivity, these techniques are of limited usefulness in the detection of bleeding sources in OGIB.

Crohn's disease (CD) is a chronic inflammatory bowel disease which primarily affects the small bowel and the colon and causes mucosal ulcerations and small bowel strictures. In some patients, CD may affect the entire GI tract including the mouth and the anus. Symptoms commonly caused by CD include abdominal pain, diarrhea and weight loss for an extented period of time. SBFT is a frequently used diagnostic procedure in the evaluation of the extent, distribution, nature and severity of the disease. Other tests include laboratory tests (blood and stool), sigmoidoscopy and ileocolonoscopy.

1.2. CAPSULE ENDOSCOPY

Capsule endoscopy (CE) uses a capsule that allows video imaging of the digestive tract. CE is a recent technology. The first videocapsule (the M2A capsule, manufactured by GIVEN Imaging Ltd, Yoqneam, Israel) was launched on the market in the year 2000. All studies presented in this report used the capsule manufactured by GIVEN. Most recently, CE technology manufactured by OLYMPUS (Tokyo, Japan) has also been launched on the market. At present, CE is used in the diagnosis of small bowel diseases. New CE devices are being developped for imaging of the esophagus.

The GIVEN capsule has a length of 26 mm and a diameter of 11 mm. The capsule contains a battery, a metaloxide semiconductor (CMOS) camera (a CCD camera in the OLYMPUS capsule), an optical lens, a diode light source (light source with automatic regulation in the OLYMPUS CE), an electronic circuit and an antenna for image transmission. As the capsule moves through the GI tract, images are transmitted by the digital radiofrequency channel at 410 Hz to a data recorder, worn on a belt outside the body. To this purpose, 8 electronic receivers connected to the data recorder are attached to the abdominal and thoracic wall. Once recorded, data are transferred to a computer for viewing and interpretation of the images. The battery life allows image transmission during 6 to 8 hours. The OLYMPUS CE battery can be turned off again as long as the capsule has not been swallowed. The OLYMPUS CE capsule also has the feature to directly visualize the images on a small screen (real time viewing). This allows determination of whether the capsule timely passes from the stomach into the duodenum and from the small bowel into the colon (in that case the examination may be stopped with no further need for follow up of possible capsule retention).

After the patient has swallowed the capsule, 2 images are transmitted every second to the portable external registration device. On average, the stomach is reached within a few minutes and the small bowel is entered after 1 hour. The capsule is aborally moved by bowel peristalsis and remains on average 3 to 4 hours within the small bowel lumen. A motility disorder or stricture may preclude a successful investigation. In case of delayed gastric emptying, the capsule can be endoscopically

introduced into the duodenum. In about 80% of the patients, the registration time of 6 to 8 hours is sufficient to visualize the entire small bowel. A major advantage of the videocapsule lies in its potential to evaluate segments of the small bowel that are not accessible to classical endoscopes. CE is a non-invasive, ambulatory, well-tolerated technique and is most frequently preferred by the patients over other visualisation techniques. According to the external experts, it is feasible to perform one procedure per day per CE recording device.

The registration time is insufficient to evaluate the terminal ileum in about 20% of the patients. This is considered a first disadvantage of CE. A second disadvantage of CE is related to the time required for viewing and interpretation of the images: for up to 8 hours of images are recorded. According to the external experts, these images can be viewed and interpreted in a time span of on average 60 minutes. A third potential disadvantage is related to the costs of CE. If one wants to evaluate the costs, an appropriate comparison with other diagnostic modalities that are currently used in the detection of small bowel diseases should be made. In the absence of an appropriate reference test or gold standard, a comparison with current medical practice should be made. In this context, one should take into account all costs and possible cost-savings related to the use of CE. Costs are not only related to the technology itself but also to additional treatments of diseases that would be undetected by classical tests only. On the other hand, possible cost savings may be related to earlier and more accurate treatment of patients with obscure GI bleeding or tumours. As establishing a diagnosis may be difficult in current medical practice, these patients are at risk of repeated negative diagnostic testing procedures and prolonged inappropriate symptomatic treatments without clear clinical improvement. Another disadvantage of CE is related to the diameter of the capsule, limiting its use in small children and patients with small bowel stricture. Finally, the videocapsule is unable to take biopsies, which is also considered a disadvantage.

2. OBJECTIVES

This KCE project is a Health Technology Assessment (HTA) of capsule endoscopy (CE). An assessment is made of the clinical efficacy and economic effectiveness of CE compared with competing diagnostic modalities in small bowel diseases.

The research questions in this assessment are the following:

- According to literature, what is the incremental *diagnostic* value of CE compared to competing diagnostic modalities in small bowel diseases? According to literature, what is the incremental *clinical* value of CE? Is a diagnosis made by CE related to therapeutic management and patient outcome?
- Is CE cost-effective compared to current diagnostic modalities?
- According to current knowledge on clinical efficacy and economic efficiency, would it be appropriate to include CE in the list of billing codes (the nomenclature on reimbursed indications)? If so, under which conditions should reimbursement be recommended?

3. METHODS AND RESULTS

KCE experts completed this project according to a standard KCE procedure. As this report is a HTA, it includes a literature review on clinical and economical evidence. To retrieve HTA-reports, systematic reviews and primary studies relevant to this topic, a systematic literature search was performed in the CRD database (HTA reports and systematic reviews) and in Medline (primary studies). If more recent HTA-reports and systematic reviews included all studies and findings from older reports, the latter were considered superseded by the more recent ones and are not discussed further in detail. Search criteria from the NICE 2004 report [3] were used in Medline (Ovid) to retrieve relevant recent primary studies. Only studies which were both prospective and comparative and not yet included as a full paper in the NICE 2004 report were retained. Economical studies were retained as well. Selected HTA reports, systematic reviews and primary studies are summarised and the evidence found is categorised according to different indications.

Expert gastroenterologists and CE manufacturers also contributed to this HTA. The Given annual and quarterly financial reports were consulted for sales volume and price.

For a better comprehension of organisational and financial aspects of CE, documentation on CE practice in foreign countries was obtained. Policy recommendations are based on a critical analysis of the collected data.

One major problem in the evaluation of CE is the lack of an appropriate non-invasive reference test ("gold standard") for the diagnosis of small bowel diseases. This renders an assessment of the possibility of CE to replace currently used diagnostic technologies more difficult. Another major problem is related to study design. Most frequently the primary endpoint is the diagnostic yield and two diagnostic technologies are compared in the same patient group, usually with small patient numbers. The fact that the comparator test has been used previously in the same patients with negative results means of course a bias in favour of the test under investigation.

Therefore, sensitivity and specificity of the diagnostic technology under investigation may be difficult to assess. A comparison with current medical practice may be helpful: how are different clinically relevant diseases actually diagnosed, how is the effectiveness and what are the costs? Subsequently it becomes feasible to evaluate the incremental effectiveness and costs of CE.

First, we looked at the clinical incremental value of CE. In case of an incremental clinical value we also evaluated the costs and the cost-effectiveness. Calculation of the gross budgettary impact of reimbursement of CE was based on the incidence of relevant gastro-intestinal diseases that cannot be diagnosed otherwise. To calculate the net budgettary impact, potential savings should also be addressed. A crude approach consists of an estimation of savings due to avoided "classical" diagnostic tests. A more refined approach includes calculation

of cost savings due to inappropriate or unnecessary treatments in case of erroneous test results on other diagnostic procedures or due to obsolete treatments in case of over-diagnosis based on false positive CE results. Such an approach requires several assumptions that cannot be substantiated based on current data. To this purpose, long term data collection is needed which is beyond the scope of this report. It should be evaluated whether or not it is possible to extrapolate findings from international studies to the Belgian situation. Therefore, data on the incidence of different relevant gastrointestinal diseases may be helpful.

3.1. METHODS

3.1.1. Literature search

HTA reports and systematic reviews were searched in the CRD database (All Databases-DARE, NHS EED, HTA) on 16 June 2005 using the search string "Capsule endoscopy" ("Capsule endoscopy/All fields – 12 Hits"). On 6 October 2005, a most recent systematic review was identified from Medline (Pubmed: clinical queries). Guidelines and documents with additional relevant information (e.g. on safety, CE findings in healthy volunteers,...) were retrieved from other databases and literature sources. Studies identified from these searches are represented in Appendix 4. Three HTA-reports [4 5 6]) and an "interventional procedures overview of wireless capsule endoscopy" [3] were identified relevant to this topic. Additional reports prior to the BCBS-HTA 2003 reports [5 6] were superseded by later ones. Despite a number of shortcomings, discussed later, a most recent systematic review by Marmo et al. [7] was also retained. These HTA reports and systematic reviews have summarised and critically appraised the evidence on the efficacy/safety of CE in patients with OGIB [4 5 3 7] and/or with CD [6 3 7].

Additionally, relevant primary studies which were both prospective and comparative were identified in Medline (Ovid) using a search strategy similar to the strategy used in the NICE 2004 report [3] (see Appendix 3). Inclusion and exclusion criteria for identification of relevant studies were: prospective and comparative studies reporting on the diagnostic performance of the procedure and not yet included in the selected HTA reports and systematic reviews; the intervention/test is CE; studies reporting at least one of the following outcomes: diagnostic yield, diagnostic accuracy, impact on patient management or patient outcome in terms of morbidity and mortality in relation to diagnostic alternatives; homogeneous patient population; English-language articles; studies published as full papers (no abstracts, editorials or proceedings).

3.1.2. Diagnostic efficacy

The hierarchy of diagnostic efficacy established by Fryback and Thornbury [8] (Appendix 6) was used to attribute a diagnostic efficacy level to the studies if possible (Table 1). This review considered all data between level 2 and 5 (excluding technical imaging quality).

Table. 1: Levels of diagnostic efficacy

1	Technical efficacy	Technical aspects of the imaging procedure
2	Diagnostic accuracy	Sensitivity, specificity, positive predictive value, negative predictive value
3	Diagnostic thinking	Likelihood ratio
4	Patient management	Therapeutic impact (changes in therapeutic choices)
5	Patient outcome	Improvement in morbidity/mortality
6	Societal	Cost-effectiveness analysis

3.2. EVIDENCE

In this section, the evidence outlined in the selected HTA-reports, systematic reviews and primary studies is summarised and categorised according to different indications. More details on these studies are provided in the evidence tables in Appendix 1, 2 and 5.

3.2.1. Obscure gastrointestinal bleeding

Evidence on the use of CE in patients with OGIB from the MSAC-HTA 2003 report [4] is outlined in Appendix 1, section 8.1.2. Studies included in this report assess the diagnostic yield of CE in patients with OGIB. As all the studies are also included in the NICE 2004 report [3], the MSAC-HTA 2003 report [4] is superseded.

The NICE 2004 report [3](Appendix 1, section 8.1.2) addresses the diagnostic efficacy of CE in patients with OGIB. All studies from the MSAC-HTA 2003 report [4] are included in this report. Evidence from the MSAC-HTA 2003 report [4] is summarized and integrated in the NICE 2004 report [3] and updated with 5 prospective, comparative studies on the diagnostic efficacy of CE in patients with OGIB (Appendix 1, section 8.1.2). One study [9] in this report is not included nor rejected in the systematic review by Marmo et al. [7]. Diagnostic yield and diagnostic accuracy (with determination of sensitivity and specificity) were assessed in 4 studies and in 1 study respectively. Studies were included up to March 2004. The search date, however, was not stated. In all 5 studies, the unit of analysis was the patient and not the lesion. The comparator test was push enteroscopy (PE) in 3 studies and small bowel series (SBS) and/or CT in 1 study. In the single study [9] which assessed diagnostic accuracy and reported diagnostic efficacy level 2 evidence, comparison of the diagnostic yield between CE and PE was not possible due to timing. The reference standard used in this study was a combination of tests to "independently verify" results. However, this was not done using an accepted methodology and the reported CE sensitivity (89%; 32/36 patients) and CE specificity (95%; 19/20 patients) may not accurately reflect CE diagnostic performance (for more details see: section 5.1.1). The same study reported capsule retention necessitating instrumental removal (non-natural excretion of the capsule) in 5/100 (5%) patients. The capsule required surgical removal in 4 patients and endoscopic

removal on PE in 1 patient. The caecum was not reached by the end of the recording time in 21/100 (21%) patients [9]. Two studies reported some level 4 evidence. Changes in patient management were reported in 25/38 (66%) OGIB patients from a first study [10] and in 41%, 69% and 87% of patients with obscure-occult, previous obscure-overt and ongoing obscure-overt bleeding respectively from a second study (patient numbers were not provided in the study) [9]. Limited information is available on changes in patient outcomes (level 5 evidence) with 2 studies merely reporting "successful surgery" in some patients but with difficulty to ascertain false positives and false negatives.

In a systematic review by Marmo et al. [7] (Appendix 1, section 8.1.2), assessment of the diagnostic efficacy of CE in OGIB patients was limited to determination of the CE diagnostic yield only. Results from 9 prospective, comparative studies (n=20-65 patients/study; total n=336 patients) were pooled. Six studies are also included in the NICE 2004 report [3]. It is unclear why 1 study on 100 patients [9], included in the NICE 2004 report [3], is not included in the systematic review by Marmo et al. [7]. The comparator was PE in 8 studies and SBFT in 1 study. CE performed better than the comparator test in 8/9 studies included in the systematic review by Marmo et al. [7]. In another study, PE performed better than CE [11] and in a most recent study, DBE performed similar to CE [12]. The diagnostic yield of CE was calculated on 289 patients. The pooled rate difference (RD) (the absolute pooled difference in the rate of positive findings between CE and comparators) was 36.9% (95% CI: 29.6-44.1) ($p<0.0001$). Compared with PE, CE had a higher probability of a positive finding: OR 4.3 (95% CI: 3.1-6.0) ($p<0.001$). Contraindications to CE (stricture, diabetes, major abdominal surgery, pacemaker) were reported in 8/336 patients (2.4%) (95% CI: 1.0-4.6). However, from the Table on contraindications it appears that 3 studies reported no data. These patients should be substracted from the total number of patients. In this scenario, contraindications were present in 8/253 (3.2%) patients. Adverse events were reported in 15/289 patients (5.2%) (95% CI: 3.7-7.8). Capsule retention was reported in 2 (2/289; 0.7%) cases and necessitated surgery in 1 and endoscopic removal in another patient. An adverse effect of PE was reported in 1/279 patients (no advance beyond the duodenal bulb). The caecum was not reached within the battery lifetime in 48/289 patients (16.6%) (95% CI: 12.5-21.4). This percentage may be higher as patients from 1 study with no data on this topic were added to the denominator. If these patients are substracted, the caecum was not reached in 18/257 (18.7%) patients. The authors conclude that superiority of CE in terms of diagnostic yield is homogeneous throughout the studies.

From our search in Medline, 5 primary studies were identified. This search was performed prior to the identification of a systematic review by Marmo et al. [7] which includes 4 of these 5 primary studies. One of these 4 studies reported limited information on changes in patient management: 7/42 patients had successful change in therapeutic approach (some level 4 information). More details on all retained primary studies are outlined in Appendix 1.

A fifth primary study, not included in the systematic review by Marmo et al. [7] is a recent study by Hartmann et al. [13] (more details from this study are provided in Appendix 1). In this study, diagnostic yield (detection of a bleeding source) of CE was compared with intraoperative enteroscopy in 47 consecutive patients with OGIB. In addition, diagnostic accuracy was assessed with intraoperative enteroscopy as the reference standard (diagnostic efficacy level 2 evidence). At present, this seems the most valid reference standard in the assessment of bleeding causes in the small bowel. Unfortunately, the use of intraoperative enteroscopy is limited by its invasiveness and risks. It can only be justified in patients with severe OGIB due to small bowel bleeding sources not found on EGD, ileocolonoscopy and PE. In these cases intraoperative enteroscopy allows detection, precise localisation and treatment of small bowel bleeding sources. The global diagnostic yield of CE and intraoperative enteroscopy was 74% (35/47 patients) and 72% (34/47 patients) respectively. In the subgroup of patients with ongoing obscure-overt bleeding, the diagnostic yield of CE and intraoperative enteroscopy was 100% (11/11) for both techniques. In the subgroup of patients with previous obscure-overt bleeding, the diagnostic yield of CE and intraoperative enteroscopy was 67% (16/24) and 71% (17/24) respectively. In the subgroup of patients with obscure-occult bleeding, the diagnostic yield of CE and intraoperative enteroscopy was 67% (8/12) and 50% (6/12) respectively. Diagnostic accuracy of CE was calculated with intraoperative enteroscopy as the reference standard and the patient as the unit for analysis: CE sensitivity was 95% (38/40 patients) and CE specificity was 86% (6/7 patients). It is noted that calculation of CE specificity is based on few patients. In this study, CE failed to reach the caecum within the battery lifetime in 16 (34%) patients. As these results represent the most severe cases from the OGIB spectrum, these findings may not be generalisable to settings with less severe cases.

Double balloon enteroscopy (DBE) is a recent and promising endoscopic examination technique for the small bowel. In a prospective, comparative study the diagnostic yield of DBE was similar to CE with concordant enteroscopic findings in the area explored by DBE in 12 of 13 patients with OGIB. Further studies are needed to confirm these initial findings [12].

Details from two outcome studies, reporting outcomes 1 year after CE for OGIB, are provided in Appendix I. In a first study by Saurin et al. on 60 patients, CE and PE were compared with the outcome at 1 year versus the initial diagnosis as a reference standard [14]. However, defining outcome for premenopausal women and for small-bowel angiodysplasia is complex. CE sensitivity was higher than PE sensitivity: 92% (95% CI: 0.82-1.00) versus 69% (95% CI: 0.53-0.87). PE specificity was higher than CE specificity: 80% (95% CI: 0.64-0.94) versus 48% (95% CI: 0.32-0.68). CE positive and negative predictive value was 62% and 87% respectively. PE positive and negative predictive value was 75% and 74% respectively. Interobserver agreement was 60% for overall CE findings and 76% for lesions with a high bleeding potential. In a second study by Neu et al. on 56 patients with OGIB, CE and a combination of 3 other comparator tests (OT) (PE, small bowel double contrast enteroclysis, angiography)

were compared with the outcome at 1 year [15]. The diagnostic yield of CE was higher than the diagnostic yield of OT: 68% versus 38% respectively. Major management changes (based on positive CE and/or OT) occurred in 21 patients and major improvement of bleeding in 44 patients. The number of positive findings on CE were associated with major changes in patient management ($p<0.05$). The number of positive findings on CE and OT but also the lowest haemoglobin value and the number of blood transfusions correlated with further bleeding episodes ($p<0.05$).

3.2.2. Crohn's disease

The NICE 2004 report [3] (Appendix 1 and 2) adresses the diagnostic efficacy of CE in patients with Crohn's disease (CD). Only a single prospective comparative study was included in the NICE 2004 report [3]; this study was updated later [16]. Therefore, the section of the NICE 2004 report [3] on CD is superseded by the primary studies retained in this report.

Critical appraisal of the most recent systematic review by Marmo et al. [7] revealed some major shortcomings in the section on CD. Although the authors clearly stated that they only included prospective and comparative trials, it is apparent from the table that at least 3 of 8 studies were not prospective comparisons and should have been excluded. In addition, it is noted in the table that two studies reported no data on "CE failure to reach the caecum". It is not stated whether Marmo et al. contacted the authors of these 2 original papers to ensure that the caecum was reached in all patients. This did not withhold Marmo et al. to add the patients of these studies to the denominator (total number of patients), thereby presenting an underestimation of the percentage of patients in whom the caecum was not visualised (8.4% instead of 10.8%). It is also unclear from the table whether patients with capsule retention should be substracted from the total number of patients or added to those with failure to reach the caecum. In the latter scenario the caecum was not reached in 14.6% of the patients. Alltogether, these shortcomings should be considered fatal flaws rendering results and conclusions of the systematic review section on CD invalid (Appendix 1, section 8.1.2, suspected or known CD).

From our search in Medline, 5 primary studies were retained. Details from these studies are provided in Appendix 1 [17 18 19 20 21]. Experience with CE in patients with known or suspected CD is limited. A total of 176 patients were evaluated in these 5 prospective and comparative studies (27-43 patients/study). CE performance was assessed in patients with suspected recurrence from known CD in 1 study (30 patients) [17], in patients with either known or newly suspected CD in 3 studies (43, 41 and 27 patients/study respectively) [19 20 21] and in patients with suspected CD in 1 study (35 patients) [18]. In the assessment of CE diagnostic efficacy, all studies reported on diagnostic yield only. A single study reported on diagnostic accuracy in a small subgroup of 13 patients with newly suspected CD [21]. Comparators varied across the studies: SBFT in 2 studies [17 18], PE and enteroclysis in 1 study [19], CT enteroclysis in 1 study [20], MRI and enteroclysis in 1 study [21]. Prior to CE examination, a

variety of different diagnostic tests had already been performed in most patients. Time intervals between these tests and CE also varied between studies. Apparently, heterogeneous patient groups (known or suspected CD, previously operated CD patients, different comparators and time intervals between tests) have been evaluated within and across studies. Therefore, results from these studies may not be generalisable. CE performed better than the comparator in 4 studies [18 19 20 21] and similar to the comparator in 1 study (SBFT) [17]. A single study [21] assessed the diagnostic accuracy of CE in the diagnosis of CD in a subgroup of 13 patients with newly suspected CD (diagnostic efficacy level 2 evidence). These 13 patients, in which a diagnosis of CD was confined after a follow up of 1 year and in whom the results of CE were compared to this final diagnosis, were part of a larger patient population of 52 patients who initially entered the study with either newly suspected or known CD. The reference standard was the final diagnosis after 12 months follow up. However, it is unclear how this final diagnosis was established and what might have been the contributing role of CE in establishing the diagnosis. It is not stated whether the assessors of the final diagnosis were blinded to the results of previous diagnostic tests. CD diagnosis was confined in 14/25 (56%) patients and rejected in 11/25 (44%) patients. CE sensitivity and CE specificity were 92% (12/13 patients) and 100% (10/10 patients) respectively. MRI sensitivity and MRI specificity were 77% (10/13 patients) and 80% (8/10 patients) respectively. Clearly, these results are based on small patient numbers and a reference test which, most likely, was not blindly assessed. In this situation, bias in favour of the test(s) under investigation is likely to occur. Therefore, these results should be interpreted with caution. Future studies should be designed to avoid such bias. Limited information on changes in patient management was provided in 2 studies (some level 4 information). A management change was reported in 16/22 (73%) patients with known CD and 14/21 (67%) patients with suspected CD [19]. CE was reported to have a therapeutic impact in 10/56 (18%) patients with CD, including 5 new CD diagnoses [20].

Most, if not all, patients underwent prior radiological investigation of the small bowel and when a stricture was found, CE was considered contraindicated. Data from the 5 retained studies revealed that a stricture was detected radiographically in 54/230 (23.5%) patients and thus CE was not performed in these patients. The remaining 176 patients all underwent CE. Adverse events were reported in a total of 8/176 (4.5%) patients and were related to capsule retention in 5/176 (2.8%) patients. The retained capsule required surgical removal in 2 patients, endoscopic removal on PE in 1 patient and was evacuated in a natural way following corticosteroid therapy in 2 patients. In 2 patients, capsule retention occurred in a stricture undetected on a prior SBFT. These capsules were removed on stricturoplasty. Other adverse events reported were: painful passage of the capsule through an inflamed ileocaecal region in 2 patients, inability to swallow the capsule in 1 patient requiring subsequent endoscopic placement of the capsule in the duodenum, repeated CE in 1 patient due to a prolonged stay within the stomach (4 hours). Only 3 studies reported on CE failure to reach the

caecum within the battery lifetime. This occurred in 20/114 (17.5%) patients.

3.2.3. Celiac disease

No prospective comparative studies were found on the use of CE in Celiac disease.

3.2.4. Polyposis

Experience with CE in patients with intestinal polyposis is limited. A total of 65 patients with Familial Adenomatous Polyposis (FAP) and of 19 patients with Peutz-Jeghers' syndrome (PJS) was evaluated in 3 comparative studies. The comparator was different in each study (Appendix 5, section 8.5.3).

In a recent comparative study, the diagnostic yield of double balloon enteroscopy appeared superior to CE in the diagnosis of small intestinal polyps. In 9 patients with known gastrointestinal polyposis, the diagnoses were discordant in 3 patients, in whom CE failed to detect any polyp. In two of three polyposis patients with concordant positive findings, DBE detected a larger number of polyps than CE. Further studies are needed to confirm these initial findings [12].

3.2.5. Pediatric studies

Experience with CE in children (≥ 10 years) is limited. A total of 42 children (mean age: 14 years) were evaluated in 2 comparative studies [22] [23]. Indications studied were bleeding, polyposis and CD.

3.3. VALIDITY AND GENERALISABILITY OF THE STUDIES

This section is an adapted and updated version of the corresponding section in the NICE 2004 report.

- Only 3 studies reported on diagnostic performance (accuracy i.e. sensitivity and specificity) of CE. In a first study [9] in patients with OGIB, sensitivity and specificity were calculated using author defined definitions. Although a combination of tests (including push enteroscopy, which some patients had already undergone) was used to "independently verify" results, this was not done using an accepted methodology such as the discrepant resolution method or a composite reference standard approach [24]. As such, sensitivity and specificity may be misleading and may not accurately reflect diagnostic performance of the procedure. In a second study in patients with OGIB, a more appropriate reference standard (intraoperative enteroscopy) was used [13]. Patients' eligibility for the invasive procedure of intraoperative enteroscopy was based on the severity of their OGIB defined on criteria and test results other than CE. These patients most likely represent the most severe cases from the spectrum of OGIB and therefore, results of this study may not be generalisable to less severe cases. In a third study, the final diagnosis after 1 year of follow up was used as the reference

standard in a subgroup of patients with newly suspected CD [21]. It was not clearly stated in the study how this diagnosis was established and whether or not the assessors of the final diagnosis were blinded to the results of prior diagnostic tests (including CE).

- In most studies diagnostic yield (number of patients identified with a lesion/total number of patients assessed) was considered the most appropriate measure of diagnostic test performance. However, diagnostic yield cannot differentiate true positives from false positives and true negatives from false negatives.
- In most studies a blinded independent assessment was made in reviewing CE test results.
- Several remarks should be made on the use of the comparator procedure(s). First, in most studies patients had undergone extensive prior investigations, often including investigation with the comparator procedure – in some cases patients were those that had normal results on other tests. Therefore, it is likely that the diagnostic yield of the comparator test is underestimated. Second, the timing of the comparator tests varied from within 3 days of having a CE investigation to 6 months. Clearly, as the time between the two tests is longer, the diagnostic yield is likely to be inaccurate (either under- or overestimated). Third, the use of different comparators in different studies limits comparison of diagnostic yield between studies.
- Studies used different definitions as to what constitutes a positive diagnosis, again limiting comparisons of diagnostic yield between studies.
- In general, the patients included in the studies are a heterogeneous group [9]. In some studies [25] [26] patients other than those with OGIB were included in the study population. It is unclear what impact this has on overall diagnostic yield, particularly given some suggestions that there are particular patient groups who are the better candidates for CE endoscopy [9] [13]. Patients included in the studies on CE performance in the diagnosis of suspected or known CD also constitute a heterogeneous group as described in section 4.12.2.
- Follow up in most of the studies was short or in some cases unclear. This limits the ability to draw conclusions on the therapeutic impact of the test or the impact on health outcomes.

4. DISCUSSION

4.1. INDICATIONS

4.1.1. Obscure gastrointestinal bleeding

Gastrointestinal (GI) bleeding is of obscure origin in an estimated 3-5% of all GI bleeding episodes. In these cases, GI bleeding sources are most commonly found within the small bowel [27].

Push enteroscopy (PE) is an alternative technique that allows direct visualisation and simultaneous treatment of lesions confined to the proximal jejununum. Limitations of PE are related to its maximal reach within the small bowel which is restricted to the first 60-120 cm. PE is technically difficult, not without risks and time consuming. As PE is poorly tolerated by the patient, this may frequently require deep sedation or even general anesthesia [28].

PE has replaced sonde enteroscopy. Sonde enteroscopy was extremely dyscomfortable to the patient and a prolonged investigation time was needed [29]. Even more invasive is intraoperative enteroscopy of the small bowel. This may be considered the true reference test or gold standard for comparison of CE findings [13]

Additional diagnostic procedures with limited utility in obscure GI bleeding are the following: RX small bowel series using barium, angiography, CT enteroclysis and scintigraphy [28]

Endoscopic and other diagnostic modalities which are currently used in the detection of small bowel bleeding sources have a rather low sensitivity and are not without risks. In the diagnosis of OGIB, CE has a relative high diagnostic sensitivity of about 2/3 (range: 31-76%) compared to PE (about 1/3; range: 13-61% for PE) [30] and is generally better tolerated and preferred by patients over other techniques. CE is advocated in case of a previous negative EGD and ileocolonoscopy. It is unclear whether PE or CE should be used next in the management algorithm. It appears that CE findings have an impact on the subsequent treatment strategy in 20-50% of patients [30]. Whether or not patient outcomes also improve remains to be established in long term follow up studies.

The external experts consider OGIB an appropriate indication for CE.

Obscure gastrointestinal bleeding - Key Messages

- **For diagnosis of bleeding sources in patients with obscure gastrointestinal bleeding (OGIB), there is evidence of diagnostic accuracy (level 2).**
- **The diagnostic yield of CE is generally higher when compared with other diagnostic modalities, but patient selection bias is present in most studies.**
- **Limited data suggest that the yield of CE is highest in overt ongoing bleeding, intermediate in overt previous bleeding and intermediate or low in occult bleeding**
- **Capsule retention necessitating surgical or endoscopic removal occurred in 0.7-5% of the patients in a trial setting.**
- **CE failed to reach the caecum within the battery lifetime in 17-34% of the patients.**

4.1.2. Crohn's disease

Crohn's disease (CD) may be associated with lesions solely confined to the small bowel in 10-40% of patients [19 20]. CE may allow visualisation of these lesions in up to 60% of CD patients [20]. Diagnosing CD requires ileocolonoscopy with visualisation of the colon and the terminal ileum. Passage through the ileocaecal valve with evaluation and biopsy of the terminal 5-15 cm of the ileum is feasible in 28-86% of the patients [17]. Prior to considering CE, a full endoscopic examination should be accomplished. In several studies comparing CE to other diagnostic tests, a prior ileoscopy was either not performed at all, performed occasionally or no details were given. Considering a short term follow up without scores on symptoms and signs as a reference test in these studies is questionable.

The role of CE in the diagnosis of CD may be limited to particular cases i.e. patients with a high clinical suspicion of CD in whom a previous ileoscopy has failed and detection of small bowel lesions would lead to a change in patient management [19]. The utility of CE in known CD patients remains unclear.

If relapse of CD is suspected, serial contrast radiographies are not routinely performed. Such examinations may require radiological investigation for hours and radiation exposure is considerable [17]. If performed by experienced radiologists, SBFT studies may prove as accurate as enteroclysis. Enteroclysis requires the infusion of barium into the duodenum through a sonde inserted through the nose or pharynx. Transit of barium contrast through the small bowel is monitored radiographically during several hours. Insertion and use of the sonde is uncomfortable to the patient and radiation exposure is considerable [17].

Presently, CE findings in healthy volunteers are scarce but highly significant. In 57/413 (13.8%) healthy volunteers discrete changes such as erosions are seen in the small bowel mucosa [31]. In patient studies, these

changes would have been classified invariably as pathological findings contributing to the diagnostic yield of CE. Constituting a catalog of normal and abnormal small bowel findings is essential but will be time consuming.

The external experts agree that at present CE is not indicated in Crohn's disease (known or suspected Crohn's disease). Current studies are merely descriptive and additional well-designed studies are needed.

Crohn's disease – Key Messages

- **Small and heterogeneous patient populations were evaluated in the different studies (CD and/or suspected CD, different previous investigations, different comparators…) and prevents generalisability of results.**
- **It is unclear which patients would benefit from CE. Future studies should address potential fields of application and their significance.**
- **The problem of false positives should be resolved. Constituting a catalog with normal and pathological CE findings is essential.**
- **Capsule retention with CE is more likely to occur in CD patients, even after a negative radiological evaluation. In such cases, unintended surgery may be required to remove the capsule.**
- **CE failed to reach the caecum within the battery lifetime in 17.5% of the patients and thus the terminal ileum, a critical segment for CD, was not visualised in these patients.**
- **At present, the available evidence is not of sufficient quantity and quality to determine the relative diagnostic performance of CE compared with alternative conventional diagnostic tests in diagnosing patients with CD. No conclusions can be made as to whether CE is an effective alternative to other tests.**

4.1.3. Celiac disease

At present, the external experts consider the use of CE in Celiac disease not indicated.

4.1.4. Familial adenomatous polyposis (FAP) and Peutz-Jegers' syndrome (PJS)

Familial adenomatous polyposis (FAP) and Peutz-Jegers' syndrome (PJS) are hereditary syndromes with a high risk of developing benign lesions or malignancies.

Following prophylactic colectomy, over 70% of FAP patients may develop duodenal adenomas, most frequently near the ampulla of Vater. Little is known on the incidence and importance of the development of polyps in the ileum and jejunum of these patients [32].

PJS is characterized by mucosal and skin pigmentation and the development of hamartomatous polyps throughout the entire GI tract and more specifically in the small bowel. PJS patients are at increased risk

for the development of malignancies. The lifetime risk for the development of small bowel cancer is 13%. Surveillance with radiographic small bowel series is advised two times a year in children aged 10 years and older. However, PSJ patients may be genetically predisposed to possible harms caused by radiation.

According to the experts, CE has the potential to become a useful tool in the follow up of selected PJS patients. Clearly, diagnostic technologies in this field are evolving.

Familial adenomatous polyposis and Peutz-Jegers' syndrome – Key Message

- **At present, the available evidence is not of sufficient quantity and quality to determine the relative diagnostic performance of CE compared with alternative conventional diagnostic tests in diagnosing patients with gastrointestinal polyposis or during follow up. No conclusions can be made as to whether CE is an effective alternative to other tests.**

4.2. COMPLICATIONS

Complications related to swallowing have been reported but are considered rare (e.g. aspiration of the capsule in the airways).

Given the risk of capsule retention in the small bowel, which may result in avoidable surgery, one should carefully consider the indication for CE. Patients need to be informed on this risk. This problem may occur in about 2% of the patients and may be higher in patients with known or suspected CD, even if patients with documented strictures have been excluded from the studies. Not all stenoses are detected on radiological investigations. Even with the recently developed soluble GIVEN "patency" capsule the risk of capsule retention cannot be excluded. Bowel obstruction seems rather rare even though the capsule may be retained for several weeks. Other localisations for potential capsule retention are pouches secondary to bowel surgery and Zenker diverticulum. Patients in whom the capsule during the image registration time has not reached the colon should be further monitored to exclude capsule retention. Passage of the capsule through a narrowed segment of the bowel may be painful.

Currently, the manufacturer recommends not using CE in patients with implantable electronic devices such as cardiac pacemakers and defibrillators. In 2 pilot studies on 5 patients with a cardiac pacemaker and another 5 patients with a defibrillator, no adverse electrical events were observed [33 34].

Complications – Key Message

- **Prior to CE, patients need to be informed on the risk of capsule retention and subsequent interventions.**

4.3. OTHER ASPECTS

4.3.1. Use in children

Pediatric use of CE is documented in children (age 10 years or more) in few studies with small patient numbers (bleeding, polyposis, CD). Preliminary findings suggest CE may have a similar safety profile as in adults. Swallowing the capsule may be dificult and precious recording time may be lost (recording time can be stopped with the OLYMPUS capsule). According to the external experts, use of CE should not be limited to adults only.

4.3.2. Patient preparation

Patients are required to abstain from food during 12 hours prior to CE examination. Eating is again allowed from 2 hours after the start of the CE examination. Normal physical activity is allowed during the investigation. Analysis of initial findings on patient preparation suggests a bowel lavage with 2 to 4 liters Golytely prior to CE. Prokinetics apparently accelerate gastric emptying but delay bowel transit [30].

4.3.3. Image analysis

After the examination has been completed, images are transmitted to a workstation (transmission time takes about 1 hour for the GIVEN CE system and about 10 minutes for the OLYMPUS CE system). During the analysis, images are projected at a higher speed. Image quality of the GIVEN CE system is considered less than the quality obtained by classical flexible video-endoscopes. Compared to flexible video-endoscopes, the total number of images per second is much less with the GIVEN videocapsule (25 vs 2 images per second respectively). Light intensity of the OLYMPUS (but not GIVEN) CE images can be adapted to changes of light intensity in the sections under investigation. Possible lesions cannot be viewed repeatedly and the optical quality is far from ideal [29].

Interobserver agreement on CE findings is considered sufficient for bleeding lesions or lesions at high risk for bleeding. This is much less the case for the detection of tumours and ulcerations.

Since 2002, the software has been extended with features for localising the capsule (with a precision of about 6 cm) and for screening images on the colour of red blood. In clinical practice, the predictive value and utility of these software facilities seems rather low.

The time required for analysing CE images by the gastroenterologist may be shortened by a multi-viewer system (2 to 4 images are viewed at the time). Trained nurse practitioners may also preselect possible pathological sequences in order to reduce the subsequent viewing time by the gastroenterologist.

5. FINANCING OF CAPSULE ENDOSCOPY

5.1. INCIDENCE OF OBSCURE GASTROINTESTINAL BLEEDING IN BELGIUM

The incidence of OGIB can be estimated based on the incidence of intestinal angiodysplasia, which is the most frequent cause of OGIB (estimated at about 50% of OGIB). In the years 2001 and 2002, respectively 455 and 510 hospital stays with a 1st or a 2ry diagnosis of "intestinal angiodysplasia with hemorrhage" were recorded (table 2). Of these, many were single admissions. We therefore estimate the number of patients per year with OGIB at about 500.

Table 2: Stays for angiodysplasia in 2001 and 2002 in Belgium (FOD/SPF Public Health)

	2001				2002			
	Stays	Patients	Stays	Stays	Stays	Patients	Stays	Stays
	1st diag	1st diag	2ry diag	1 & 2	1st diag	1st diag	2ry diag	1 & 2
Gastroduodenal angiodysplasia without hemorrhage (**537.82**)	58	53	283	341	80	71	388	468
Gastroduodenal angiodysplasia with hemorrhage (**537.83**)	146	132	153	299	147	132	197	344
Intestinal angiodysplasia without hemorrhage (**569.84**)	186	181	625	811	232	218	770	1002
Intestinal angiodysplasia with hemorrhage (**569.85**)	204	186	251	**455**	240	210	270	**510**

One way to estimate the annual incidence of OGIB in Belgium is to extrapolate data from other western countries. The annual incidence of GI bleeding in the US is conservatively estimated at approximately 100 episodes per 100 000 persons, accounting for approximately 300 000 hospitalizations per year [35]. In the Belgian situation with a population of approximately 1/30 of the US, an estimated 10.000 hospitalizations per year for GI bleeding can be calculated from the US data. Approximately 5% of all GI bleeding episodes are considered OGIB, frequently caused by a bleeding source in the small bowel. Thus, OGIB may account for an estimated 500 hospitalisations per year in Belgium. The maximum yearly incidence of OGIB in Belgium was estimated by the external experts at 800 cases.

5.2. ECONOMIC ANALYSIS OF CAPSULE ENDOSCOPY

The costs associated with diagnosing obscure bleeding and treating the anemia can be significant: physician visits, emergency department visits, inpatient hospitalizations, upper and lower endoscopies, blood transfusions. The diagnostic work-up must rule out potential sources of bleeding and determine the site and aetiology of bleeding.

The HTA-MSAC 2003 report [4] assessed the cost-effectiveness of the M2A (Given) Capsule Endoscopy in OGIB. A modelled economic evaluation compared CE with SBS radiography and found that M2A Capsule Endoscopy was associated with lower total health costs overall with an estimated saving of 1007 AUD (632 €) per patient. The key assumptions in the economic model were: the mean yield of M2A Capsule Endoscopy is 60%; a positive yield with M2A Capsule Endoscopy will prevent all further diagnostic procedures; the ongoing treatment costs of OGIB are at least 683 AUD (429 €) per patient per year. A reduction in the uncertainty around these assumptions would improve the reliability of the results of the economic model.

Two articles from Goldfarb et al in 2002 [36] and 2004 [37] addressed respectively the cost of diagnosing obscure bleeding and of Crohn's disease (CD).

The first article found that CE technology on a per-unit cost was comparable to other current endoscopic procedures. On top, that technology requires training of the providers and developing professional standards for use. However the authors suggest a potential net cost saving through an earlier diagnosis, reduction in repetitive diagnostic procedures, reduced complications associated with the diagnostic procedures and reduction in intermediate treatment costs. They reported a differential yield of 25% with regard to push enteroscopy in finding the cause of bleeding. The technology results also in less pain, discomfort and anxiety for the patient and a high negative predictive value when there was no finding with CE.

The second paper assessed the economic value of CE in the diagnosis of Crohn's disease. This paper is not discussed as the clinical value of CE in the diagnosis of CD has not yet been fully established. One of the co-authors of both papers, Blair Lewis, is actually one of the 3 members of the Medical Advisory Board of Given Imaging.

5.3. REIMBURSEMENT STATUS IN SEVERAL EUROPEAN COUNTRIES

Currently, CE is reimbursed in some countries (table 3), mainly for OGIB. Few countries have included CE in their package of reimbursed ambulatory care. UK, Sweden and Denmark cover the cost of the procedure for inpatients.

Table 3: Reimbursement of CE

	USA	Australia	New Zealand	Switzerland*	Italy	Portugal
Consumables & equipment	413 €	754 €	Unk.	686 €	Unk.	Unk.
Physician fee	158 €	332 €	Unk.	297 €	Unk.	Unk.
Procedure (sum)	571 €	1 086 €	1 444 €	983 €	935 €	798 €

ECB exchange rates at Oct 11 2005: 1 EUR = 1.2022 USD, 1.5929 AUD, 1.7318 NZD, 1.5474 CHF
*There is not yet a definitive agreement between Santé Suisse and the Swiss gastroenterologists.

In Switzerland, a reimbursement is planned for patients who have OGIB with negative upper and lower endoscopies.

In Australia, CE is limited to patients with OGIB, which can only be established when the cause of bleeding has not been identified by upper GI endoscopy and colonoscopy. The reimbursement is limited to patients who have a history of GI bleeding, and cannot be used for patients who are presenting with their first bleeding episode.

For benefits to be payable under this item, CE must be provided within 6 months of the prerequisite upper GI endoscopy and colonoscopy. Any bleeding after that time is considered to be a new episode. It is not expected that CE would be provided more than once in an episode of bleeding, or provided to the same patient on more than two occasions in a twelve month period.

The Conjoint Committee comprises representatives from the Gastroenterological Society of Australia (GESA), the 125 Royal Australasian College of Physicians (RACP) and the Royal Australasian College of Surgeons (RACS). For the purposes of that reimbursement, specialists or consultant physicians performing this procedure must have endoscopic training recognised by The Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy, and the Health Insurance Commission notified of that recognition.

The reimbursement was introduced into the Schedule on an interim basis following a recommendation of the Medical Services Advisory Committee (MSAC). Interim funding until 30 April 2007 is being provided to facilitate collection of Australian evidence of the long term safety, effectiveness, and cost-effectiveness of this procedure. Data collection and analysis is being conducted by GESA.

Continuation of funding is dependent on the progress of this data collection. Therefore providers of this service are strongly encouraged to take part in the data collection process. Further information on the data collection process is available from the GESA

"*Capsule endoscopy to investigate an episode of obscure gastrointestinal bleeding, using a capsule endoscopy device approved by the Therapeutic Goods Administration (including administration of the capsule, imaging, image reading and interpretation, and all attendances for providing the service on the day the capsule is administered) 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."
http://www7.health.gov.au/pubs/mbs/mbsmay05/mbsmay05.pdf

5.4. SALES OF CAPSULES FOR CAPSULE ENDOSCOPY

Worldwide

Since the 3d quarter of 2001, 270 000 PillCam Small Bowel (SB) were sold at an actual rate of 10 000 per month. Japan has not yet launched the PillCam SB.

The actual PillCam SB weekly utilization rate is extracted from the last quarterly financial report of Given Imaging (QIII 2005). The figure is equal to 1/13 of the number of SB capsules reordered during the last quarter divided by the number of installed bases at the end of the previous quarter (every starter kit contains 10 SB PillCam). The weekly utilization rate in the US and elsewhere is respectively 1.18 and 0.58 capsules, or 60 capsules per year per installed base in the US and 30 capsules in other countries.

Belgium

At present, CE technology is not reimbursed by the RIZIV/INAMI. The GIVEN CE technology was initially introduced (without reimbursement) in the diagnosis of small bowel diseases in the gastroenterological departments of 6 University Hospitals (Hôpital Erasme Brussels, AZ VUB Jette, UZ Gent, Clin. Univ. St-Luc Brussels, UZ Gasthuisberg Leuven, CHU Liège) and more recently also in the UZ Antwerpen. According to the external experts, 80 to 90% of their patients with OGIB are patients referred by other gastroenterologists. The external experts do not support the routine interpretation of CE recordings by a GI endoscopist who has not seen the patient, in contrast to the centralized interpretation of CE images collected in other hospitals as described by Farnbacher et al. [38]

According to the distributor of Given Imaging, 9 centres were in operation during the year 2004 and a 10th centre started at Q III 2005. Two hundred and thirty wireless capsules were sold in 2004 and ± 260 are expected for the year 2005.

The more recent OLYMPUS CE technology is currently being evaluated in a single Belgian hospital. Data from these Belgian centres indicate that about 450 CE examinations have been performed during the last 3 years. It is estimated that about 150 to 200 CE examinations were performed during the past year in 6 Belgian university hospitals. This means that on average, each centre performed about 30 CE examinations during the past year.

A reimbursement of the CE procedure for all OGIB cases will mean an increase of the actual number of CE. We hypothesize a figure of 400

procedures with an annual growth rate of 15%, to say a 5-year doubling time to reach 800 procedures by the end of the 5th year.

5.5. COST OF GOODS IN DIFFERENT COUNTRIES

The price of the same material can diverge considerably from USA to Europe (table 4) despite the fact that the company has 2 production lines installed in Israel (Yoqneam) and a back-up line in Ireland.

Table 4: Pricelist of material in several countries

	USA	Australia	France	UK	Germany	Switzerland	Belgium
Rapid workstation	12 061 €	Unk.	Unk.	Unk.	Unk.	19 773 €	19 750 €
Data Recorder & aerial belts	4 533 €	Unk.	Unk.	Unk.	Unk.	8 353 €	9 600 €
Installed base	16 595 €	35 771 €	34 498 €	24 794 €	25 955 €	28 126 €	29 350 €
PillCam SB	374 €	562 €	510 €	434 €	509 €	597 €	510 €

Local prices, VAT excluded for European countries;
ECB exchange rates at Oct 11 2005: 1 EUR = 1.2022 USD, 1.5929 AUD, 0.6868 GBP, 1.5474 CHF
USA: Goldfarb et al, 2002 [36]; Australia: Assessment report MSAC application 1057 Aug. 2003; France: CEDIT; UK: Mylonaki et al, 2003 [29]; Germany: Farnbacher et al, 2004 [38]; Switzerland: Lasermed AG, Switzerland; Belgium: Meda NV, Aartselaar

5.6. COSTS OF MATERIAL

Actual need in workstations for CE in Belgium

The upper figure of 800 procedures could be achieved with 4 workstations or an occupancy rate of 100% at the end of the period.

Assumptions

Number of workstations and data recorders needed: 4

Maximal number of weekly investigations per recorder: 4

Mean occupancy rate of the recorders: 77 % (50% at start, 100% at the end)

Annual growth rate of tests: 14.87%

Inflation rate: 2.50%

5-year interest yield: 4.00%

Annual depreciation rate: 20.00%

USD exchange rate: 1.2022

Capital goods VAT included

Work stations Rapid 3 : 4 x 14 594 €
Data recorders DR2, aerial belts : 4 x 5 485 €
TOTAL CAPITAL GOODS : 4 x 20 079 €

Depreciation

Year	€ per tests		Tests	End value	NPV
	Actual	At end value			
1	27.94 €	32.69 €	459	15 005 €	**12 333 €**
2	28.64 €	32.22 €	528	17 011 €	**13 982 €**
3	29.36 €	31.75 €	606	19 243 €	**15 816 €**
4	30.09 €	31.30 €	696	21 782 €	**17 903 €**
5	30.84 €	30.84 €	800	24 676 €	**20 282 €**
			3 089	**97 717 €**	**80 316 €**

NPV: Net present value calculated at a 4.0% interest yield.

Service and capsules

The costs of services and capsules are based on the current revenues of Given Imaging and obtained from the figures of the 2004 financial report of the company for the services and of the QIII 2004 for the capsules. In the year 2004, the revenues of Given Imaging for services were 2 712 000 $ for 1 640 installed bases at the end of the previous year (table 6), or 1 653.7 $ per base >1-year old.

Table 6: Cost of Pillcam SB and of services

Descriptor	Revenues	Units at end of 2003	Units at end of QIII 2004	$ per item	€ per item
Service	2 712 000 $	1 640		1 653.66 $	1 664.39 €
PillCam SB, 10 pieces	10 361 740 $		22 407	462.23 $	465.20 €

The figure was converted in Euro, a 21% VAT added and inflated at a 2.5% annual rate. Services are supposed to be paid anticipatively at start of the year from the 2^{d} till the 5th year but costs of services are spread over the total number of procedures performed during the 5-year period. For the 4 installed bases, the service contracts amount 6 660 € per year, VAT included.

5.7. PROVISIONAL BUDGET

According to the external experts, image viewing and interpretation time requires on average 60 minutes. A technician/nursing time of 30 minutes is also required. The technician/nursing labour time is estimated at an hourly cost of 40.00 €. The gastroenterologist fee covers the 60 min.

reading time needed to screen the down-loaded small bowel images at a cost of 120.00 €.

The results are shown in table 7. The cost of material represents 78% of the total expense. The cost of the CE procedure can be set at 303 000 € the first year to 584 000 € the fifth year.

That does not include the supplementary expenses for day-care admission. According to the external experts day-care admission will be required in 50% of the elderly patients with severe anemia and in patients unable to travel back home in between the two visits the same day.

Table 7: Five-year financial planning

	Year 0 *2005*	**Year 1** **2006**	**Year 2** **2007**	**Year 3** **2008**	**Year 4** **2009**	**Year 5** **2010**
Number of tests	*400*	**459**	**528**	**606**	**696**	**800**
SB capsule	*465.20 €*	476.83 €	488.75 €	500.97 €	513.49 €	526.33 €
Depreciation	*27.26 €*	27.94 €	28.64 €	29.36 €	30.09 €	30.84 €
Maintenance and repair	*12.26 €*	12.57 €	12.88 €	13.20 €	13.53 €	13.87 €
Material (sum)	*504.72 €*	517.34 €	530.27 €	543.53 €	557.11 €	571.04 €
Technician	*20.00 €*	20.50 €	21.01 €	21.54 €	22.08 €	22.63 €
Gastroenterologist fee	*120,00 €*	123,00 €	126.08 €	129,23 €	132,46 €	135,77 €
Cost per investigation (sum)	*644.72 €*	**660.84 €**	**677.36 €**	**694.30 €**	**711.65 €**	**729.44 €**
Annual budget	*257 888 €*	**303 326 €**	**357 646 €**	**420 746 €**	**495 308 €**	**583 552 €**

Year 0 = reference year

6. RECOMMENDATIONS

6.1. EXISTING CLINICAL EVIDENCE

The existing evidence for clinical indications for CE in the diagnosis of small bowel diseases is still limited. According to the grading system used in this report, only the indication of OGIB reached evel 2 evidence (sensitivity and specificity). Some level 4 and 5 evidence has been reported as well. Results from most studies on OGIB were homogeneous in indicating a higher diagnostic yield of CE versus the comparator test. Patient selection bias could often not be excluded.

In other indications (Crohn's disease, Celiac disease, Polyposis), the available evidence is not of sufficient quantity and quality to determine the relative performance of CE compared with alternative conventional diagnostic tests in diagnosing these diseases. No conclusions can be made as to whether CE is an effective alternative to other tests.

A number of problems remain to be resolved. Most studies merely reported on the diagnostic yield (number of patients identified with a lesion/total number of patients assessed). However, diagnostic yield cannot differentiate true positives from false positives and true negatives from false negatives. In OGIB non-bleeding small angiomas continue to be a challenge to the clinician as to whether these are the true causes of the bleeding. The diagnostic accuracy of CE in OGIB has been determined only in a single study (with intraoperative enteroscopy as the reference standard) of patients with severe OGIB. When CE is implemented in Belgium, one should be aware that CE most likely has its highest diagnostic accuracy in patients with severe OGIB like those studied by Hartmann et al. [13]. When less severe cases of OGIB are examined with CE the diagnostic yield will inevitably be lower with a higher risk of false positives and false negatives. Such a situation may lead to erroneous decisions on patient management with an increased risk for inappropriate treatment. As a number of discrete changes such as erosions or small hemagiomas also occur in healthy volunteers, constituting a catalog of normal and abnormal CE results is essential.

From the perspective of the patient, there are three major issues related to CE: accessibility, benefits and risks. Accessibility is determined by the dispersion of CE centres across the country, and provision of reimbursement. The benefits of CE are related to a generally better tolerance by the patient compared to some other diagnostic procedures and its additional value in the diagnosis of causes of OGIB. Risks of CE are incomplete visualisation of the small bowel and most importantly capsule retention which may require unintended surgery.

6.2. INDICATIONS FOR CAPSULE ENDOSCOPY

Based on the existing clinical evidence, the KCE recommends OGIB as an appropriate indication for CE. All patients with OGIB who are eligible for CE should have anemia (no specific cut-off value). According to the definition of OGIB and prior to considering CE, all patients should have had at least one negative previous ileocolonoscopy and at least one

negative examination of the upper GI tract (EGD with or without PE). The last upper GI tract exam should have been performed within a time period of 6 months prior to CE. No age limit should be introduced; clinical judgement should be decisive as when to perform CE in children.

6.3. FUTURE SCOPE

Currently, based on the evidence discussed in this report, one might consider CE a valuable tool in the detection of bleeding source(s) in patients with OGIB. However, there are still a number of technical and clinical problems to be resolved. Technical problems are related to image quality, the percentage of CE failure to reach the caecum and the risk for capsule retention that all may be improved. Clinical problems that should be addressed in future studies include determination of the place of CE in the diagnostic algorithm of OGIB (CE prior to or after PE, future place of DBE relative to other diagnostic modalities including CE), more precisely determining diagnostic accuracy in different patient categories (overt ongoing bleeding, overt previous bleeding and occult bleeding), determination of the probability of small non-bleeding angiomas as the cause of OGIB. It is clear from this report that there is still a need for well designed studies with an appropriate statistical methodology. New future studies might reveal new insights in the diagnostic and clinical value of CE, as compared to existing methods such as PE and new methods such as DBE. Results from these studies could allow for adaptations in planning and decision making.

At present, additional studies on potential indications for CE other than OGIB are required.

6.4. ORGANISATION, FINANCING AND QUALITY

The KCE recommends that the introduction of CE technology in Belgium is restricted to a limited number of centres. A first reason for a limited introduction of CE is related to the relative small number of patients with OGIB who are considered appropriate candidates for CE (an estimated absolute maximum of 800 patients per year in Belgium). A second reason is related to the expertise required to perform and interpret CE. The external experts proposed a minimum of 30 CE procedures per year to ensure quality. Procedures should be performed by a senior endoscopist. The external experts do not support the routine interpretation of CE recordings by an expert who has not seen the patient.

Minimum criteria for the approval of centres to perform CE should include a sufficiently high local population of patients investigated and treated for OGIB. Aside from geographic location, an objective hospital selection criterium could be based on the number of angiodysplasias encoded as the primary or secondary diagnosis of hospital admission.

To ensure accessibility, centres performing CE should be dispersed in an equal fashion across the country. Given the possible distance between a patients' residency and the hospital with CE facilities and the presence of

severe anemia and/or bad general condition, a certain number of patients may require a one day hospitalization. This also has an associated cost.

A total number of 4 centres would be sufficient for the recommended indication of OGIB as up to 200 CE procedures can be performed on a yearly basis using a single CE device. A second data recorder may be required in the larger centres. The total estimated amount per year of 300.000 Euro for 2006 up to 600.000 Euro for 2010 can be divided over the selected centres e.g. by a convention system. A yearly activity report including demographic characteristics of patients tested, clinical indication and CE findings, should be provided by each centre.

To further ensure and improve quality of CE it is recommended to constitute an atlas of normal and abnormal CE findings. In addition, it is recommended that future research on CE should be based on well-designed studies and a uniform collection of data.

Recommendations – Key Message

- **CE is recommended in the indication of obscure gastrointestinal bleeding (OGIB).**
- **However, future developments should address currently incompletely resolved technical and clinical problems related to CE in OGIB. Studies should be well-designed and based on a uniform standard for data collection.**
- **For reasons of volume and quality the implemention of CE in Belgium should be restricted to a limited number of centres.**
- **The expected maximum budget for CE in Belgium is estimated at about 600 000 € after 5 years.**

7. APPENDICES

7.1. APPENDIX 1: EVIDENCE TABLES

7.1.1. Primary studies

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
OBSCURE GI BLEEDING COMPARATIVE STUDIES				
**Hartmann et al (2003)[39] Ludwigshafen, Germany July 2001 – October 2002 33 patients with obscure occult GI bleeding during last 6 months, negative EGD and colonoscopy (37 patients before work up) 19 men, 14 women Mean age 58 years, range 15-88	PE (CE images evaluated 5-10 days after PE)	Outcomes reported: Diagnostic yield (bleeding site diagnosed) PE: 7/33 patients (21%), one not detected by CE CE: 25/33 patients (76%)	Complications: PE: none CE: none	Investigator blinded to result of the other exam.
Van Gossum et al (2003)[11] Brussels, Belgium 21 patients with obscure GI	PE (within one week after CE)	Outcomes reported Diagnostic yield: lesions that can explain bleeding, global yield: all GI lesions, specific yield: GI lesions beyond reach of EGD Interobserver agreement for CE	Complications Capsule blocked in appendiceal stump in one patient, retrieved using colonoscopy.	Both procedure were performed blindly

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
bleeding and negative EGD and colonoscopy (overt bleeding in 5, occult bleeding in 16) 7 men, 14 women Mean age 60 years, range 18-81		Global yield CE: 52% Global yield PE: 61% Specific diagnostic yield was 20% for both methods Interobserver agreement CE was 85%		
Adler et al (2004)[40] Rochester, Minnesota, USA 20 patients with obscure GI bleeding, negative EGD and colonoscopy in last 2 months 8 men, 12 women Mean age 65.5 years, range 38-80	PE (after CE)	Outcomes reported: Diagnostic yield Definitive causes of bleeding (presence of blood alone not sufficient) Interpreter agreement CE Diagnostic yield CE: 14/20 (70%) PE: 5/20 (25%) Definitive findings CE: 6/20 (30%), 5 underwent targeted endoscopic or surgical treatment based on CE and PE findings PE: 2/20 (10%) Interpreters CE agreed completely in 18/20 (90%)	Complications CE: none PE: none	CE video files reviewed by a second blinded physician for assessing interinterpreter reliability Mean time of CE video image review was 60 minutes
Mata et al (2004)[28]	PE (within 1 week after capsule)	Outcomes reported Diagnostic yield (a bleeding source identified or evidence of active bleeding)	Complications CE: One capsule removed by	Both techniques were blindly performed by separate examiners

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
Barcelona, Spain July 2002 – February 2003 42 consecutive patients with obscure GI (overt bleeding in 26 patients and occult in 16), normal EGD and colonoscopy with ileoscopy in last month. 22 men, 20 women Mean age 55 years, range 16-84		Change in therapeutic approach Diagnostic yield CE: 31/42 (74%), (angiodysplasia > fresh blood without lesion) PE: 8/42 (19%), no additional diagnoses made by PE Successful change in therapeutic approach in 7 patients	laparoscopy because of jejunal stricture One patient expelled capsule only after 48 days In 2 patients procedure was repeated because of long oesophageal transit time and capsule malfunction PE: none	Mean time of CE video image review was 82 min
Hartmann et al (2005)[13] Two-center study, Germany August 2002 – December 2003 47 consecutive patients with obscure GI bleeding (ongoing overt bleeding in 11 patients, previous overt bleeding in 24 and occult in 12) and normal results on EGD, ileocolonoscopie and PE 30 men, 17 women Mean age 61 years, range 18-88	Intraoperative enteroscopy (within 7 days after CE) (open laparotomy with enteroscope through an enterotomy)	Outcomes reported Diagnostic yield (source of bleeding) -CE found a bleeding source in 35/47 (74%) patients, more frequently in overt ongoing (11/11 – 100%) than in overt previous (16/24 – 67%) and occult bleeding (8/12 – 67%) -Intraoperative enteroscopy found a bleeding source in 34/47 patients (72%) also more frequently in overt ongoing (11/11 – 100%) than in overt previous (17/24 – 71%) and occult bleeding (6/12 – 50%). Bleeding sources were angiectasis in 22 patients, ulcers in 5 patients and diverse rare lesions in the other 7 patients. Angiectatic lesions were endoscopically treated with argon plasma coagulation or resected. Other lesions were resected surgically resected and confirmed histologically	Complications CE: none Intraoperative enteroscopy: no severe complications in 46/47 patients – 1 patient died after intraoperative enteroscopy due to peritonitis after laparotomy CE failed to reach the caecum in 16 (34%) patients	Eclusion criteria: pregnancy, low grade iron deficiency anemia (Hb > 10 g/dL), bleeding sources outside the small bowel Assessors blinded to CE and intraoperative enteroscopy findings Findings classified as positive, suspicious or negative Mean time of CE video image time was about 1 hour

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
		Diagnostic accuracy (with intraoperative enteroscopy as the criterion standard for comparison of CE results in a per patient analysis) CE sens: 95% (38/40 pts) and CE spec: 75% (6/7 pts) CE-PPV : 95% and CE-NPV 86%		
OBSCURE GI BLEEDING OUTCOME DATA				
Saurin et al (2003 and 2005)[14] Lyon, France April 2001 – December 2001 60 patients with obscure GI bleeding and a negative endoscopic work-up last 2 months (overt bleeding in 28, occult bleeding in 32), CE results for 58 patients 27 men, 33 women Mean age 58 years, range 21-79 13 women were premenopausal 58 patients with both exams, 56 with follow-up	PE (within 3 days after CE)	Outcomes reported Diagnostic yield (small bowel lesions with potential for bleeding) Variability of CE results between observers Outcome at one year versus initial diagnosis CE: 40/60 (67%), 19 patients with lesions both on CE and PE PE: 22/60 (37%), including 3 patients missed with CE Agreement between observers was 60% overall, but 76% for lesions with a high bleeding potential Outcome : Sensitivity (95% CI): CE: 0.92 (0.82-1.00)	Complications CE : no analysis for 2 patients, battery problems in one patient and no data transfer in another.	Blinded comparison Defining outcome is complex for premenopausal women and for small-bowel angiodysplasia. Critique on Pennazio et al, 2004 : 50% of patients excluded for calculation true and false positives

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
		PE: 0.69 (0.53-0.87) Specificity (95% CI): CE: 0.48 (0.32-0.68) PE: 0.80 (0.64-0.94) CE: PPV 0.62, NPV 0.87 PE: PPV 0.75, NPV 0.74		
Neu et al (2005)[15] Multicenter (n=5) prospective study, Germany Unspecified 12 month period 56 patients with obscure GI bleeding (OGIB) and negative EGD and ileocolonoscopy. Patients had clinical signs and symptoms and/or anemia with a minimum hemoglibin (Hb) value of 12 g/dL and the severity of OGIB was clinically severe enough to justify all of the standard tests Bleeding was obscure-overt in 37 pts and obscure-occult in 19 pts 26 men, 30 women Mean age 63 years, range 18-82 years	PE, small bowel double-contrast enteroclysis, selective angiography of the celiac trunk and mesenteric vessels	Outcomes reported Diagnostic yield of CE (detection of small bowel lesions actively bleeding or with bleeding potential) compared to the diagnostic yield of three other comparator tests (OT) Follow up results on diagnoses and management (data for at least 6 months except for those who died) (mean 13 months; range 3-25 months) Analysis of management and outcome changes Correlation of management and outcome changes with test results and clinical parameters CE: positive in 38/56 (68%) OT: positive in 21/56 (38%); 15/21 positive cases were positive on PE CE positive in 19/35 (54%) cases with negative OT OT positive in 2/18 (11%) cases with negative CE	Complications CE: no data	Patient inclusion criteria are rather vague CE results unblinded to endoscopists for PE Sequence of investigations unclear and variable Higher proportion of active bleeding sites or lesions with high bleeding probability in OT (81%) than in CE (58%) The extra contribution of CE to OT in the diagnosis of other than vascular lesions (tumour, Crohn, NSAID ulcer) with the potential of major changes in patient management and a favourable outcome related to this change in

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
		Major management changes (based on positive CE and/or OT) in 21 pts Major improvement in bleeding activity in 44 pts Major management changes were mainly in the group with other than vascular lesions and up to 89% of negative cases on CE or OT had a favourable outcome The number of positive findings on CE were associated with major management changes ($p < 0.05$) The number of positive findings on CE and OT as well as the lowest Hb value and the number of blood transfusions correlated with further bleeding episodes ($p < 0.05$) Diagnosis by CE and OT of other than vascular lesions (tumour, Crohn, NSAID ulcer) led to a favourable outcome in 7/11 (64%) and in 3/4 (75%) cases respectively. Negative findings on CE and OT were associated with no further bleeding in 14/18 (78%) and 28/35 (80%) cases respectively		mangement is unclear. Details on the number of these specific lesions and their detection by CE and/or OT are lacking
CROHN'S DISEASE				
Buchman et al (2004)[17] Chicago, IL, USA	SBFT (CE within one week after SBFT, 12 patients showing a stricture	Outcomes reported Grading lesions: grade 0 (no active disease) to grade 3 (ulceration, spontaneous bleeding,	Complications Capsule retained in 2/30 patients with CE detected stricture, both	Blinded evaluation Interpretation time

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
30 consecutive patients with clinically suspected CD recurrence 22 female, 8 male Mean age 36.9 years, range 21-80	with proximal bowel dilation on SBFT were excluded)	and/or strictures) Patient satisfaction Grading CE: 21/30 with active CD (6 had normal SBFT) SBFT: 20/30 with active CD (5 had normal CE) All 30 patients preferred CE (14 definitely) over other procedures	treated with strictuloplasty.	CE: 35-70 min SBFT: 10-30 min Capsule retention risk not fully eliminated after SBFT. "CE failure to reach the caecum" in 2 patients (in addition to the 2 patients with capsule retention)
Eliakim et al (2004)[18], final report of Eliakim et al (2003)[16] Haifa, Israel 35 consecutive patients with suspected CD 13 female, 22 male Mean age 28.4 years, range 19-57	SBFT followed by CE (if no stricture on SBFT, 0 patients excluded), followed by entero-CT (all procedure completed within 3 months)	Outcomes reported Diagnostic yield: medically significant or explaining the patients reason for referral Diagnostic yield CE: 27/35 (77%), CE confirmed radiological findings in 9 patients, extended involvement in 6 and ruled out the radiological suspicion of CD in 10 (all confirmed by ileoscopy) SBFT: 23% Entero-CT: 20%	Complications: none	CE reader blinded for other exams No data on "CE failure to reach the caecum"
Chong et al (2005)[19] Melbourne, Australia May 2002 – November 2003	Enteroclysis (double-contrast small-bowel follow through) and PE. CE two weeks after PE and	Outcomes reported Diagnostic yield Effect on patient management. Diagnostic yield	Complications CE: one patient could not swallow capsule (was placed in duodenum), no capsule retention	Blinded study No major discrepancy between the CE interpretations by the two

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
Two groups 22 patients with known CD 5 men, 17 women, mean age 39.8, range 17-68 21 patients with suspected CD 10 men, 11 women, mean age 35, range 20-80 45 patients recruited, 43 with CE and PE, enteroclysis in all but 6 patients	enteroclysis if no stricture.	Known CD CE: CD lesions seen in 17/22 (77%) PE: CD lesions in 3/22 Enteroclysis: 4/21 Suspected CD CE: CD lesions seen in 2/21 (10%) PE: 0/21 Enteroclysis: 0/16 Management change reported for 16 known CD (73%) and 14 /21 (67%) suspected CD patients.	Enteroclysis: failed in 6 (tube displaced in 4, one patient did not tolerate the tube, one showed rapid transit of the contrast through the small bowel)	gastroenterologists. "CE failure to reach the caecum" in 6 patients
Voderholzer et al (2005)[20] Berlin, Germany August 2001 – November 2003 56 consecutive CD patients (diagnosis was newly established based on CE findings in 5 patients), EGD and ileocolonoscopy within last 2 weeks 26 men, 30 women mean age 35.8 years 15 patients were excluded with	CT enteroclysis (followed by CE if no stricture < 10 mm)	Outcomes reported Diagnostic yield Therapeutic impact Jejunal or ileal CD lesions CE: 25/41 (61%), 5/41 with large lesions, 3 missed CT enteroclysis: 12/41, 8/41 with large lesions, 8 missed ? Terminal/neoterminal ileum CD lesions CE : 24/41 (43%) CT enteroclysis : 20/41 Therapeutic impact of CE in 10 patients (incl 5 new diagnoses of CD).	Complications CE: Pain at passing inflamed ileal segment in 2 patients Capsule retention in 2 patients (one at terminal ileum, passed after corticosteroid therapy and one at jejunum, removed using PE) One CE had to be repeated because the capsule remained for 4 hours in the stomach.	Evaluation: one investigator per technique CE analysis took about 1.5h per patient "CE failure to reach the caecum" in a total of 10 patients

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
stenosis 41 patients, 18 mean, 23 women underwent CE 14/56 patients had undergone previous iliocaecal resection and another 2 had segmental small intestinal resection				
Albert et al. (2005)[21] Halle (Saale), Germany May 2002 – December 2003 52 consecutive pts with newly suspected CD (n=25 patients) or known CD (n=27 patients) 13 man, 39 women mean age : 36.6 years (men); 39.7 years (women) age range 18 to 72 years	MRI and enteroclysis (double contrast fluoroscopy), followed by CE within 10 days (in 1 patient: 6 weeks) if no small bowel stricture < 12 mm	Outcomes reported Diagnostic yield Final diagnosis after 12 months follow-up Patient's acceptance Detection of small bowel lesions in pts with known CD (n=27; 16 had previous bowel surgery): Enteroclysis: 16/27 (59%) - stricture detected in 12 pts MRI: 22/27 (81.5%) – stricture detected in 1 additional pt CE: 13/14 (93%) – typical features of small bowel CD (CE was not done in 13 pts due to stricture) Diagnostic yield of CE vs MRI (NS) CE was the exclusive diagnostic tool in 2 pts Pts with suspected CD (n=25) Diagnosis: confirmed in 14/25 pts (56%) and rejected in 11/25 pts (44%) Detection of small bowel lesions in pts with	Complications CE: capsule retention in a small bowel stricture undetected on abdominal ultrasound and enteroclysis in 1 pt (abdominal colicky pain; excretion of the capsule 72 hours later after IV coticosteroids) MRI: claustrophobia in 2 pts; refusal in 1 pt Enteroclysis: transnasal tube not tolerated in 1 pt	Suspicion of CD based on a combination of clinical and biochemical features and after exclusion of other potential causes (with microbiological stool test, endoscopy, abdominal ultrasound and cross-sectional imaging) Originally 81 pts: 28 pts were excluded after a definitive diagnosis by basic procedures or when clinical management would not be affected by potential small bowel involvement (1 pt underwent urgent surgery) Blinded evaluators for MRI, enteroclysis and CE Not stated whether blind assessment of the final diagnosis (used as a reference standard in the

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
		final CD diagnosis: Enteroclysis: 4/14 (28.6%) MRI: 10/13 (77%) CE: 12/13 (92%) Diagnostic accuracy of CE vs MRI in suspected CD based on the final diagnosis: CE sens 92% (12/13) and CE spec 100% (10/10) MRI sens 77% (10/13) and MRI spec 80% (8/10) CE was the exclusive diagnostic tool in 2 pts Follow-up data in 22 pts: CD diagnosis remained unchanged in all cases Patients' acceptance: CE was found less stressing than MRI and enteroclysis (questionnaire responses in 22 pts)		determination of diagnostic accuracy) No data on "CE failure to reach the caecum" Enteroclysis is the least sensitive CE only slightly more sensitive than MRI The marginal superiority of CE would probably not alter diagnostic decision making in the individual pt
POLYPOSIS				
Caspari et al (2004)[41] Bonn, Germany 20 consecutive patients with Peutz-Jeghers' syndrome (PJS; n=4) or familial adenomatous polyposis (FAP, n=16) 14 male, 6 female	MRI (if no stricture detected, CE was performed the next day)	Outcomes reported Polyps, categorized by size into 4 groups: 0-5mm to >15mm CE: 448 polyps identified in 8 patients MRI: 24 polyps identified in 4 PJS patients 0-5mm only detected using CE, 5-15mm: more often detected using CE >15mm: equally well detected (yet some are missed using either technique)	Complications: none	Blinded evaluators for MRI and CE MRI identified 2 desmoid tumors in a FAP patients CE identified active bleeding area in PSJ patient Relevance of the many small polyps sees in PJS unclear Both MRI and CE may be

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
Median age 39 years				adequate for small-bowel screening in PJS patients
Mata et al (2005)[42] Barcelona, Spain March 2003 – March 2004 24 consecutive patients with FAP (n=20) or PJS (n=4) Mean age 35 years 12 man and 12 women 1 PJS patients had segmentary small bowel resection before, 12 FAP patients had colectomy	SBFT (CE after one week if no potential obstruction detected)	Outcomes reported Number and location of polyps Change in patient management CE: 44 polyps (25 in duodenum, 8 in jejunum and 11 in ileum) detected in 7/24 patients (29%) SBFT: 12 polyps (5 in duodenum, 6 in jejunum and 1 in ileum) detected in 3/24 patients (12%), all were PJS patients, no additional patients over CE Change in management based on CE findings: 3 FAP patients underwent polypectomy (tubular or tubulovillous adenoma with low-grade dysplasia in all 3 cases)	Complications CE: none SBFT: none	Two investigators each performing one technique, blinded for the patient data
Schulman et al (2005)[32] Bochum, Germany 40 consecutive patients, 29 patients with FAP and 11 patients with PJS FAP: 17 men, 12 women, median age 42 years, range 15-56 PJS: 2 men, 9 women, median	PE in FAP EGD, PE, (MR)-enteroclysis, and surgical specimens in PJS Conventional endoscopy procedures were performed within 3 weeks after CE	Outcomes reported Polyps detected, number, size, location. Impact on management. 21/29 FAP patients had duodenal polyps on EGD and duodenoscopy, 2 were missed on CE 16 out of these 21 patients had polyps also in jejumum detected both with PE and CE 5/21 also in distal jejunum and ileum detected by CE only.	Complications Two capsules were retained in a pouch, one of these capsule retentions was associated with perianal pain. Capsules were removed endoscopically. One unrecognized disconnection of the data recorder after 3 hours.	CE and endoscopy findings compared by one of three independent study investigators. Endoscopists and radiologists were blinded to CE findings. CE is inferior to study periampullary region compared with EGD and duodenoscopy

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
age 34 years, range 23-58 25/29 FAP patients had colorectal surgery before 10/11 PJS had undergone one or more small bowel resections		Only 1/29 patient had polyps located distal jejunal or ileal only, and detected using CE. 10/11 PJS patients had polyps with CE and also with all other tests combined. All 5 symptomatic PJS patients had polyps on CE, confirmed using intraoperative endoscopy where done CE found polyps in 4 out of 5 asymptomatic patients and CD in one patients with chronic diarrhea. In 8/11: additional findings on CE v PE. Impact CE on management in all PJP patients.		Use of CE in FAP may be more selective compared with PJS, where CE could be used as first line surveillance procedure.
PEDIATRIC STUDIES				
Argüelles-Arias et al (2004)[22] Seville, Spain 12 patients with clinical suspicion of CD not confirmed with traditional methods (gastroscopy, coloscopy and SBFT, ileoscopy with biospy in 50%) 4 girls, 8 boys Mean age 14 years, range 12-16	none	Outcome Diagnostic yield CE identified lesions suggestive of CD in 7/12 (58%), the majority of lesions were in the ileum. Lesions consisted of aphtous lesions, erosions and/or ulcers	Complications CE: none	
Guilhon de Araujo et al	Comparison with	Diagnostic yield	Complications	CE interpreted by two

Study details	Comparator	Key efficacy findings	Key safety findings	Comments
(2005)[23] Montréal, Canada 30 patients (20 with suspected CD, 6 with polyposis, and 4 with obscure GI bleeding) 17 boys and 13 girls Mean age 14.1 years, range 10-18	normally used procedures; all performed within last 4 weeks before CE (except angiography) Possible CD: colonoscopy and SBFT Polyposis : gastroscopy, colonoscopy and SBFT Obscure bleeding: gastroscopy, colonoscopy, mesenteric angiography	CE in suspected CD: 12/20 (60%), 10 with lesions compatible with CD Traditional investigations: 0/20 (suspicious but nondiagnostic in 5/20) CE in polyposis: 3/6, identical as for other methods, but 50% more polyps on CE CE identified source in three out of 4 patients with obscure bleeding, vs 0/4 using standard endoscopic examinations	One capsule expelled after corticoid treatment (no symptoms)	investigators, one fully blinded. Interobserver concordance for number of lesions (mucosal ulcerations, polyps, vascular abnormalities) was 86%.

Studies included in the NICE 2004 report are marked with (*) or with (**) when more details are provided in this report.

7.1.2. HTA-reports and systematic reviews

OBSCURE GASTROINTESTINAL BLEEDING IN ADULT PATIENTS

Study details	Key efficacy findings	Key safety findings	Comments
MSAC-HTA report (2003): systematic review[4] Australia Literature search date: October 2002 and March 2003 (Medline) 16 comparative studies on diagnostic efficacy: 6 papers and 10 abstracts (n=12-59/study; total n= 389) Comparator: PE in 14 studies, SBS in 1 study and intraoperative in 1 study 9 comparative and 15 non-comparative studies reported adverse event data 63 studies (50 in abstract form) assessed for safety were listed in Appendix C of the report incomplete studies: CEDIT (2003)	Diagnostic yield (percentage definite diagnosis) Yield of CE: range 31% to 81% Yield of comparator: range 5% to 81% The yield of CE was higher than that of the comparator in 1 study, similar to the comparator (intraoperative) in 1 study and lower than the comparator (PE) in 1 study Bayesian meta-analyses results (CE vs SBS) Main analyses Diagnostic yield: 0.58 vs 0.035 95% Credibility Interval: 0.463-0.677 vs 0.005-0.120 Odds Ratio: 37.3 vs 37.3 95% Credibility Interval: 9.43-270.97 vs 9.43-270.97 Sensitivity analyses Diagnostic yield: 0.64 vs 0.039 95% Credibility Interval: 0.576-0.698 vs 0.006-0.137	Adverse events Comparative data (from 9 studies) In 7 studies no adverse events were reported Adverse events, considered to be unrelated to the study procedure, were reported in 2 studies: -study 1: 5/59 patients had bleeding, abdominal pain, abdominal pain with nausea, abdominal pain with nausea and vomiting or vomiting only -study 2: 2/41 patients had mild abdominal pain or death due to coronary occlusion Non-comparative data (from 15 studies) In 9 studies no adverse events were reported Adverse events were reported in 6 studies: -study 1: 1/1 capsule was lodged in the cricopharyngeus -study 2: 2/35 had mild abdominal pain -study 3: 1/4 had abdominal pain associated with delayed passage	Meta-analysis provided an indirect comparison: SBS versus PE SBS was determined to be the main comparator; trials with PE as a comparator were used as indirect evidence in the efficacy assessment of CE Definition of a positive diagnosis varied across studies Sensitivity analysis includes abstracts and unpublished studies Data from studies limited to patients with severe obscure GI bleeding were excluded from the analysis Studies (papers and abstracts) with <10 patients were excluded from the efficacy evaluation but

Study details	Key efficacy findings	Key safety findings	Comments
	Odds Ratio: 42.9 vs 42.9 95% Credibility Interval: 10.98-317.35 vs 10.98-317.35 Limited information on changes in patient management and health outcomes	-study 4: 1/259 had obstructive symptoms -study 5: 1/1 capsule lodged in a bronchus -study 6: 1/1 capsule retention with small bowel obstruction Delayed passage or non-passage 20 studies reported cases of delayed passage or non-passage of the capsule	adverse events and safety findings from these studies were included Safety reporting was generally of a poor standard
NICE report (2004)[3] UK The evidence on CE in patients with obscure GI bleeding is based on the MSAC-HTA report (systematic review) and is updated with 5 comparative studies published after the literature search date of the systematic review (n= number of patients receiving capsule) Pennazio et al. (2004)[9] (n=100) Saurin et al. (2003)[43] (n=60) Mylonaki et al. (2003)[29] (n=52) Buchman et al. (2003)[10] (n=20) Hara et al. (2004)[25] (n=52)	Study 1 Diagnostic yield of CE was highest in patients with obscure-overt bleeding (92.3%; 95% CI 82-100%), intermediate in obscure-occult bleeding (44,1%; 95% CI 29-59%) and lowest in previous obscure-overt bleeding (12.9%; 95% CI 1.2-25%) Diagnostic accuracy: CE sensitivity=88.9% (32/36 patients) and CE specificity=95% (19/20 patients) CE findings led to changes in management in 86.9% of patients with ongoing obscure-overt bleeding and 69.2% and 41.4% of patients with previous obscure-overt bleeding or obscure-occult bleeding respectively Study 2 Diagnostic yield of CE: 40/58 (69%) Diagnostic yield of PE: 22/58 (37.9%)	Complications 5 patients (5%) had non-natural excretion of the capsule (study 1) no complication observed during the study with either type of technology (study 2) 1 patient had delayed passage; technical problems e.g. battery power expiring (study 3) natural excretion of the capsule in all patients (study 4)	Study 1 Comparison of CE with PE not possible due to timing A greater proportion of patients with ongoing obscure-overt bleeding underwent further investigations CE sensitivity and CE specificity based on only a small number of patients Indpendent verification not available for all patients Study 2 Inter-observer concordance was good in patients with obvious bleeding and in negative studies but decreased in patients with

Study details	Key efficacy findings	Key safety findings	Comments
Study design was prospective in studies 1-4 and retrospective in study 5 Comparator : PE in studies 1-4 ; SBS and/or CT in study 5	Study 3 Diagnostic yield of CE in identification of a bleeding source in the small bowel: 34/50 (68%); yield of CE including diagnosis outside the small intestine: 38/50 (76%). Diagnostic yield of PE in identification of a bleeding source in the small bowel: 16/50 (32%); yield of PE following a second enteroscopy and finding of another source and including diagnosis outside the small intestine: 38/50 (38%). Yield of CE>PE in identifying bleeding sources ($p<0.05$) Changes in therapy following positive CE in 25/38 patients (7 patients had surgery) Patient satisfaction. CE preferable to PE (49/50 patients); CE uncomfortable but only at swallowing (2/50); PE painful (34/50) Study 4 Diagnostic yield in identification of a bleeding source: CE 12/20 (60%) patients versus PE 2/13 patients (15%)(PE refused by 7 patients) CE led to successful surgical resection in 3 patients Study 5 Diagnostic yield of CE versus SBS in identification of a bleeding source : CE 19/40 (47.5%) patients versus SBS 1/40 (2.5%) patients.		less clinically relevant lesions Study 3 Not reported how patients had positive CE findings and positive PE findings Unclear what a successful result means Disagreement on interpretation as to the source of bleeding in 2/38 patients Study 4 Unclear what successful determination of a bleeding source means Results for PE based on small numbers due to refusals Study 5 Heterogeneous group of patients Demographic data not presented on the 42 patients meeting inclusion criteria Results not reviewed blinded

Study details	Key efficacy findings	Key safety findings	Comments
	Diagnostic yield of CE versus CT in identification of a bleeding source : CE 12/19 (36.5%) patients versus SBS 4/19 (21%) patients Surgical results reported on some patients but difficult to ascertain false positives and false negatives		6 diagnostic investigations performed >3 months from CE
Marmo et al. 2005 – systematic review[7] Italy Literature search up to March 2005 9 prospective, comparative studies on diagnostic efficacy (n=20-65/study; total n= 336) Comparator: PE in 8 studies, SBFT in 1 study	Diagnostic yield of CE (289 patients) Pooled RD (the absolute pooled difference in the rate of positive findings between CE and comparators): 36.9% (95% CI: 29.6-44.1) (p< 0.0001) Higher probability of a positive finding on CE compared with PE: OR 4.3 (95% CI: 3.1-6.0) (p< 0.001)	Contraindications Contraindications to CE were reported in 8/336 cases (2.4%) (95% CI: 1.0-4.6): small bowel stricture, previous major abdominal surgery, pacemaker and diabetes (each in 2 patients respectively) Adverse events Adverse events of CE were reported in 15/289 patients (5.2%) (95% CI: 3.7-7.8) and were related to capsule retention in 2 cases. Removal by surgery in 1patient and by endoscopy in 1 patient. Adverse effects of PE in 1/274 patients (no advance beyond the duodenal bulb) Failure to visualize the caecum The caecum was not visualized in 48/289 patients (16.6%) (95% CI: 12.5-21.4)	Superiority of CE is consistent and homogeneous throughout the studies No separate analysis on overt and occult bleeding Unclear why the study of Pennazzio 2004 was not included From the Table on contraindications it appears that 3 studies reported no data. These patients should be substracted from the total number of patients: in this scenario contraindications were present in 8/253 (3.2%) cases From the Table on "CE failure to reach the caecum" it appears that 1 study reported no data. These patients should be substracted from the total number of patients: in this case the caecum was not reached in 48/257 (18.7%) patients.

Abbreviations used: HTA – Health Technology Assessment; CE – capsule endoscopy; PE – push enteroscopy; SBS – small bowel series; SBFT - small bowel follow through; RD - rate difference; OR – odds ratio; CI - confidence interval
Table adapted from NICE Interventional Procedures Overview: Wireless capsule endoscopy – 29 June 2004

SUSPECTED OR KNOWN CROHN'S DISEASE

Study details	Key efficacy findings	Key safety findings	Comments
NICE report (2004)[3] UK The evidence on CE in patients with suspected or known CD is based on 4 studies and 1 abstract. Only 1study was comparative (Eliakim 2003)[16] and is updated later	The evidence indicates that CE identifies small bowel lesions suggestive of CD in 43-71% (9/21-12/17) patients with normal findings on conventional tests. Three studies reported that CE findings had changed patient management, with two studies reporting clinical improvement in 83-100% (10/12-9/9) of patients	No complications reported from studies. Another study reported capsule retention in 1/60 patients Although Specialist Advisors considered CE a safe procedure, they also felt that the most likely adverse event was that the capsule might become lodged in narrowed areas of the small bowel, causing bowel obstruction. This complication is more likely in patients with suspected CD compared to those with OGIB	The available evidence is of insufficient quantity and quality to determine the relative diagnostic performance of CE in diagnosing unselected patients with suspected CD Specialist Advisors noted a lack of comparative data in relation to existing technology. The main indication for CE and its place in the diagnostic work-up of patients is still to be defined
Marmo et al. 2005 – systematic review[7] Italy Literature search up to March 2005 8 prospective, comparative studies on diagnostic efficacy (n=17-56/study; total n= 273) Comparator: SBFT in 5 studies, enteroclysis in 2 studies and CT enteroclysis in 1 study	Diagnostic yield of CE (237 patients) Significant heterogeneity between the studies (Q=17.41 – p<0.01) Pooled RD: 44.5% (95% CI: 30.9-58.0) (p< 0.0001) (from a random effect model) Higher probability of a positive finding on CE: compared with enteroclysis (OR 5.4 and 95% CI: 3.0-9.9) compared with SBFT (OR 7.2 and 95% CI: 2.3-71.4)	Contraindications Contraindications to CE were reported in 31/ 268 cases (11.6%) (95% CI: 8.0-16.0): small bowel stricture at pre-CE radiology in 30 cases and previous major abdominal surgery in 1 patient. Higher probability of the presence of a stricture as a contraindication to CE in CD patients compared to OGIB patients (OR 21.05, 95% CI: 5.24-182.83) Adverse events All adverse events were related to capsule retention in 7/237 cases (3%) (95% CI: 1.2-6.0). Surgical removal in 5 cases, endoscopic removal in 1 patient and natural passage after 3 days of	INVALID results and conclusion due to inclusion of 3 non-comparative studies and underestimation of "CE failure to reach the caecum" Significant heterogeneity among studies prevents generalisability of results to the whole population No separate analysis on suspected and known CD From the Table on "CE failure to reach the caecum" it appears that 2 studies reported no data. It would be more appropriate to substract these patients from

Study details	Key efficacy findings	Key safety findings	Comments
		steroids in 1 patient Failure to visualize the caecum The caecum was not visualized in 20/237 patients with CD (8.4%) (95% CI: 5.2-12.7)	the total number of patients: in this case the caecum was not reached in 20/185 (10.8%) patients. It is unclear from the Table whether patients with capsule retention should be substracted from the total number of patients or added to those with failure to reach the caecum. In the latter scenario the caecum was not seen in 27/185 (14.6%) patients

7.2. APPENDIX 2: EXISTING HTA-REPORTS ON CAPSULE ENDOSCOPY

Rapid review of the medical literature and specialist opinion: National Institute for Clinical Excellence (NICE) Interventional Procedures Overview. Wireless capsule endoscopy[3]. Literature search date is not stated but studies were included up to March 2004
Safety No significant complications were reported in the studies. The most commonly reported adverse events associated with the procedure were abdominal pain, nausea, and vomiting. Delayed passage of the capsule was also reported in a number of studies and in the majority of cases was resolved without incident. In a study of 200 patients done to assess the complications associated with the use of capsule endoscopy (CE), 6 (3%) patients had complications associated with the procedure. This included 1 patient who was unable to swallow the capsule, 1 patient who inadvertently aspirated the capsule and 2 patients who experienced delayed passage and had to have surgery to remove the capsule. The Specialist Advisors considered that this was a safe procedure. They felt that the most likely adverse event was that the capsule might become lodged in narrowed areas of the small bowel, causing bowel obstruction. One Advisor commented that this complication was more likely in patients with suspected Crohn's disease (CD) rather than obscure gastrointestinal bleeding (OGIB).
Efficacy Obscure gastrointestinal bleeding (OGIB) The published evidence suggests that wireless capsule endoscopy (CE) can detect a bleeding source in 31-76% of patients with OGIB. In all studies, wireless CE had a higher diagnostic yield (proportion of patients identified with a lesion) than the comparator test. However, in most cases patients had undergone extensive prior investigations, which is likely to decrease the diagnostic yield of the comparator procedures. It is also not possible to determine the relative diagnostic performance (ability to correctly diagnose both positive and negative disease) of wireless CE compared with alternative conventional diagnostc tests. Several studies reported that CE findings had changed patient management, but limited details were given as to whether change in management improved health outcomes. Suspected Crohn's disease The evidence indicates that wireless CE identifies small bowel lesions suggestive of Crohn's disease in 43-71% (9/21-12/17) patients with normal findings on conventional tests. Three studies reported that CE findings had changed patient management, with two studies reporting clinical improvement in 83-100% (10/12-9/9) of patients. The available evidence, however, is not of sufficient quantity and quality to determine the relative diagnostic performance of wireless CE compared with alternative conventional diagnostic tests in diagnosing unselected patients with suspected Crohn's disease. The Specialist Advisors noted a lack of comparative data in relation to existing technology. They also considered that the main indication for the procedure and its place in the diagnostic work up of patients was still to be defined.
Specialist Advisor's opinions The main utility of CE will be in the diagnosis of OGIB although these patients present relatively infrequently. Potential expansions for the role of CE in terms of screening and in the evaluation of inflammatory bowel disease, but these are by no means established at this point. Clinical follow up will be necessary to confirm the value of the CE findings. The experience in relation to CE is that it performs at least as well as barium follow through and enteroscopy, but that these procedures are complementary and should not be regarded as competitors. There is a substantial interest worldwide in CE.
Issues for consideration by the Interventional Procedure Advisory Committee (IPAC) The place of this procedure in the management of patients with OGIB or suspected CD is still unclear i.e. will it be used incrementally/triage or as a replacement test? There appears to be a significant interest in the use of this procedure – further studies are continually being published.

HTA Review: Medical Services Advisory Committee (MSAC). Wireless capsule endoscopy for patients with obscure digestive tract bleeding[4]. Literature search date: October 2002 and March 2003 (Medline)
Safety Adverse events The adverse events associated with the use of the capsule endoscopy in patients with obscure gastrointestinal (GI) bleeding appear to be infrequent and mild in nature. The most commonly reported adverse events associated with capsule endoscopy are abdominal pain, nausea, and vomiting. Delayed passage of the capsule has also been associated with abdominal pain and hospitalisation in a single patient. In another patient the retention of the capsule was associated with GI obstructive symptoms. In other isolated cases the capsule became lodged in a patient's bronchus and in a patient's throat. In both of these cases the capsule was removed without complication. Delayed passage In general, reporting on the passage of the capsule in the available literature was poor. Delayed passage or lodgement of the capsule was reported in less than five per cent (27/581) of all patients included in studies which systematically reported capsule passage data. Delayed passage or lodgement of the capsule was asymptomatic in all but one of these cases. In 37 per cent (10/27) of these events the capsule had to be surgically removed from the patient. In the majority of these cases (6/10) the capsule was removed at the time of planned surgical management. In practice, the delay of the capsule through the GI tract often aids the clinician in the diagnosis of previously undetected strictures.
Effectiveness Due to the lack of a suitable reference standard for capsule endoscopy, diagnostic yield (the number of patients with a pathological lesion identified/the total number of patients assessed) was used as the measure of diagnostic test performance. This measure is likely to overestimate the diagnostic capabilities of both the comparator and the procedure. At present due to the lack of a valid reference standard only level 3 and 4 evidence is available to describe the effectiveness of capsule endoscopy. 16 studies met the criteria for inclusion in the effectiveness review of capsule endoscopy. Only one small (13 patients) head-to-head trial comparing capsule endoscopy to small bowel series radiology (SBS) was identified at the time of assessment. Therefore a meta-analysis incorporating evidence from the head-to-head study of capsule endoscopy versus SBS, as well as indirect evidence from studies comparing capsule endoscopy to push enteroscopy and PE to SBS was undertaken. The summary point estimates of diagnostic yield for the two tests determined in the main analysis were: 58 per cent (CI 46.3-67.7%) for capsule endoscopy and 4 per cent (CI, 0.5-12.0%) for SBS. These point estimates of diagnostic yield were surrounded by wide credibility intervals due to the limited quantity of SBS data available. Despite this fact, the odds ratio of diagnostic yield of capsule endoscopy versus SBS was statistically significant (37.3 CI, 9.43-270.97) and favoured capsule endoscopy, In summary, based on the available evidence capsule endoscopy has a significantly greater diagnostic yield compared with SBS radiology.

Table from: NICE Interventional Procedures Overview: Wireless capsule endoscopy (2004)[3].

HTA Review: Blue Cross Blue Shield Association. Wireless capsule endoscopy for obscure digestive tract bleeding[5]. Literature search date: July 2002 This review reports on three published studies including a total of 72 subjects. Two of these studies were conducted in patients with obscure digestive tract bleeding suspected to be of small bowel origin, and the third study was conducted in patients with suspected small bowel disease, most of whom had obscure digestive tract bleeding.
Conclusions The body of evidence is relatively small; however obscure digestive tract bleeding suspected to be of small bowel origin is a relatively infrequent condition and thus the availability of subjects for investigation may be limited. No significant complications from wireless capsule endoscopy were reported in these studies. The findings of the two comparative studies illustrated that wireless capsule endoscopy demonstrates additional small bowel lesions generally beyond the reach of conventional push enteroscopy in 25–50% of cases studies. Wireless capsule endoscopy revealed additional suspicious or definite findings in 65–100% of cases when compared with small bowel barium radiographic studies. In some cases, this additional information can lead to changes in management that would improve health outcomes.

Table from: NICE Interventional Procedures Overview: Wireless capsule endoscopy (2004)[3].

HTA Review: Blue Cross Blue Shield Association. Wireless capsule endoscopy for small-bowel diseases other than obscure GI bleeding[6]. Literature search date: November 2003 This review reports on three published studies, two abstracts and 9 relevant case reports included in 2 published case series.
Conclusions For initial diagnosis of suspected Crohn's disease when all conventional diagnostic tests including SBFT have failed to reveal bowel lesions suggestive of Crohn's disease, the evidence suggests that wireless capsule endoscopy may demonstrate small bowel lesions suggestive of Crohn's disease in a significant proportion of patients ranging from 43–71%. Furthermore, patients diagnosed with Crohn's disease by wireless capsule endoscopy were reported to improve after treatment for Crohn's disease, which represents an improvement in health outcomes. However, the available evidence is not of sufficient quantity and quality to determine the relative diagnostic performance of wireless capsule endoscopy compared with alternative conventional diagnostic tests in diagnosing unselected patients with suspected Crohn's disease. Thus no conclusions can be made as to whether wireless capsule endoscopy is an effective alternative to conventional tests.

Table from: NICE Interventional Procedures Overview: Wireless capsule endoscopy (2004)[3].

7.3. APPENDIX 3: LITERATURE SEARCH

The following search strategy was used in Medline (Ovid) on 27 May 2005. The same search strategy has also been used in the NICE 2004 report on capsule endoscopy.

Database: Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations, Ovid MEDLINE(R)

Search Strategy:

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1 wireless capsule endoscopy.mp. (97)

2 capsule endoscopy.mp. (267)

3 videocapsule endoscopy.mp. (4)

4 (camera adj4 pill).mp. [mp=ti, ot, ab, nm, hw] (3)

5 Wireless capsule enteroscopy.mp. (8)

6 WCE.tw. (58)

7 (Given$ adj4 capsule).mp. [mp=ti, ot, ab, nm, hw] (2)

8 or/1-7 (332)

9 exp CAPSULES/ (5960)

10 exp Video-Assisted Surgery/ (1741)

11 exp Endoscopy, Gastrointestinal/ (29322)

12 9 or 10 (7699)

13 12 and 11 (126)

14 8 or 13 (390)

15 14 not 6 (332)

The search was repeated on 5 October 2005 and additional papers published after the previous search date were retrieved.

7.4. APPENDIX 4: OVERVIEW OF HTA-REPORTS AND SYSTEMATIC REVIEWS

The CRD database (All Databases-DARE, NHS EED, HTA) was searched on 16/06/05 using the search string ""Capsule endoscopy" ("Capsule endoscopy/All fields – 12 Hits). The HTA reports and Systematic Reviews found were the following:

- CEDIT (Comité d'Evaluation et de Diffusion des Innovations Technologiques) has made recommendations in December 2003 on the use of CE in France in December 2003. CEDIT. Wireless capsule endoscopy for bowel examination – systematic review, expert panel. Comite d'Evaluation et de Diffusion des Innovations (CEDIT) 2001.
- The National Horizon Scanning Centre (UK) has published a "New and Emerging Technology Briefing" on the use of the M2A videocapsule in the diagnosis of small bowel diseases (July 2002). M2A capsule endoscopy for the diagnosis of small bowel disorders – horizon scanning review. National Horizon Scanning Centre (NHSC) 2002.
- CCOHTA (Canadian Coordinating Office for Health Technology Assessment) has published "Wireless capsule endoscopy" in their series "Issues in Emerging Technologies" (December 2003). Actual issues on CE endoscopy are briefly described. Referentie: Brodsky, L. M. (2003). "Wireless capsule endoscopy." Issues Emerg Health Technol(53): 1-4. - Wireless capsule endoscopy. Brodsky L. Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2003 (Issues in Emerging Health Technologies Issue 35).
- MUHC (McGill University Health Centre) has published a HTA report on the utility of CE in the diagnosis of small bowel diseases (March 2003). Referentie: Costa, V. and J. Brophy (2003). "Should the MUHC approve the video capsule endoscopy system in the diagnosis of small bowel abnormalities?" Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC): 38.
- MSAC (Medical Services Advisory Committee) has published a HTA report on the M2A videocapsule (December 2003). M2A(R) capsule endoscopy for the evaluation of obscure gastrointestinal bleeding in adult patients. Medical Services Advisory Committee (MSAC) 2003 (MSAC Application 1507): 159.
- Blue Cross Blue Shield Association has published a HTA report on the use of CE in the diagnosis of small bowel bleeding (February 2003). Wireless capsule endoscopy. Blue Cross Blue Shield Association. Blue Cross Blue Shield Association (BCBS) 2003 (TEC Assessment 17: 21).

- Blue Cross Blue Shield Association has published a HTA report on the use of CE in the diagnosis of small bowel diseases other than obscure gastrointestinal bleeding. Wireless capsule endoscopy for small-bowel diseases other than obscure GI bleeding. Blue Cross Blue Shield Association. Blue Cross Blue Shield Association (BCBS) 2003 (TEC Assessment 18: 18).
- Wireless capsule endoscopy. Hayes, Inc.. Hayes, Inc. 2003: 31. (Not Available).
- Wireless capsule endoscopy. Ontario Ministry of Health and Long-Term Care. Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS) 2003:31.
- Ruano-Ravina A, Rey-Liste T. Effectiveness of endoscopic capsule for the detection of small-bowel bleeding of unknown origin and for the diagnosis of Crohn's disease. Med Clin (Barc). 2004;123(2):70-6.
- The National Institute for Clinical Excellence (UK) has published an "Interventional procedures overview of wireless capsule endoscopy" (January 2004). Wireless capsule endoscopy for investigation of the small bowel. National Institute for Clinical Excellence (NICE) 2004 (Interventional Procedure Guidance 101): 2. [3]

The following Systematic Review was identified in Medline (Ovid) (search in Medline, Pubmed, clinical queries, on 6/10/05):

- Marmo R, Rotondano G, Piscop R, Bianco MA, Cipolletta L. Meta-analysis: capsule enteroscopy vs. conventional modalities in diagnosis of small bowel diseases. Aliment Pharmacol Ther. 2005; 22: 595-604.

Guidelines, reviews and HTA documents identified from other databases and literature sources:

- Zuckerman GR, Prakash C, Askin MP, Lewis BS. AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology 2001; 118: 201-221.
- Rösch T, Ell C. Update from the German Society of Gastroenterology and Metabolic Diseases, section Endoscopy. Rosch T, Ell C. Position paper on capsule endoscopy for the diagnosis of small bowel disorders. Z Gastroenterol. 2004;42(3):247-59.
- Rey JF, Gay G, Kruse A, Lambert R. European Society of Gastrointestinal Endoscopy guideline for video capsule endoscopy. Endoscopy. 2004;36(7):656-8.

7.5. APPENDIX 5: OVERVIEW OF PROSPECTIVE AND COMPARATIVE STUDIES

7.5.1. Obscure gastrointestinal bleeding

Prospective and comparative studies of different diagnostic modalities in the detection of small bowel bleeding in the same patients (English–language publications, no abstracts). Studies are categorized according to the year of publication. Studies included in the NICE 2004 report are marked with (*) or with (**) when more details are provided in this report.

Publication	Comparator	Number of patiënts
*Costamagna, 2002[26]	SBS (small bowel series)	13
*Ell, 2002[44]	PE (push enteroscopy)	32
*Lewis, 2002[45]	PE	20
**Hartmann, 2003[39]	PE	33
*Saurin, 2003[43]	PE	60
*Mylonaki, 2003[29]	PE	50
*Buchman, 2003[10]	PE	20
Van Gossum, 2003[11]	PE	21
*Pennazio, 2004[9]	PE	100
*Hara, 2004[25]	SBFT CT	40 19
Adler, 2004[40]	PE	20
Mata, 2004[28]	PE	42
Hartmann, 2005[13]	Intraoperative enteroscopy	47
Overall CE in obscure GI bleeding		499
Overall with CE vs PE data	PE	342

7.5.2. Crohn's disease

Prospective and comparative studies of different diagnostic modalities in the diagnosis or follow up of CD in the same patients (English-language publications, no abstracts). Studies are categorized according to the year of publication. Studies included in the NICE 2004 report are marked with (*) or with (**) when more details are provided in this report.

Publication	Comparator	Number of patients
*Eliakim, 2003 and 2004[16, 18]	SBFT	35 CD
Buchman 2004[17]	SBFT	30 with suspected CD recurrence
Chong, 2005[19]	PE Enteroclysis PE Enteroclysis	21 suspected CD 22 known CD
Voderholzer, 2005[20]	CT enteroclysis	41 CD (incl 5 new CD)
Albert, 2005[21]	Enteroclysis MRI Enteroclysis MRI	27 known or suspected CD
Overall		176

7.5.3. Polyposis

Prospective and comparative studies of different diagnostic modalities in the diagnosis or follow up of polyposis in the same patients (English-language publications, no abstracts). Studies are categorized according to the year of publication.

Publication	Comparator	Number of patients
**Caspari, 2004[41]	MRI	20 (4 PJS, 16 FAP)
**Mata, 2005[42]	SBFT	24 (4 PJS, 20 FAP)
**Schulman, 2005[32]	FAP: PE PJS: EGD, PE, enteroclysis, and surgery	29 FAP 11 PJS
Overall		65 FAP, 19 PJS

7.6. APPENDIX 6: DIAGNOSTIC EFFICACY

Hierarchy of diagnostic efficacy

Fryback and Thornbury have described a hierarchy of diagnostic efficacy, which is used as the basis of this report [8]. Efficacy is defined as the probability of benefit from a medical technology to individuals in a defined population under ideal conditions of use [46]. In other words: can the diagnostic test work? This is not the same as effectiveness, which assesses the test's ability to work in the real world: does it work in clinical practice? Finally, in efficiency the test's financial implications are considered: is it worth it? [47] The model presented here mainly assesses the test's efficacy, although cost-effectiveness considers its efficiency.

The model is characterized by a change in perceived goals. It is hierarchical: on one extreme are endpoints describing only the technical performance of the test, on the other extreme are endpoints pertaining to the value of the diagnostic technology to society. If a test performs poorly at one level, it is unlikely to perform well at a higher level. The reverse, however, is not true: increases in the technical performance of a test will not necessarily guarantee improvement at a higher level, for example effect on patient outcome.

A diagnostic test does not necessarily have to have demonstrated effectiveness at each level before it can be used in clinical practice [48], but using this approach the possible gain and remaining uncertainty on the test's efficacy is clearly presented.

Level 1: technical efficacy

The technical efficacy of a test refers to the ability to produce usable information.

The *test's feasibility* and *operator dependence* refer to in what circumstances and by whom the test can be performed.

The *analytical sensitivity* is the ability to detect small quantities of the measured component. This should be distinguished from the diagnostic sensitivity, the ability of a test to detect disease.

The precision or *reproducibility* of results is the ability to obtain the same test results on repeated testing or observations. It is influenced by analytical variability and observer interpretation. Analytical variability consists of inaccuracy and imprecision. Inaccuracy implies systematic error, such as calibration error. Imprecision implies random error. Agreement between two continuous test methods can be expressed in a regression analysis or Bland & Altman plots [49]. A correlation coefficient does not provide information on agreement. The agreement between two observers (interobserver) or the same observer on different occasions (intraobserver) can be expressed with a kappa statistic.

It is often assumed that the technical efficacy does no longer need to be evaluated once a test is being used in clinical practice. However, in our review on molecular tests for the detection of enterovirus, the technical efficacy of the tests was insufficient to recommend its use in clinical

practice, despite the fact that the test is currently used in patients with suspected meningitis.

Level 2: diagnostic accuracy

This level refers to the test's ability to detect or exclude disease in patients compared with a criterion standard or reference test. Test characteristics are sensitivity, specificity, predictive values, likelihood ratios and ROC curves.

Sensitivity and specificity are the most widely used outcome measures, but are sensible to spectrum bias. Spectrum bias may occur when the study population has a different clinical spectrum (more advanced cases, for instance) than the population in whom the test is to be applied [50 51]. If sensitivity is determined in seriously diseased subjects and specificity in clearly healthy subjects, both will be grossly overestimated relative to practical situations where diseased and healthy subjects cannot be clinically distinguished in advance [52 53]. This design has been called 'inappropriate case-control design' in the pilot assessments.

Predictive values, with the positive predictive value being the proportion of patients with a positive test result that actually has the disease and the negative predictive value the proportion of patients with a negative test result that does not have the disease, are dependent on disease prevalence in the study sample. For example, in a situation where disease prevalence is very low, say 1%, the negative predictive value of the test will be easily over 95% as already 99% of the population do not have the disease. Prevalence and the setting in which patients were recruited should be noted to reflect on this.

The *likelihood ratios* show how a test result alters the pre-test probability into a post-test probability, using Bayesian reasoning. The pre-test probability depends on the prevalence of the target condition and the results of previous tests, for example history, clinical examination, imaging or laboratory tests.

Another outcome measure which is sometimes used, is the *number needed to diagnose*, analogous to the number needed to treat in intervention studies. However, using this measure it is assumed that diagnostic testing is always done to rule in a target condition, to diagnose the target condition, while in clinical practice tests are also used to rule out a target condition.

Finally, test accuracy can be illustrated using an *ROC curve*. The ROC curve graphs test sensitivity versus 1-specificity for various cut-off points. The area under the curve provides a summary measure of the test performance. It also allows comparison of two different tests by testing the two areas under the curve or by testing partial areas under the curve in which the test is most useful.

Clearly, the first level of diagnostic efficacy, technical efficacy, contributes to the diagnostic accuracy. But it also becomes apparent that there may be a point beyond which improvement in technical performance no longer improves diagnostic accuracy. Assuming therefore that diagnostic

accuracy can be estimated on the basis of technical accuracy studies is not correct.

Level 3: diagnostic thinking

This level of diagnostic efficacy is concerned with assessment of the effect of test information on diagnostic reasoning and disease categorization. Studies on diagnostic thinking serve as a proxy for estimating the effect of a test on patient care. Patients' outcome can not be influenced by the diagnostic technology unless the physician is led to do something different than would have been done without the test information.

Using the *likelihood ratio* and calculating the post-test probability, this change in diagnostic thinking can be computed. However, the pre-test probability of a disease is not always available in clinical practice and depends not only on setting, but also on patient characteristics and other selection processes, such as referral and the results or previous tests. Clinicians who wish to apply the Bayesian properties of diagnostic tests require accurate estimates of the pre-test probability of target disorders in their area and setting. These estimates can come from five sources: personal experience, population prevalence figures, practice databases, the publication that described the test or one of a growing number of primary studies of pre-test probability in different settings [54].

An alternative are studies that empirically test the *change in the physician's subjective assessment* on the probability of disease. In these studies, physicians are asked to estimate the probability of disease before knowing the test result, and estimating it again after the test result has been disclosed. Efficacious tests are those that significantly increase or lower pre-test probabilities assumed by the physician or computed by likelihood ratios using Bayesian reasoning.

One major difficulty with this level of diagnostic efficacy is that it is not always known what post-test probability of disease should be used as a threshold. Which probability of disease is low enough to exclude disease, which is high enough to treat the patient? These thresholds will differ according to the target condition and the treatments that are available [55].

Level 4: therapeutic impact

The most efficacious tests at this level are those that lead to the institution of a new management strategy. Studies can assess this empirically by comparing the intended management before the test result is known with that after the test result has been disclosed. In what *proportion of patients did the information change the intended management?* In some cases, management changes are considered not only in the patient himself, but also in other persons, for example prophylactic measures in case of an infectious outbreak. These prospective case-series, however, can be subject to bias such as selection bias. The lack of a concurrent control group may lead to confounding, as there is no information on those patients not enrolled in the study and therefore not receiving the new technology. These considerations underscore the need for randomized controlled trials. But, in the absence of RCT's they do play an important role as an intermediate.

Level 5: patient outcome

The ultimate goal of health care is to improve patient outcome. For diagnostic tests that are expensive, dangerous or widely used, knowledge about patient outcome efficacy seems particularly important. It is at this level that expected harm, such as burden, pain, risk, can be weighed directly against its expected benefit, such as improving life expectancy, quality of life, avoiding other test procedures, etcetera.

The *randomized controlled trial* is the study design the least prone to bias to estimate these harm and benefit. However, it is not always feasible to perform an RCT for ethical, financial or other reasons. In those cases, case-series collected before and after the introduction of a new test technology or case-control studies may provide some of the answers.

A methodological difficulty with this level is that the independent contribution of test technology to patient outcomes may be small in the context of all the other influences and therefore very large sample sizes may be required. But, in spite of these difficulties, RCT's on diagnostic tests are feasible. Various designs are possible, according to the specific research question [56].

Some tests, however, will never be able to prove a change in 'objective' patient outcomes such as mortality or morbidity, simply because there is no treatment available at this moment that has an impact on these outcomes. This is the case in for example dementia or Amyotrophic Lateral Sclerosis (ALS). A diagnostic test will therefore never produce a difference in mortality, but may improve *quality of life measures* by giving the patient (and the carer) an affirmative diagnosis and providing an explanation for the signs and symptoms the patient experiences.

Level 6: cost-effectiveness analysis

This level goes beyond the individual risks and benefits, but assesses whether the cost for use of a given test is acceptable for society. Is the price for the positive effect on patient outcome worthwhile? Resources can not be allocated twice; money spent on one technology can not be spent on another.

Cost-effectiveness studies compute a cost per unit of output. Any of the measures of the previous levels can be used as input, for example cost per surgery avoided, cost per appropriately treated patient, cost per life year gained or cost per quality adjusted life year gained. Final outcomes, such as life years gained or QALYs gained, are preferred over intermediate outcomes in economic evaluations, as they allow comparisons across a broader range of health interventions, e.g. diagnostic and therapeutic interventions. Because data on these outcomes and costs of the diagnostic and subsequent therapeutic paths are not routinely available from observations, modelling becomes inevitable to examine the cost-effectiveness of diagnostic tests. The validity of the model input parameters is crucial for the credibility of the model. The values of all input variables must be based on solid evidence

obtained from literature or observations. Sensitivity analyses can illustrate the robustness of the conclusions, by demonstrating the sensitivity of the results to changes in the values of remaining uncertain input parameters.

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18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02

Renseignements

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