

PILLCAM ESO CAPSULE FOR THE EVALUATION OF ESOPHAGEAL DISEASE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) is asked to review the scientific evidence for the use of PILLCAM ESO for the diagnosis of diseases of the esophagus.

To date, the gold standard for screening patients with esophageal disease has been the conventional esophagogastroduodenoscopy (EGD or conventional endoscopy (CE)). More recently, studies have investigated the role of esophageal capsule endoscopy (ECE) in the evaluation of patients with esophageal disease who otherwise would warrant screening with CE. To date, the only FDA approved ECE device is the PillCam ESO (PillCam™ ESO, Given diagnostic system: Given Imaging, Yoqneam, Israel).

This assessment summarizes the peer reviewed, published trials of PillCam ESO in the evaluation of patients with symptoms of or known esophageal disease and surveillance of patients at risk for esophageal varices.

BACKGROUND

Diseases of the esophagus include gastroesophageal reflux disease (GERD), esophagitis, Barrett's Esophagus (BE), gastroesophageal varices and bleeding, among others. Esophageal varices develop as a consequence of portal hypertension and are present in about half of patients with cirrhosis^{1,2}. Portal hypertension is commonly a manifestation of end stage liver disease and cirrhosis which leads to architectural distortion and increased resistance of flow through the liver. About ten million Americans are suffering from cirrhosis³. Variceal bleeding occurs in up to one-third of patients with esophageal varices⁴ and is associated with 10% to 20% mortality over six weeks^{2,4} and with up to 50% mortality with the index hemorrhage⁵. Risk factors for variceal bleeding include the size of the varices, the endoscopic presence of variceal red spots, the severity of liver disease (Child class) and current alcohol use². Patients with medium to large varices that have not bled should be considered for prophylaxis with non-selective beta blockers or with endoscopic variceal ligation². Esophagogastroduodenoscopy (EGD) is the current gold standard for the diagnosis of esophageal

varices and it is recommended that all patients undergo screening EGD to rule in or out the presence of varices at the time of diagnosis of cirrhosis^{2, 4} and then periodically thereafter depending upon the size of the varices and the severity of the liver disease⁴.

Gastroesophageal reflux disease (GERD) is a multifaceted illness defined by chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus⁶. The most common manifestation of GERD is heartburn, which is a daily symptom for almost 20% of adults in the United States, though only about two percent of adults have objective evidence of reflux esophagitis^{7, 8}. The incidence of GERD increases with age, significantly rising after the age of 45. Exact epidemiological data are difficult to obtain, however, since there is no specific "gold standard" for establishing the diagnosis. Several factors may contribute to the development of GERD. In most patients, reflux occurs as a result of poor tone or incompetence of the lower esophageal sphincter and transient relaxations of the sphincter. Such transient lower esophageal sphincter relaxations occur normally, but are more frequent in patients with GERD⁸. Esophageal mucosal damage is related to the potency of the acidic gastric fluid and the amount of time it is in contact with the mucosa. In addition, about one-third of patients with severe GERD also have diminished peristaltic clearance and delayed gastric emptying that may potentiate GERD⁹.

GERD has varied presentations that may be divided into three categories: typical symptoms (heartburn and regurgitation); extraesophageal symptoms (chest pain, cough and reactive airway disease) and complications (ulcerations, strictures, BE, cancer). Stricture formation occurs in about 10% of patients with esophagitis and BE is present in ten percent to 20% of patients with chronic reflux^{10, 11}. It is the result of chronic reflux induced injury to the esophageal squamous epithelium. The most serious complication of BE is esophageal adenocarcinoma, one of the fastest increasing cancers in the United States and the developed world^{3, 11}.

Gastroenterological societies in the United States and Europe recommend screening patients with chronic GERD for BE, patients with BE for esophageal adenocarcinoma and patients with cirrhosis and/or known varices for esophageal varices.

PillCam ESO

Along with the PillCam SBO and PillCam R COLON, the PillCam ESO (PillCam™ ESO, Given diagnostic system: Given Imaging, Yoqneam, Israel) is one of the Food and Drug Administration (FDA) approved wireless capsule endoscopic technologies developed for the non-invasive imaging of the gastrointestinal tract. Prior CTAF systematic reviews and others have favorably evaluated the safety and efficacy of the PillCam SBO for the evaluation of obscure gastrointestinal bleeding presumed to be of small bowel etiology and the PillCam SBO for the evaluation of Crohns disease of the small bowel¹². The PillCam R COLON has not yet undergone systematic review by CTAF.

The PillCam ESO is the only device currently approved exclusively for visualizing the esophagus, however similar devices are in development and a recent study reported results for the FDA pivotal trial comparing the Endocapsule EC (Olympus America, Allentown, PA) with the PillCam ESO¹³. The PillCam ESO is a dual camera wireless endoscope similar in size and function to the PillCam SBO but designed specifically for use in the esophagus for evaluation of patients suffering from esophageal disorders such as esophageal varices, GERD and BE. The second generation of the PillCam ESO (the PillCam ESO 2) was approved by the FDA in May 2007. It measures 11 mm x 26 mm, weighs less than 4 grams and, unlike the PillCam SBO, contains a light source and an imaging device at both ends of the capsule. The PillCam ESO takes up to 18 images per second as it passes down the esophagus over about 20 minutes. After fasting for two hours, the patient swallows the capsule while lying on his or her back and must remain supine while the exam table is raised by 30-degree angles every two minutes over a six-minute period until assuming an upright position. Images are obtained for 20 minutes via a sensor and data recorder attached to the patient's chest and waist. Software allows for real time viewing during passage of the capsule¹⁴. Images are then downloaded to a workstation for review. The capsule is usually passed naturally by the patient within 24 hours.¹⁵⁻

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Advantages and disadvantages of PillCam ESO

In earlier reports on the PillCam SBO, patients preferred the capsule over the alternatives presumably because it was felt to be more convenient and less invasive than traditional endoscopic techniques for visualizing the small bowel¹⁸. Screening with the wireless capsule ameliorates some of the disadvantages of EGD such as the requirement for conscious sedation, decreased work

productivity and the small risk of complications⁴. Enhanced adherence with screening could improve outcomes. However, upper endoscopy (EGD) is considerably less complex than traditional techniques for visualizing the small bowel such as push enteroscopy. A general disadvantage of all wireless capsule endoscopy (WCE) is that currently it is purely a diagnostic test with no capability of biopsy or therapeutic intervention¹⁹.

WCE is currently used for the evaluation of obscure gastrointestinal bleeding presumed to be of small bowel etiology (e.g.: Tatar, 2006²⁰; Hara, 2004²¹; Fireman, 2004²²; Lewis, 2005²³) and has been shown to be useful for the evaluation of known or suspected Crohn's disease as well as for evaluation of small bowel tumors and malabsorption disorders^{24, 25}.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The Given® Diagnostic System with PillCam™ESO (Yoqueam, Israel) received FDA 510(k) clearance on November 24, 2004 as substantially equivalent to legally marketed predicate devices.

Indications for Use:

The Given® Diagnostic System with the PillCam™ESO Capsule is intended for the visualization of esophageal mucosa.

The Given® Agile Patency Capsule (Given Imaging Ltd., Israel) received FDA 510(k) clearance on May 8, 2006.

It is intended to verify adequate patency of the gastrointestinal tract prior to the administration of the PillCam video capsule in patients with known or suspected strictures.

TA criterion1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials and reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “PillCam ESO”, “(esophageal) capsule endoscopy”, “wireless endoscopy” and “esophageal disease”, “esophageal varices”, “gastroesophageal reflux disease (GERD)” or “BE” from 1966 to August 2008. The bibliographies of systematic reviews and key articles were manually searched for additional references. Abstracts of citations were reviewed and all relevant articles reviewed in full.

The published, peer reviewed literature of WCE for the evaluation of esophageal disease mainly consists of uncontrolled case series. The literature regarding the use of PillCam ESO in the evaluation of esophagitis and BE is limited to small, single site studies. However, a recent multicenter prospective trial of esophageal capsule endoscopy compared with EGD in the evaluation of esophageal varices was recently published (de Franchis et al 2008) that allows for conclusions regarding effectiveness of PillCam ESO for this indication. In this trial designed as an equivalence study, patients were evaluated by capsule followed by EGD by separate investigators blinded to each other’s results. No similar study exists comparing the effectiveness of WCE with EGD in the evaluation of other esophageal disease.

Outcomes assessed in these studies included the identification of esophageal pathology such as esophagitis and BE (compared with EGD), the diagnosis and grading of esophageal varices, patient acceptance of the procedure, and adverse events associated with the esophageal capsule endoscopy.

Overall, the scientific evidence permits conclusions concerning the effectiveness of PillCam ESO regarding health outcomes only for evaluation of esophageal varices. The scientific evidence does not permit conclusions concerning the effectiveness of PillCam ESO regarding health outcomes for evaluation of other esophageal pathology.

21 additional references were reviewed, but did not meet criteria for inclusion in this assessment. (References 52-72).

Level of evidence: 3, 4, 5

TA Criterion 2 *is met for surveillance of patients at risk for esophageal varices* and not met for other indications.

TA Criterion 3: The technology must improve net health outcomes.

In the first pilot trial to report on the esophageal capsule endoscopy (ECE), Eliakim et al (2004) compared results obtained with CE with ECE in 17 patients with esophagus related complaints such as GERD²⁶. Compared with the gold standard CE, the ECE identified esophageal pathology in all 12 patients who had positive findings on CE. In addition, the ECE identified pathology in an additional patient not identified by CE (this was considered a false positive finding).

Eliakim et al (2005) report on multi-center study of 106 patients (93 with chronic GERD and 13 with known BE) who underwent standard endoscopy (SE) followed by PillCam ESO²⁷. Patients enrolled in the study had prior histologic confirmation of BE or had chronic GERD symptoms and were referred for endoscopy. Patients with history of dysphagia were excluded. (For other exclusion criteria see Delvaux, 2008²⁸). One hundred nine patients were referred for study; one patient was unable to swallow the capsule and images were not adequately captured in two others. Median recording time was 245 seconds (6-1,678 seconds) and median number of esophageal frames obtained was 980 (24-6,712 frames). The intention to treat (ITT) analysis for any esophageal findings was sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90%, 95%, 97% and 85%. In the intention to treat analysis for detection of Barrett esophagus, the WCE had a sensitivity, specificity, PPV and NPV of 92%, 99%, 97% and 96% and for esophagitis was 85%, 99%, 97%, and 92% respectively. A patient satisfaction questionnaire rated the WCE significantly higher (more comfortable) on all measures including pain during the procedure, discomfort after the procedure and ease of swallowing/insertion. One expert (Lin et al, 2007²⁹) has pointed out, however, that the use of an adjudication committee may have led to unblinding of results and bias in favor of greater agreement between ECE and EGD. In addition, in some patients there was lack of confirmed diagnosis of BE (BE) by biopsy which may have led to an overestimate of ECE diagnostic accuracy.

Lin et al. (2007) report on a prospective, blinded, multi-center study of patients with chronic GERD and surveillance patients with known BE²⁹. Ninety-six subjects were enrolled and underwent ECE followed by sedated EGD that day. Six subjects had uninterpretable results including two whom had the capsule retained in the esophagus proximal to the Z-line. Mean transit time was 177.6 +/- 180.4 seconds. Mean ECE reading time ranged from 7.8 to 14.75 minutes per reading. ECE identified 14 of 21 patients with true BE (sensitivity=67%) and 58 of 69 patients without BE (specificity=84%). Positive and negative predictive value were 22% and 98% respectively. Adverse events were uncommon; two patients had the capsule retained in the esophagus and one subject complained of mild throat pain after EGD. They conclude that ECE in its current form cannot be recommended as a primary screening tool for BE.

Sharma et al (2008) report on the diagnostic accuracy of ECE in patients with GERD and BE¹⁰. A total of 100 patients with symptoms of GERD and those undergoing surveillance for BE were enrolled at two sites in the United States. Study exclusion criteria were consistent with other research on ECE. Six patients were excluded from the analysis: four were unable to swallow the capsule and in two patients' images were not captured adequately. Of the 94 who completed the study, BE was suspected in 53 patients and confirmed by EGD and biopsy in 45 patients; erosive esophagitis in 18 patients and hiatal hernia in 70. The sensitivity, specificity, PPV and NPV of ECE for diagnosing BE in patients with chronic GERD was 67%, 87%, 60% and 90% respectively. The sensitivity, specificity, PPV and NPV of ECE for diagnosing erosive esophagitis in patients with GERD was 50%, 90%, 56% and 88% respectively. Based on these disappointing results, the authors conclude that conventional EGD continues to be the gold standard for evaluation of patients with chronic GERD and undergoing surveillance for BE.

Eisen et al (2006) report on a pilot study at three sites of 32 patients with prior endoscopic confirmation of varices referred for detection of esophageal varices. They found that the PillCam ESO detected 100% of the varices found on EGD (n=23 patients); however they were unable to analyze the extent of agreement in the grading of the varices. To be useful in clinical practice, WCE should be able to accurately size the varices as size is an important determinant of the need for prophylaxis and further surveillance.

Rubenstein et al (2007) report on the cost utility of screening hypothetical 50 year old white men with symptoms of GERD for BE¹¹. They report that in their model, EGD prevented 60% of cancer deaths while ECE prevented 53% of cancer deaths. Both strategies were cost effective but they conclude that EGD is the preferred strategy. Similar studies are needed that also take into account patient preferences.

Delvaux et al (2008) compared the diagnostic yield of WCE with CE in 98 patients with suspected esophageal disease (GERD, esophagitis, BE and varices). The two study centers "artificially enriched" the patient population so as to achieve a two-thirds prevalence of esophageal abnormalities²⁸. Subjects were excluded if they had swallowing problems or any risk for or known obstruction, prior abdominal surgery (except appendectomy or cholecystectomy), pregnant, pacemaker or implant, or those needing an MRI within one week following the study. Patients underwent CE followed by PillCam ESO within 24-48 hours. WCE results were read by three investigators blinded to the results of the CE and capsule findings were exchanged between the two centers conducting the study to ensure complete blinding. Diagnostic yield was defined as a 'significant finding' without taking into account the significance of the finding. Of the 98 patients, 53 were men with a mean age of 53. Indications for the study were mainly symptomatic GERD (n=32) and screening for varices (n=30). The CE found 86 lesions in 62 (65%) of patients compared with 60 significant findings by WCE (diagnostic yield of WCE=62.5%). Overall agreement (positive and negative findings) between CE and WCE was moderate with a per patient kappa = 0.42 and per finding kappa = 0.40; and the PPV of WCE to detect an esophageal abnormality was 80%. The kappa was lower for agreement between CE and WCE for specific findings (k=0.26 to 0.39). The authors speculate that study results were disappointing for WCE in this study in part because prior studies had examined limited, homogeneous subsets of patients at a single site, and the quality of the capsule recordings in this study were of moderate quality, with 25% considered poor quality because the Z line could not be identified. The authors conclude that large comparative studies are needed in non-specialized units to better evaluate esophageal capsule endoscopy.

Lapalus et al (2006) compared CE with PillCam ESO in 21 patients with end-stage liver disease (ESLD) in screening for presence of esophageal varices³⁰. Patients were un-sedated for both

exams. WCE identified varices in 16 out of 19 patients (84%) and identified 100% of grade 2 or higher varices. All patients preferred the WCE to an un-sedated CE.

Galmiche et al (2008) enrolled 89 patients referred for EGD to five centers in France for GERD symptoms³¹. Seventy seven patients completed the study. Patients underwent EGD followed by WCE; results from the WCE were read by a total of ten blinded investigators with experience in reading results from small bowel capsule studies. Overall, WCE had high sensitivity for detection of esophagitis (mucosal breaks) but fairly low sensitivity for detection of endoscopically suspected esophageal metaplasia (ESEM). Kappa values for interobserver agreement for the diagnosis of esophagitis and ESEM were $k=0.67$ (0.49-0.85) and $k=0.49$ (0.17-0.81) respectively.

Sanchez-Yague et al (2006) report on results from WCE in patients who refused to undergo EGD³². They report clinical findings (esophagitis, varices) but they will not be discussed here as no comparison was made with the gold standard EGD so diagnostic accuracy cannot be determined. They also report patient centered findings regarding acceptability of WCE. These are reported in Table 1.

Pena et al (2008) report on a small, single site study comparing ECE with EGD in the screening and surveillance of cirrhotic patients for esophageal varices³³. Twenty patients were enrolled in the study (of 36 patients asked to participate) and underwent ECE followed by standard EGD with conscious sedation. All patients were able to swallow the capsule, but in two patients ECE failed to adequately visualize the esophagus. The overall sensitivity of ECE for detection of varices was 68% with a specificity of 100%. However, ECE identified 82% of varices grade 2 or higher. They found no difference in overall satisfaction scores between ECE and EGD and all subjects stated they would be willing to undergo either study again if instructed by their physician.

A multi-center, international prospective study was recently published that assessed the diagnostic performance of CE with the PillCam ESO for screening and surveillance of esophageal varices in patients with portal hypertension⁴. The primary end-point of the study was the accuracy of ECE in identifying esophageal varices; secondary objectives were to assess the accuracy of ECE in grading

varices and differentiating small from medium/large varices and to assess patient centered outcomes. The study was designed assuming that a difference of $\leq 10\%$ between ECE and EGD would demonstrate equivalence. Inclusion criteria included signs/symptoms of portal hypertension with indications for screening or surveillance endoscopy for esophageal varices. Exclusion criteria were similar to other studies. Patients underwent ECE per the usual protocol followed by EGD performed under "light" sedation within 48 hours. ECE was read by blinded gastroenterologists. Investigators developed a reproducible and 'simple' grading system for esophageal varices for the ECE based on circumference of the capsule picture frame as a reference point (so that large varices occupied more than 25% of the circumference). A total of 290 patients were enrolled at 11 centers. Overall, EGD identified varices in 180 patients (62.5%) and ECE identified them in 152 patients (difference 15.6%). ECE identified varices in 13 patients not confirmed by EGD. Since EGD is considered the gold standard, sensitivity and specificity of ECE for detection of varices was 84% and 88% with a positive LR of 7.0. There was concordance between ECE and EGD in 247 of 288 cases (86%. kappa=0.73). Performance of ECE was better in the centers that enrolled larger numbers of patients. In 277 of 288 patients, ECE and EGD were in complete agreement regarding grading of varices (79%). In 17 cases graded as large varices by EGD, the varices were not seen in four (1.4%) and were graded as small in 13 (4.5%). Four adverse events were reported, two involving capsule retention secondary to unsuspected esophageal strictures. In the patient satisfaction assessment, perception and satisfaction was significantly better with ECE than with EGD. The authors conclude that EGD should remain the gold standard for identifying and grading esophageal varices since the ECE failed to reach statistical equivalence with EGD. They recommend, however, that ECE should be considered for patients unwilling or unable to undergo EGD.

Table 1 summarizes the peer reviewed, published trials of PillCam ESO in the evaluation of patients with symptoms of or known esophageal disease and surveillance of patients at risk for esophageal varices.

Table 1.

Published Trials of PillCam ESO in Esophageal Disease

Study	Participants and Methods	Device Used	Outcomes	Complications	Comments
Eliakim et al, 2004 ²⁶	N=17, pilot study, esoph complaints	PillCam ESO and CE	Accuracy=92%	None reported	First generation PillCam ESO
Eliakim et al, 2005 ²⁷	Multicenter pivotal trial n= 106 chronic GERD	PillCam ESO and CE	Overall ITT Sens, Spec, PPV and NPV = 90% and 95%, 97% and 85%	None reported	1. Blinded adjudication cttee reviewed discrepant findings—may have biased final results. 2.Dx of BE by ECE not always confirmed by biopsy.
Eisen et al 2006 ⁵	N=32; 3 site pilot study Detection of varices	PillCam ESO and CE	Sens=100% Specif=77% LR=4.3	none	Unable to assess accuracy of WCE in sizing varices
Lapalus et al 2006 ³⁰	N=21, pts w ESLD, 1 center	Unsedated CE and PillCam ESO	Accuracy of WCE for esoph varices=84%	1 pt unable to swallow capsule	ESLD patients prefer WCE over unsedated EGD
Sanchez-Yague et al (2006) ³²	N=30, pts with GERD and screening for varices who refused EGD	PillCam ESO	Clinical findings not reported here as there was no comparison with EGD; 2 pts reported difficulty swallowing capsule; 1 pt reported pain with capsule transit	n/a	All pts who had undergone prior EGD (n=10) rated WCE as more comfortable
Lin et al (2007) ²⁹	Multicenter N=96	PillCam ESO and CE	Sens=67%; Specif= 84%; PPV=22%; NPV=98% for BE	Capsule retained in 2 pts (removed by EGD)	WCE had only modest sensitivity for detection of BE
Sharma et al (2008) ¹⁰	100 pts referred for EGD for chronic GERD and BE surveillance	PillCam ESO and CE	Sens, spec, PPV and NPV of ECE for diagnosing BE in patients with chronic GERD was 67%, 87%, 60% and 90% respectively and for diagnosing erosive esophagitis was 50%, 90%, 56% and 88%	4% could not swallow capsule	
Delvaux et al (2008) ²⁸	N=98, 2 centers, esoph complaints	PillCam ESO and CE	PPV=80% NPV=61% K=0.42 per pt K=0.40 per finding	none	WCE showed only modest sensitivity in spite of artificial prevalence enrichment
De Franchis et al (2008) ⁴	Multi-center ,multinational study of 288 patients screened or surveillance for esophageal varices	PillCam ESO and EGD	Overall agreement between ECE and EGD was 85.8%	4 adverse events (1.4%) - 1 with EGD and 3 with ECE	Primary end-point of study of 10% equivalence between ECE and EGD was not met
Galmiche et al (2008) ³¹	89 pts referred for chronic reflux	PillCam ESO and CE (unsedated)	Sens, specif, PPV and NPV for esophagitis and ESEM = 79%/60%; 94%/100%; 83%/100%; 92%/95%	4 pts unable to swallow capsule	WCE technique failed in 6 pts
Pena et al (2008) ³³	N=20; detection of varices	PillCam So and GD	Overall sensitivity=68%	none	Sensitivity of ECE better (82%) for detection of larger varices

Patient Safety

Overall, over 200,000 capsules have been deployed worldwide, mainly small bowel capsules, with no deaths reported¹⁹. The use of the capsule endoscopy in patients with pacemakers or other implanted devices is contraindicated, though patients with pacemakers were not systematically excluded from some of the studies of WCE³⁴. Other contraindications to WCE include patients with swallowing disorders, those with known or suspected gastrointestinal obstruction, fistula or stricture, and pregnancy. Patients with dementia may not be capable of cooperating with WCE.

The major potential adverse event associated with WCE is capsule retention. This is an infrequent event occurring in approximately 0.7% - 13% of patients who underwent WCE of the small bowel. One study found that capsule retention occurred in 13% of patients with known Crohn's Disease³⁵. Other risk factors for capsule retention or entrapment include use of non-steroidal anti-inflammatory drugs, prior abdominal radiation, Crohn's enteritis and prior major abdominal surgery³⁶. Capsule entrapment almost always occurs at the site of bowel pathology so that surgical intervention to remove the capsule may then also address the underlying problem³⁷. Dissolvable "patency capsules" are being used that are swallowed first by the patient and can then identify the site of entrapment via a radiofrequency signal before the capsule dissolves^{38, 39}. One recent review of contraindications to WCE concluded that the procedure can be performed safely in almost all clinical settings and that the only "true" remaining contraindications are obstruction/pseudo-obstruction and pregnancy⁴⁰.

Many of the published series of PillCam ESO report on small numbers (≤ 100) of patients. With such small numbers, data regarding safety may be unreliable, especially for infrequent complications.

TA criterion 3 is not met for either.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The main established alternative to PillCam ESO for the diagnosis of esophageal disease is upper endoscopy, also referred to as EGD or CE. EGD is the current gold standard for the diagnosis of

esophageal varices and is recommended for all patients to rule in or out the presence of varices at the time of diagnosis of cirrhosis². It is also the current 'gold standard' for the evaluation of patients with chronic GERD, dyspepsia, dysphagia, and surveillance of BE, among other problems.

EGD is performed by passing a flexible endoscope through the patient's mouth into the esophagus, stomach, and duodenum. It is the best method for examining the entire upper gastrointestinal mucosa and for obtaining biopsies of abnormal appearing tissue for histologic diagnosis, for example, to confirm BE. In BE, the esophagus is lined with columnar epithelium instead of the normal squamous epithelium. Histologically it appears as intestinal metaplasia and is suspected at the time of EGD when the endoscopist has difficulty visualizing the squamo-columnar junction (the "Z line") at its normal location, and by the presence of inflamed appearing mucosa. BE is confirmed by biopsy⁴¹.

EGD also safely allows for endoscopic therapy when indicated, such as dilation of an esophageal stricture. In the United States, most patients referred for EGD receive conscious sedation, though it may be safely performed with topical anesthesia. Risks associated with upper endoscopy are generally quite low and generally consist of bleeding and perforation⁴². The overall risk of an adverse event with endoscopy (EGD or colonoscopy) is often put at <1:1000 procedures, but many experts feel that even this low event rate overestimates the risk in most patients, particularly when the procedure is elective. Complications related to diagnostic evaluations are rare. A survey conducted more than 30 years ago estimated that the overall complication rate based on over 200,000 EGD examinations was 0.13%⁴³. A more recent retrospective, single site study from Great Britain that examined the safety of current EGD found an overall causal death rate of 1 in 9000 patients⁴⁴.

Some experts have suggested that screening for esophageal varices in all patients with known cirrhosis should not be standard of care in light of the cost and the significant inconvenience for patients^{1, 42}. The alternative would be empiric treatment with beta-blockers for all patients known to have varices as they have been shown to significantly decrease the incidence of bleeding. A recent analysis concluded, however, that in general, screening is a reasonable strategy and that EGD is a more efficient means of screening for esophageal varices than is capsule endoscopy^{1, 11}.

Dyspepsia is a common symptom that refers to burning discomfort in the upper abdomen that is frequently chronic or recurrent. While some causes of dyspepsia are referable to the esophagus (such as GERD or esophagitis), dyspepsia may also be caused by peptic ulcer disease and less commonly by gastric malignancies. Even with a careful history, it is not possible to localize the site of pathology underlying dyspepsia in up to half of patients⁴². EGD offers a clear advantage over ECE in the work-up of patients with dyspepsia as it allows for accurate visualization and biopsy of the entire upper gastrointestinal tract to the duodenum.

Unsedated transnasal gastroscopy (Dumortier et al 2003) has been touted as a more acceptable alternative to CE but it is not in widespread use in the United States and has not been compared with WCE in peer reviewed studies⁴⁵. String capsule endoscopy (SCE), in which the capsule is retrieved and disinfected thus allowing for multiple passages across the esophagus, is another emerging technology that in one study was found to have similar sensitivity and specificity to EGD for the visual diagnosis of BE⁴⁶. As with transnasal gastroscopy, more research is needed to identify the role of this technology in esophageal disease.

TA criterion 4 is not met for either.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

The peer reviewed, published data are not sufficient to conclude that the efficacy and safety of PillCam ESO has been established in the investigational setting, let alone under conditions of usual medical practice. Whether PillCam ESO will be useful in diagnosing esophageal disorders in individuals in community settings under conditions of usual medical practice remains to be demonstrated.

TA criterion 5 is not met for either.

CONCLUSION

de Franchis et al (2008) conclude that three issues need to be considered in determining whether ECE is a valid alternative to EGD: performance (or diagnostic accuracy), cost and patient preference⁴. Based on the peer reviewed, published literature to date of PillCam ESO compared with EGD for the evaluation of patients with symptoms of or known esophageal disease and surveillance of patients at risk for esophageal varices, it is the opinion of this assessment that the performance of ECE is not equivalent to EGD for the evaluation of patients with esophageal symptoms or known disease, and that EGD should remain the current gold standard. While some studies (notably Eliakim et al, 2005²⁷) found that ECE has comparable diagnostic accuracy to EGD, most of the larger, multi-site trials conclude that ECE is not equivalent to EGD and that further refinement of the technology is needed. As research continues to evolve with new innovations such as better image capture^{47, 48}, simpler ingestion protocols^{49, 50} and magnetic controllers that allow the examiner to control the position and angle of the camera from outside of the body⁵¹, among others, the diagnostic yield of the wireless esophageal capsule is likely to improve. Since much of the published, peer reviewed literature comparing the diagnostic accuracy of the ECE with CE was done with earlier generations of the PillCam ESO that captured fewer images per second and therefore had inferior sensitivity than the current version, it is likely that this technology will demonstrate significantly improved diagnostic accuracy in the next few years. In most of the studies comparing ECE with EGD to date, patient populations were enriched with patients with esophageal pathology so as to enhance the likelihood of abnormal findings. These patients were carefully screened so as to exclude gastric or duodenal pathology since the ECE is not designed to evaluate pathology below the esophagus. However, symptomatic patients referred for evaluation from real world clinical practices are likely to have disease below the lower esophageal sphincter which is likely to be detected by conventional EGD but missed by esophageal capsule. For ECE to meet TA 5 criteria, it will have to demonstrate that it is useful outside of the investigational setting.

This assessment does not consider cost as a factor in evaluating the safety and efficacy of new technology. However, cost is always a consideration in use of new technology and some investigators have begun to examine the cost utility of ECE versus EGD (e.g. see Rubenstein et al, 2007¹¹).

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Finally, most of the research to date has found that ECE is a relatively safe technology and is significantly preferred by patients over EGD. EGD usually requires sedation and is rated as less pleasant and more inconvenient than ECE. Some patients simply refuse to undergo EGD. However, since EGD is generally a safe and widely available procedure, ECE cannot be recommended as an alternative until its performance is substantially equivalent to EGD.

DRAFT RECOMMENDATION

It is recommended that PillCam ESO *does not* meet CTAF TA criteria 3-5 for efficacy and improvement in health outcomes for the evaluation of esophageal disease.

October 15, 2008

RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of the PillCam ESO for the evaluation of esophageal disease.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Palmetto Government Benefit Administrators, the Medicare carrier for California considers the use of ECE reasonable for esophageal varices in certain patients (L27570). CMS does not cover the use of ECE for the evaluation of GERD (L28316).

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)

The AASLD recommends screening EGD for the diagnosis of esophageal and gastric varices when the diagnosis of cirrhosis is made (Garcia-Tsao et al, 2007).

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)

The AGA will provide an opinion and a representative to the meeting.

AMERICAN SOCIETY OF GASTROINTESTINAL ENDOSCOPY (ASGE)

The ASGE Technology Status Evaluation Report: wireless capsule endoscopy was published in 2006 in the journal *Gastrointestinal Endoscopy*. In the SUMMARY it is noted that "The esophageal capsule uses similar technology (to the wireless capsule endoscopy for small bowel) but clinical data on its use are limited."

AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG)

The ACG is being consulted for an opinion.

ABBREVIATIONS USED

CTAF	California Technology Assessment Forum
GERD	Gastroesophageal reflux disease
EGD	Esophagogastroduodenoscopy
CE	Conventional endoscopy
ECE	Esophageal capsule endoscopy
FDA	Food and Drug Administration
WCE	Wireless capsule endoscopy
DARE	Database of Abstracts of Reviews of Effects
SE	Standard endoscopy
PPV	Positive predictive value
NPV	Negative predictive value
BE	BE
ESLD	End-stage liver disease
ESEM	Endoscopically suspected esophageal metaplasia
SCE	String capsule endoscopy
ITT	Intention to treat

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