Clinical Policy Title: Capsule Endoscopy for Visualizing the Gastrointestinal Tract

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Lines of Business: Arbor Health Plan clinical policies are subject to all applicable laws and government regulatory requirements of the geographical areas served. Refer to the pertinent government and plan documents for each geographical area for guidance. Individual member benefits must be verified.

Policy Definition: Arbor Health Plan covers health care service/items when they are a Plan benefit, medically necessary and not prohibited from coverage by state or federal laws and/or regulatory requirements. This Arbor Health Plan clinical policy addresses the medical evidence supporting the use of capsule endoscopy.

Arbor Health Plan considers the use of capsule endoscopy to be clinically proven as the effectiveness of its use has been established in peer reviewed professional literature for use in specific clinical circumstances. These clinical policies, along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any State or plan specific definition of medically necessary, are considered by Arbor Health Plan when making coverage determinations.

Coverage Policy:
Arbor Health Plan considers the use of capsule endoscopy to be clinically proven; and therefore, a finding of medical necessity is supported when the following criteria are met:

A.) The procedure is carried out by a gastroenterologist with training in capsule endoscopy, AND
B.) The procedure is being perform for at least one of the following indications:

Policy contains:
- Capsule endoscopy for the small bowel.
- Capsule endoscopy for the esophagus.
- Capsule endoscopy for the colon.
• Patients with objective evidence of gastrointestinal blood loss and/or iron-deficiency anemia when other diagnostic methods performed during the same period of illness have failed to identify the source of bleeding and the small bowel is suspected as the source of bleeding.

OR

• For re-evaluation of patients with a confirmed diagnosis of Crohn's disease who remain symptomatic after appropriate treatment or who have an onset of new symptoms suggestive of Crohn's disease at an undiagnosed small bowel region, when:
  o Imaging studies and/or upper or lower endoscopic examination fail to reveal the location or extent of the pathology, and
  o Treatment decisions would be affected by the results of the test.

OR

• For initial diagnosis of patients in whom there is strong clinical suspicion of Crohn's disease (with abdominal pain, weight loss, diarrhea, anorexia, bleeding and biochemical indicators of inflammation) when prior colonoscopy is negative and when treatment decisions would be affected by the results of the test.

OR

• For diagnosis of patients with clinical symptoms suggestive of a malabsorption syndrome (e.g. celiac disease) when prior serology or gastrointestinal endoscopy are nondiagnostic.

OR

• Patients with suspected small bowel tumor when imaging studies or gastrointestinal endoscopic findings have failed to confirm presence of a tumor.

OR

• For surveillance of small bowel tumors in patients with Lynch syndrome or inherited polyposis syndromes such as familial adenomatous polyposis or Peutz-Jeghers syndrome every 3 years beginning at age 8 years.

OR (FOR MEDICARE MEMBERS ONLY)

• For evaluation of possible small bowel involvement for patients with Crohn's disease with a known diagnosis of colitis of an indeterminate type affecting the colon.

A finding of medical necessity is not supported for all other uses of capsule endoscopy.

Limitations:
Arbor Health Plan considers the use of capsule endoscopy to be investigational; and therefore, a finding of medical necessity is not supported for ANY of the following criteria:
• Patients with known or suspected intestinal obstruction, fistulas, strictures, or swallowing abnormalities since these abnormalities may hinder passage of the capsule.
• Patients who are pregnant.
• Patients with implanted cardiac pacemakers without prior clearance by a cardiologist.
• For patients with implantable cardiac defibrillators unless they are observed in a hospital setting with continuous cardiac monitoring.
• History of abdominal irradiation.
• Gastric emptying or motility disorders.
• The use of any patency system for verification of gastrointestinal patency prior to capsule endoscopy.
• The use of magnetic resonance imaging after having completed capsule endoscopy until the patient has passed the capsule.

Alternative Covered Services: Arbor Health Plan provides coverage for upper and lower endoscopies by network providers for appropriate indications.

Background:
Capsule endoscopy (also known as wireless video endoscopy or video capsule endoscopy) (CE) is an ingestible video camera originally developed to visualize the small bowel, which has been difficult to examine by colonoscopy and esophagogastroduodenoscopy (EGD) from accessible orifices. More recently, double-ended capsules have been developed for the noninvasive examination of the esophagus and colon. During CE, the patient swallows a small digestible pill the size of a multi-vitamin that contains a video camera. The camera takes multiple pictures per second and sends wireless electronic signals to a data recorder. The data are downloaded into a computer program that captures the picture images for analysis. The capsule is excreted naturally by the body within eight to seventy two hours after ingestion. CE usually is performed in a physician’s office or outpatient clinic, does not require sedation and is usually well tolerated. The major complication of CE is capsule retention.

According to the American Society for Gastrointestinal Endoscopy (ASGE) (2006), contraindications to CE include:

• Known or suspected gastrointestinal (GI) obstruction, strictures, or fistulas based on the clinical picture or pre-procedure testing.
• Swallowing disorders.
• Pregnancy.

ASGE (2006) recommends using CE cautiously in patients with cardiac pacemakers. During CE there is a theoretical potential for interference from the digital radiofrequency communication between the capsule
and the data recorder, but published reports on small series of patients have shown no significant interference with pacemaker or implantable cardiac defibrillator function, or with the CE images. CE was found to be safe in patients who were monitored and studied in a hospital setting. Because large studies are not available, it may be advisable that patients with implanted cardiac devices are evaluated by a cardiologist before CE and patients with ICDs be observed in a hospital setting with continuous cardiac monitoring. (Qureshi 2006) ASGE also recommends that patients not undergo MRI after having completed CE until they have passed the capsule; the capsule can be easily identified on plain radiographs, and this should be performed if there is any question. (Tech report 2006)

Available capsules

CE systems are available for examination of the esophagus, small bowel and colon. As of this writing, the United States Food and Drug Administration (FDA) has approved three CE systems as Class II 510(k) non-exempt devices for small bowel imaging in adults. They are the PillCam® SB and SB2 (Given Imaging, Ltd, Yoqneam, Israel), the ENDOCAPSULE (Olympus Corporation, Allentown, PA) and, recently, the MiroCam® Capsule Endoscope System (IntroMedic Co., Ltd., Seoul, South Korea). Newer generation capsules have added features for detecting red color, which may facilitate identification of bleeding sites. Modifications of the PillCam® have been approved for use in children age 2 years or older. The PillCam® ESO has been FDA-approved for visualization of the esophageal mucosa in adults and children age 18 years or older. Similar to other PillCam® versions, the PillCam® COLON is designed for visualization of the colon mucosa. It has not yet received FDA-approval.

The AGILE® patency system (Given Imaging, Ltd, Yoqneam, Israel) was developed for use as an accessory to the PillCam® video capsule. The AGILE® system is FDA-approved for verifying adequate patency of the gastrointestinal tract prior to administration of the PillCam® video capsule in patients with known or suspected strictures in adults and children from 2 years of age. When its passage is blocked by a stenosis or tumor, the patency capsule dissolves within 40–80 hours after ingestion. Patency of the GI tract is demonstrated if the capsule is excreted whole.

Although the capsule is easily ingested and swallowed by most individuals, persons with oropharyngeal or mechanical dysphagia, gastroparesis, pill phobia, known or suspected anatomical abnormalities and small children may have problems ingesting the device. For these situations, insertion devices such as the disposable AdvanCE™ capsule endoscope delivery device (US Endoscopy, Mentor, OH) allows for direct placement of video capsules into the stomach or small intestine through the working channel of a standard endoscope. AdvanCE™ has been designed to be used in conjunction with the PillCam® SB video capsule.
Training and competency

ASGE (2005) recommends independent credentialing and appropriate documentation of competence in CE. Documentation may include formal training in CE during GI fellowship or completion of a hands-on course with a minimum of 8 hours of continuing medical education (CME) credit, endorsed by a national or international GI or surgical society and review of first 10 capsule studies by a credentialed capsule endoscopist. The practitioner should be competent and have privileges to perform EGD, colonoscopy, and (for small intestine CE) enteroscopy. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition training guidelines require training and competency in CE before clinical use. (Leichtner 2013)

Small bowel indications

A meta-analysis of 227 English-language original studies found that obscure gastrointestinal bleeding (OGIB) was the most common indication for small bowel CE (66.0%), and angiodysplasia was the most common finding (50.0%). (Liao 2010) Other common indications were definite or suspected Crohn’s Disease (CD) (10.4%), clinical symptoms only (10.6%), others (7%), neoplastic lesions (3.5%) and celiac disease (1.7%). In the 142 studies (11,979 procedures) that reported completion rates, the overall pooled completion rate was 83.5% (95% confidence interval (CI): 82% to 85%). The pooled completion rates for the indication of OGIB and CD were 83.6% (95% CI: 80.9% to 86%) and 85.4% (95% CI: 79% to 90.8%), respectively. The main reasons for incomplete examination were battery exhaustion, capsule retention, technical failure and poor small-bowel preparation. A relatively high capsule retention rate is associated with definite or suspected CD (2.6%) and neoplasms (2.1%) compared with OGIB (1.2%). (Liao 2010)

Indications for the small bowel for which evidence from systematic reviews are available are included in the results Table 1.

Obscure gastrointestinal bleeding (OGIB)

OGIB is defined as occult or overt bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including colonoscopy and EGD. (ASGE 2010) Conventional upper and lower endoscopies fail to identify a source of bleeding in approximately 5% of patients. (Hayes 2013) These patients are then referred for investigation of the small bowel. Intraoperative enteroscopy is the reference standard for evaluating the small bowel, but other less invasive diagnostic methods are preferred, including radiographic studies, angiography, deep enteroscopy, and other imaging studies. As a noninvasive imaging modality, CE may have a role in the diagnostic work up of these patients. (Hayes 2013)

Evidence from systematic reviews and meta-analyses indicate that the overall quality of evidence is moderate for prospective studies to poor for all others. (Hayes 2013, Xie 2012) The evidence is limited by small sample sizes (for prospective studies), the lack of well-defined reference standards, blinding, and standardized follow-up. The results suggest that CE is safe, has adequate diagnostic yield and is sensitive for
detecting bleeding source in patients who are referred for small bowel investigation following a negative or nondiagnostic.

EGD and colonoscopy. For patients with suspected small bowel tumors, a small number of studies suggest CE may be used when imaging studies or gastrointestinal endoscopic findings have failed to confirm a tumor. Since small bowel tumors would be a significant finding at CE and are often missed by other methods of investigation, detection of a tumor would potentially alter management and improve outcomes, and, even for malignant lesions, treatment is potentially curative in the absence of metastatic disease.

CE was not found to be cost-effective as an initial diagnostic strategy compared with double balloon enteroscopy. (Gerson 2008) CE may have an immediate impact on patient management, and the impact on health outcomes appears comparable to double-balloon enteroscopy, small bowel follow-through and angiography. Because capsule retention was the most important complication, CE in patients with bowel obstructions or swallowing disorders was not recommended.

Crohn’s Disease

Crohn’s disease (CD) is a progressive, inflammatory bowel disease. While CD occurs in people of all ages, it generally starts in people between the ages of 13 and 30 years. (NIDDIC 2011) CD most commonly affects the ileum, and colonoscopy with ileoscopy combined with biopsy is the first-line investigation for the diagnosis of suspected CD. Approximately 30% of cases require an investigation of the proximal small bowel. A number of diagnostic procedures exist, but there is currently no consensus on how they should be used. (Hayes 2011) Radiographic contrast studies, enteroclysis and nuclear scans such as scintigraphy have low sensitivity and are now being replaced by advanced enteroscopic techniques, most importantly, double-balloon enteroscopy, or cross-sectional imaging methods such as magnetic resonance enterography (MRE). (Hayes 2011a)

Evidence from 3 systematic reviews suggests CE is safe and easy to use, has high diagnostic yield and is sensitive for the detection of CD, and may have equivalent or superior accuracy to other small bowel investigations. (Xie 2012, Gilbert 2011, Hayes 2011a) However, the evidence of comparative effectiveness is limited by a high risk of selection and outcome bias. Its clinical application is limited by the need for prior bowel investigation to exclude patients with bowel obstructions and by its uncertainty as a predictor of disease absence in patients with negative or equivocal prior endoscopic and radiological tests. In addition, CE is not able to evaluate disease severity or take biopsies at the time of investigation, as other modalities such as MRE and double-balloon endoscopy can. The addition of CE after ileocolonoscopy and negative CT enterography or small-bowel follow-through was not cost-effective, including in patients with a high pretest probability of disease. (Levesque 2010)

The impact of CE findings on patient management is unknown, and the resultant impact on health outcomes is uncertain. However, a consensus of experts agreed that CE may lead to benefits that are not
evident from the limited available data, particularly in a small number of patients for whom it is very difficult to reach a diagnosis of CD and CE may be the only option. (Gilbert 2011) Many new diagnoses of CD currently made via CE occur in patients who are being evaluated for OGIB. Therefore, CE may have a role in excluding CD in adult patients with suspected CD and inconclusive results on upper and lower endoscopy, and in adult patients with known CD in whom recurrence is suspected. (Gilbert 2011) CE in patients with known or suspected bowel obstructions or swallowing disorders was not recommended.

**Peutz-Jeghers syndrome/Inherited polyposis syndromes**

Peutz-Jeghers syndrome (PJS) is a rare genetic disorder characterized by the development of noncancerous hamartomatous polyps in the gastrointestinal tract (particularly the stomach and intestines) and cancer predisposition. Birth prevalence has not been reliably established, but estimates range widely from 1:25,000 to 1:280,000. PJS can occur in any racial or ethnic group. Most cases of PJS are caused by mutations in the \textit{STK11} gene that alters the structure or function of the \textit{STK11} protein, disrupting its ability to restrain cell division. This can lead to the formation of multiple polyps in the stomach and intestines during childhood or adolescence, which can cause recurrent bowel obstructions, chronic bleeding, and abdominal pain. (McGarrity 2013)

Diagnosis of Peutz-Jeghers syndrome (PJS) is based on a constellation of family history, mucocutaneous macules, PJS-type intestinal polyps, and presence of a \textit{STK11} mutation. Upper endoscopy plus small bowel examination using MR enterography or CE is recommended beginning at age 8 years or when symptoms occur. Distal small-bowel polyps that are beyond the reach of conventional endoscopy have been managed with barium contrast upper-gastrointestinal series with a small bowel follow-through. Recent advances allow for better diagnosis and eradication of small-bowel polyps, oftentimes without laparotomy and with a decrease in the radiation burden related to frequent surveillance. New diagnostic procedures include CE, CT enterography and MR enterography. Balloon-assisted enteroscopy allows for removal of deep small-bowel polyps. Occasionally intraoperative enteroscopy and enterotomy is needed for removal of large distal small-bowel polyps. (McGarrity 2013)

Various protocols have been suggested for monitoring stomach, small and large bowel, breasts, testicles, ovaries, uterus, and pancreas by various procedures as early as birth and as frequently as once a year. Current surveillance protocols are controversial and not evidence-based, due to the relative rarity of the condition. A systematic review reported patients with PJS are markedly at risk for several malignancies, in particular gastrointestinal cancers and breast cancer, with relative risks ranging from 9.9 to 18 in comparison with the general population over the course of their lifetime. (van Lier 2010) On the basis of these elevated risks, routine endoscopic surveillance with polypectomy is recommended every 3 years beginning at age 8 years to detect malignancies in an early phase and to remove polyps that may be premalignant and may cause complications, so as to improve outcome. (McGarrity 2013)

One systematic review found preliminary evidence comparing CE to alternatives for detecting PJS. (MSAC 2007) The evidence suggests CE is a safe, well-tolerated procedure compared with small bowel examination
by barium follow-through radiography. CE is better at detecting the number of polyps and extent of polyposis and may change patient management in situations where radiographic examinations produce false negative results. CE for small bowel surveillance of PJS is likely to be as effective and as cost-effective as small intestine x-ray. However, the evidence was limited by relatively small number of available studies, small numbers of enrolled subjects and inconsistent use of various reference standards. There is a learning curve for reporting CE studies in PJS and appropriate training is essential.

Four small feasibility studies published since 2007 confirm the findings of the systematic review. Gastineau et al (2012) found that while CE is easily feasible in 27 children with PJS, the practice of systematic and repeated procedures in managing risk of further obstructive complications needs to be validated prospectively. Postgate et al (2009) found CE is a feasible, safe, and sensitive test for small bowel polyp (<10 mm) surveillance compared with barium enterography, and was significantly more comfortable than BE and preferred by patients. Ohmiya et al (2010) discovered polyp detection rates that were comparable or superior to fluoroscopic enteroclysis and double-balloon enteroscopy in 18 patients. As a surveillance tool in 19 adults with PJS, Gupta et al (2010) determined no significant difference between CE and MR enterography for the detection of polyps > 10 mm or in the number of patients in whom > 10 mm polyps were detected, but MR enterography may be less prone to missing large polyps, more reliable in their size assessment and preferred equally to CE by patients. CE in patients with known or suspected bowel obstructions or swallowing disorders was not recommended.

**Celiac disease**

Celiac disease is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals. (Ludvigsson 2012) Celiac disease is one of the most common causes of chronic malabsorption. Estimates of the prevalence of celiac disease in the general population vary widely because of serological test strategies, biopsy definitions and patient sampling, but most large scale population-based studies in Western Europe and the United States report prevalence rates between 0.5% and 1.0%. (For more information on celiac disease testing, please refer to Clinical Policy #02.07.01)

Non-invasive visualization of small bowel mucosa may help assist diagnosis of celiac disease in selected patients. CE allows for inspection of the entire small bowel and is able to detect villous abnormalities often found in celiac disease. Two meta-analyses found that compared to pathology, the overall pooled CE sensitivity ranged from 71% to 94% and pooled specificity ranged from 88-99.6%. (Rokkas 2012, El-Matary 2009) These results argue against the routine use of CE as an alternative to small bowel biopsy, but it may be a reasonable alternative in some patients, especially those unwilling to undergo gastroscopy because of its perceived inconvenience and discomfort.

**Small bowel diseases in children**
One systematic review evaluated 14 studies and 1 meta-analysis of CE in children with various small bowel diagnoses, the most common being CD, OGIB and malabsorption/celiac disease. (Hayes 2011b) Children were generally referred for CE after negative or inconclusive results on upper and lower GI endoscopy. The results suggest CE using PillCam® is feasible in pediatric patients with acceptable technical success rates, has overall acceptable diagnostic yield and diagnostic accuracy, and a positive impact on patient management in children age 5 years and older. The results indicate that CE may have an adjunctive role in the detection of small bowel diseases in children age 5 years and older. However, the risk of endoscopic capsule insertion devices, which were needed in all children younger than 4 years old and in some older children, has not been investigated sufficiently. Success will likely depend more on the maturity level and confidence of the child than chronologic age because many older children and teenagers fail or refuse to attempt to swallow the capsule.

**Esophageal indications**

Esophageal pathologies include gastroesophageal reflux disease (GERD), esophageal varices, esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. GERD is more serious form of gastroesophageal reflux, which occurs when the lower esophageal sphincter opens spontaneously, for varying periods of time, or does not close properly and stomach contents rise up into the esophagus; GERD occurs in approximately 20% of the population. Esophageal varices are enlarged veins located at the lower end of the esophagus that may rupture and bleed massively. Cirrhosis is the most common cause of esophageal varices. Esophagitis is inflammation and ulcers in the lining of the esophagus with GERD being the most common cause. (NIDDIC 2013)

Barrett’s esophagus is characterized by intestinal metaplasia, a condition in which the tissue lining the esophagus is replaced by tissue similar to the intestinal lining. The true prevalence of Barrett’s esophagus is unknown, but it is estimated to affect 1.6 to 6.8% of the population. The average age at diagnosis is 55, and Barrett’s esophagus is uncommon in children. (NIDDIC 2013) The exact cause of Barrett’s esophagus is unknown, but GERD is a risk factor for the condition. Between 5 and 10% of people with GERD develop Barrett’s esophagus. Other risk factors include obesity, specifically high levels of belly fat, and smoking. Some studies suggest that genetics, or inherited genes, may play a role. Factors that may reduce the risk of developing Barrett’s esophagus include *Helicobacter pylori* infection, frequent use of aspirin or other non-steroidal anti-inflammatory drugs and high intake of fruits, vegetables, and vitamins. (NIDDIC 2013)

The risk of esophageal adenocarcinoma in people with Barrett’s esophagus is about 0.5 percent per year. Typically, dysplasia, classified as low grade or high grade, appears before esophageal adenocarcinoma develops. Endoscopic surveillance is performed periodically to monitor persons with Barrett’s esophagus for signs of cancer development. There is no consensus regarding how often surveillance endoscopies should be performed, but in most cases, more frequent endoscopies are recommended for people with high-grade dysplasia compared with low-grade or no dysplasia. (NIDDIC 2013)
Two systematic reviews evaluated the use of esophageal CE (PillCam® ESO) primarily for the detection of Barrett’s esophagus. (Bhardwaj 2009, Hayes 2008) CE is safe to use and patients often preferred CE over conventional EGD. Compared with either conventional endoscopy or histology as a reference standard, the diagnostic accuracy of CE was lower (no tests of statistical significance available). One limitation of CE for assessment of Barrett’s esophagus is the need for conventional endoscopy for biopsy confirmation. Absolute contraindications to CE include presence of known or suspected intestinal obstruction, fistulas, or strictures, esophageal stricture, or swallowing abnormalities. Initial conventional endoscopy appears more effective and less costly compared with CE under base-case conditions for patients with chronic GERD undergoing screening for BE. (Gerson 2007) The evidence for evaluation of esophageal varices is limited to two small studies of high prevalence populations suggesting comparable validity to EGD with patients preferring CE over EGD. (Hayes 2008)

These results indicate the modality of choice for detection of Barrett’s esophagus is conventional endoscopy. Additional research is needed to determine the role of esophageal CE in patients with esophageal indications who are unlikely to require biopsy confirmation for diagnosis, to address the limitations of esophageal CE and to evaluate modifications of the ingestion protocol to improve visualization of esophageal pathology.

Colon indications

According to the American Cancer Society, colorectal cancer is the third leading cause of death due to cancer and the third most commonly diagnosed cancer in the US; in 2011 an estimated 141,210 people will be diagnosed with colorectal cancer and about 49,380 people will die of the disease. Colonoscopy is the standard procedure for colon evaluation and screening, but its invasiveness, perceived inconvenience and suboptimal performance, and limited endoscopy resources may restrict its use in large, population-based screening programs. (ACS 2011)

Other minimally invasive methods for visualizing the colon are available that may complement colonoscopy and serve as additional screening tools for the early detection of colorectal cancer and adenomatous polyps. They are CT colonography, MR colonography, double-contrast barium enema and CE (PillCam® Colon). As with colonoscopy, patients undergo colon preparation and bowel cleansing before the capsule examination.

Limited evidence from two systematic reviews found CE to be safe and acceptable to patients but less sensitive than colonoscopy for detecting polyps in average risk or high risk populations; its accuracy in the detection of cancer had not been studied adequately. (OHTAC 2009, Spada 2010) There was insufficient evidence to determine its effectiveness in colorectal cancer screening in average risk populations. Other considerations for CE were that interpretation of images requires special training and a large number of images must be viewed. The PillCam® Colon would not replace colonoscopy, because any abnormal finding would require further investigation using colonoscopy. The cost-effectiveness of CE depends mainly on its ability to improve compliance to CRC screening beyond that of colonoscopy. (Hassan 2008)
An additional multicenter study involving 320 patients with known or suspected colonic disease showed that CE is a safe method of visualizing the colonic mucosa through colon fluids without the need for sedation or insufflation. (Van Gossum 2009) Adverse events reported by the patients were mild and attributed to the colon preparation. The sensitivity and specificity of CE for detecting polyps 6 mm or larger were 64% (95% CI, 59 to 72) and 84% (95% CI, 81 to 87), respectively, and the sensitivity and specificity for detecting advanced adenomas 6 mm or larger were 73% (95% CI, 61 to 83) and 79% (95% CI, 77 to 81), respectively. However, the sensitivity of CE for detecting colonic polyps, advanced adenomas, and colorectal cancer was relatively low in comparison with colonoscopy. It appears that colon cleanliness significantly influences the sensitivity of CE.

**Study types consulted in preparing this policy:** *Systematic reviews*, which synthesize results qualitatively or pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies, use pre-determined transparent methods to minimize bias, effectively applying scientific methods to a review to enhance the reliability of the findings; thus, they are rated highest in evidence grading hierarchies. *Economic analyses* (e.g. cost-effectiveness, -benefit or -utility studies) that report both costs and outcomes ideally based on randomized controlled trials, but excluding simple cost studies, also rank near the top of evidence hierarchies. Table 1 details the available systematic reviews and economic analyses for CE visualization of the gastrointestinal tract.

**Results:**

Results of upper and lower GI endoscopic procedures are presented typically in terms of detection rate, or diagnostic yield, which is the likelihood that a test or procedure will provide the information needed to establish a diagnosis. For CE, diagnostic yield is expressed as the ratio of the number of positive detections divided by the total number of CE procedures. Diagnostic yield is determined as much by appropriateness criteria used to improve patient selection as by the sensitivity of the test. Moreover, higher diagnostic yield does not necessarily equate to higher diagnostic accuracy or improved therapeutic impact. A high diagnostic yield may actually be the result of inclusion of false-positive results, whereas low diagnostic yield does not necessarily indicate lower accuracy, and could result from an accurate reflection of a low incidence of the pathology in question. (Xie 2012)

A majority of studies included in the systematic reviews in Appendix 1 represent patients in whom CE was performed only after other established endoscopic or imaging procedures had been carried out and their findings were negative or indeterminate. In this highly selected group, a higher probability of the disease of interest is likely, with a corresponding and potentially misleading higher diagnostic yield for CE relative to prior methods.

**Summary of Clinical Evidence:** See Appendix 1
Professional Society Guidelines:

Guidelines are based generally on systematic reviews, where available, and consensus with evidence grading.

American College of Gastroenterology

- Crohn’s: Evaluation of small bowel in patients with known or suspected CD: “It is currently recommended that radiographic studies (small bowel follow through, CT enterography, or magnetic resonance enterography) be performed prior to VCE in patients with CD to assess for the presence of unsuspected small intestinal strictures. Small bowel strictures, which occur frequently in patients with known CD, are considered to be a contraindication to VCE for fear of capsule retention. A patency capsule, which can be administered prior to the use of a VCE to assess for the presence of significant strictures, has recently become available.” (Lichtenstein, 2009).
- Barrett’s esophagus: The ACG noted “although intriguing, this technique cannot be recommended in the screening setting at this time.” (Wang, et al. 2008).

American Gastroenterological Association

- OGIB: Patients with OGIB and iron deficiency anemia and negative workup on EGD and colonoscopy need comprehensive evaluation, including CE to identify an intestinal bleeding lesion. CE findings may assist in the follow-up evaluation of patients with OGIB. Further invasive investigations can be deferred in patients with OGIB and negative findings on CE. (Raju 2007).

American Society for Gastrointestinal Endoscopy

- Peds: Although WCE is approved for children 10 years and older, it has been applied successfully in children as young as 2 years of age. For children who cannot swallow, capsule endoscopic placement can be performed. (ASGE 2008).
- Peds: Indications for CE in children include evaluation of the small-bowel mucosa for evidence of Crohn’s disease, occult bleeding, celiac disease, polyps, graft-versus-host disease, lymphangiectasia, and disease contributing to growth failure or abdominal pain. CE is FDA approved in children 2 years of age and older. Success depends more on the maturity level and confidence of the child than chronologic age because many older children and teenagers fail or refuse to attempt to swallow the capsule. (ASGE 2012).
- Chronic diarrhea: CE not recommended for routine evaluation. (Shen 2010).
- GERD: The precise role of these technologies [CE] for diagnosing or managing Barrett’s epithelium is unclear at this time. (ASGE 2007).
- Barrett’s esophagus: EGD recommended as the preferred surveillance modality. (ASGE 2012).
- OGIB: We recommend urgent EGD or colonoscopy in patients with active overt OGIB. To evaluate the small bowel for occult OGIB, VCE is recommended as the first diagnostic test if no contraindications. For those patients with inactive overt OGIB, we suggest VCE, deep enteroscopy, PE, and/or colonoscopy. We suggest that, in patients with negative VCEs and continued bleeding, repeat VCE be considered,
particularly if the clinical state changes from obscure to overt bleeding or if the hemoglobin level drops by _4 g/dL. (ASGE 2010).

- Contraindications: Patients with known or suspected GI obstruction, strictures, or fistulas based on the clinical picture or pre-procedure testing; Patients with swallowing disorders; Pregnancy. Use cautiously in patients with cardiac pacemakers. Patients should not undergo MRI after having completed a capsule endoscopy until they have passed the capsule. The capsule can be easily identified on plain radiographs, and this should be performed if there is any question. (Tech report 2006).

- Elderly: During CE there is a theoretical potential for interference from the digital radiofrequency communication between the capsule and the data recorder, so the presence of a cardiac pacemaker or ICD is considered a relative contraindication to CE. Recently, reports on small series of patients have been published showing CE to be safe in patients who were monitored and studied in a hospital setting. No significant interference with pacemaker or ICD function was seen, and there was no interference with the CE images. Because large studies are not available, it may be advisable that patients with implanted cardiac devices are evaluated by a cardiologist before CE and patients with ICDs be observed in a hospital setting with continuous cardiac monitoring. (Qureshi 2006).

**American College of Radiology**

- OGIB: No clear consensus on whether CE or CT is more effective, and they may be complementary. CE “usually appropriate” for evaluation of lower GI tract OGIB when colonoscopy is negative. (ACR 2011).

**Training and competency**

- NASPGHAN: Training guidelines include training and competency in CE. (Leichtner 2013)
- ASGE: Completion of a gastrointestinal endoscopy training program that included training in the recognition and management of small intestinal diseases (for small intestine CE). Be competent and have privileges to perform EGD, colonoscopy, and (for small intestine CE) enteroscopy. Familiarity with the hardware and software systems. Training via one of the following:
  - Formal training in CE during GI fellowship.
  - Completion of a hands-on course with a minimum of 8 hours CME credit, endorsed by a national or international GI or surgical society and review of first 10 capsule studies by a credentialed capsule endoscopist (ASGE 2005).

**Glossary of terms:**

**Angiodysplasia:** abnormal vascular growth or development.

**Angiography:** the radiographic visualization of the blood vessels after injection of a radiopaque substance.

**Barium enema:** a special x-ray of the large intestine, which includes the colon and rectum.

**Barrett’s esophagus:** a condition in which the tissue lining the esophagus is replaced by tissue similar to the intestinal lining.
Celiac disease: an autoimmune digestive disease that damages the villi of the small intestine and interferes with absorption of nutrients from food due to exposure to gluten.

Crohn’s disease: an inflammatory bowel disease that causes inflammation of the lining of the digestive tract, which can lead to flare-ups.

Deep enteroscopy: uses one or two balloon systems to advance the endoscope through the small bowel by alternately inflating and deflating balloons, and pleating the small bowel over an insertion tube like a curtain over a rod.

Diagnostic yield: the likelihood that a test or procedure will provide the information needed to establish a diagnosis.

Double-balloon enteroscopy: enteroscopy using a two-balloon system; also known as push enteroscopy

Enteroclysis: fluoroscopic X-ray of the small intestine.

Enteroscopy: procedure of using an enteroscope for the direct visualization of small bowel for diagnostic or therapeutic purposes; typically has one or more channels to enable passage of instruments (as forceps or scissors).

Esophageal varices: an abnormally dilated and lengthened vein, artery, or lymph vessel.

Esophagitis: inflammation of the esophagus.

Fistula: an abnormal passage that leads from an abscess or hollow organ or part to the body surface or from one hollow organ or part to another and that may be surgically created to permit passage of fluids or secretions.

Gastroesophageal reflux disease (GERD): is a digestive disorder that affects the lower esophageal sphincter caused by the return of the stomach's contents back up into the esophagus.

Ileocolonoscopy: a procedure whereby the colonoscope is pushed through into the small bowel from the colon.

Inherited polyposis syndromes: any of several inherited diseases (as Gardner's syndrome or Peutz-Jeghers syndrome) characterized by the formation of many polyps in the gastrointestinal tract.

Intussusception: a condition in which one segment of intestine “telescopes” inside of itself, causing an intestinal obstruction.

Mucocutaneous macules: a patch of cells made up of or involving both typical skin and mucous membrane that is altered in color but usually not elevated and that is a characteristic feature of Peutz-Jeghers syndrome.
Obscure gastrointestinal bleeding: bleeding from the gastrointestinal tract that persists or recurs without an obvious etiology after upper endoscopy, colonoscopy, and radiologic evaluation of the small bowel (such as by small bowel follow-through or enteroclysis). Obscure bleeding is subdivided into overt or occult, depending upon the presence or absence of clinically evident bleeding.

Peutz-Jeghers syndrome: a familial polyposis inherited as an autosomal dominant trait and characterized by numerous polyps in the stomach, small intestine, and colon and by melanin-containing spots on the skin and mucous membranes especially of the lips and gums.

Push enteroscopy: see double-balloon enteroscopy.

Scintigraphy: a diagnostic technique in which a two-dimensional picture of internal body tissue is produced through the detection of radiation emitted by a radioactive substance administered into the body.

Small bowel follow-through: also called small bowel series, is a radiologic examination of the small intestine.

Stenosis: a narrowing or constriction of the diameter of a bodily passage or orifice.

Stricture: an abnormal narrowing of a bodily passage (as from inflammation, cancer, or the formation of scar tissue).

Related Policies: Arbor Health Plan Utilization Management Program Description

REFERENCES

Professional Society Guidelines


**Peer-Reviewed References**


**Other references used in policy guidance**


**Clinical Trials**

Searched capsule AND endoscopy | Open Studies | endoscopy (39 records) on August 29, 2013: 14 relevant to this policy

8. "Evaluation of the Applicability of the CDEIS to Data Obtained by the Colonic Capsule Endoscopy in Crohn’s Disease." [http://ClinicalTrials.gov/show/NCT01183845](http://ClinicalTrials.gov/show/NCT01183845)

Centers for Medicare and Medicaid Services (CMS) National Coverage Determination

No NCD for Capsule Endoscopy identified.


Centers for Medicare and Medicaid Services (CMS) Local Coverage Determinations

**Document Types:** NCD, MCD, LCD (Final)

**Keyword:** capsule endoscopy

**Keyword Lookup Type:** Entire Document

**Keyword Search Type:** All Words

**States:** Florida, Illinois, Indiana, Kentucky, Louisiana, Missouri - Entire State, Nebraska, New Jersey, Pennsylvania, Rhode Island, South Carolina

Search results: [http://www.cms.gov/medicare-coverage-database/search/search-results.aspx?LCDId=30141&ContrId=48&ver=24&ContrVer=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCD%7cMCD&PolicyType=Final&s=12%7c19%7c20%7c22%7c23%7c29%7c36%7c38%7c45%7c47%7c48&KeyWord=capsule+endoscopy&KeyWordLookUp=Doc&KeyWordSearchType=And&kq=true&bc=IAAAABABABAAAA%3d%3d](http://www.cms.gov/medicare-coverage-database/search/search-results.aspx?LCDId=30141&ContrId=48&ver=24&ContrVer=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCD%7cMCD&PolicyType=Final&s=12%7c19%7c20%7c22%7c23%7c29%7c36%7c38%7c45%7c47%7c48&KeyWord=capsule+endoscopy&KeyWordLookUp=Doc&KeyWordSearchType=And&kq=true&bc=IAAAABABABAAAA%3d%3d)
## LCD Procedure Medicare States

<table>
<thead>
<tr>
<th>LCD</th>
<th>Procedure</th>
<th>Medicare</th>
<th>States</th>
</tr>
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<tbody>
<tr>
<td>L30141</td>
<td>Capsule Endoscopy</td>
<td>MAC - Parts A/B</td>
<td>Missouri</td>
</tr>
<tr>
<td>L30141</td>
<td>Capsule Endoscopy</td>
<td>MAC - Parts A/B</td>
<td>Indiana</td>
</tr>
<tr>
<td>L30141</td>
<td>Capsule Endoscopy</td>
<td>MAC – Parts A/B</td>
<td>Nebraska</td>
</tr>
<tr>
<td>L30141</td>
<td>Capsule Endoscopy</td>
<td>Part A/B</td>
<td>Wisconsin</td>
</tr>
<tr>
<td>L30141</td>
<td>Capsule Endoscopy</td>
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<td>Fl., In, La, Ne, SC, RI, NJ</td>
</tr>
<tr>
<td>L31838</td>
<td>Endoscopy by Capsule</td>
<td>MAC - Parts A/B</td>
<td>Kentucky</td>
</tr>
<tr>
<td>L31585</td>
<td>Upper GI Endoscopy/Visualization</td>
<td>MAC - Part A</td>
<td>South Carolina</td>
</tr>
<tr>
<td>L32686</td>
<td>Wireless Capsule Endoscopy</td>
<td>MAC - Parts A/B</td>
<td>Louisiana</td>
</tr>
<tr>
<td>L29008</td>
<td>Wireless Capsule Endoscopy</td>
<td>MAC - Part A</td>
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</tr>
<tr>
<td>L29310</td>
<td>Wireless Capsule Endoscopy</td>
<td>MAC - Part B</td>
<td>Florida</td>
</tr>
</tbody>
</table>

**Commonly Submitted Codes:**
Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

**Group 1 Paragraph:** For Wireless Capsule Endoscopy of the Small Intestine ONLY:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>91110</td>
<td>Gastrointestinal tract imaging, intraluminal (e.g. capsule endoscopy), esophagus through ileum, with interpretation and report.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>280.0</td>
<td>Iron deficiency anemia, secondary to blood loss (chronic)</td>
<td></td>
</tr>
<tr>
<td>555.0 - 555.9</td>
<td>Regional enteritis [Crohn's disease]</td>
<td></td>
</tr>
<tr>
<td>558.1 - 558.9</td>
<td>Other and unspecified noninfectious gastroenteritis and colitis</td>
<td></td>
</tr>
<tr>
<td>578.0 - 578.9</td>
<td>Gastrointestinal hemorrhage</td>
<td></td>
</tr>
<tr>
<td>579.0</td>
<td>Celiac disease</td>
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<tr>
<td>759.6</td>
<td>Other hamartoses (Peutz-Jeghers syndrome)</td>
<td></td>
</tr>
<tr>
<td>280.9</td>
<td>Iron deficiency anemia, unspecified</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Code</td>
<td>Description</td>
<td>Comment</td>
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<tr>
<td>-------------</td>
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<tr>
<td>C17.0-C17.9</td>
<td>Malignant neoplasm of small intestine</td>
<td></td>
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<tr>
<td>D50.0-D50.9</td>
<td>Iron deficiency anemia</td>
<td></td>
</tr>
<tr>
<td>K50.00-K50.919</td>
<td>Crohn’s Disease (Regional Enteritis)</td>
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</tr>
<tr>
<td>K90.0-K90.9</td>
<td>Intestinal malabsorption</td>
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<tr>
<td>K92.0</td>
<td>Hematemesis</td>
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<td>K92.1</td>
<td>Melena</td>
<td>MELENA</td>
</tr>
<tr>
<td>K92.2</td>
<td>Gastrointestinal hemorrhage, unspecified</td>
<td></td>
</tr>
<tr>
<td>Z15.09</td>
<td>Genetic susceptibility to other malignant neoplasm</td>
<td></td>
</tr>
<tr>
<td>Z86.010</td>
<td>Personal history of colonic polyps</td>
<td></td>
</tr>
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</table>

<table>
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<tr>
<th>HCPCS Level II</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

Disclaimer: Arbor Health Plan has developed clinical policies to assist with making coverage determinations. Arbor Health Plan clinical policies are based on guidelines from established industry sources such as Centers for Medicare and Medicaid (CMS), State regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer reviewed professional literature. These clinical policies, along with other sources, such as plan benefits and state and federal laws and regulatory requirements, are considered by Arbor Health Plan when making coverage determinations. Arbor Health Plan clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Arbor Health Plan clinical policies are reflective of evidence based medicine at the time of review. As medical science evolves, Arbor Health Plan will update its clinical policies as necessary. Arbor Health Plan clinical policies are not guarantees of payment.

ATTACHED: Appendix 1
# APPENDIX 1: Summary of Clinical Evidence Capsule Endoscopy

<table>
<thead>
<tr>
<th>Citation</th>
<th>Indication</th>
<th>Main Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small bowel CE</strong></td>
<td></td>
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</tr>
<tr>
<td>Hayes 2013</td>
<td>Obscure gastrointestinal bleeding (OGIB)</td>
<td>Systematic review of 25 studies: 17 prospective comparative studies of CE with other small bowel investigations, 2 randomized comparative studies of 2 different capsule endoscopes (n=50 to 218 patients), 6 case series and chart reviews of CE for OGIB/IDA (n=427 to 911 patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Quality of evidence: moderate, limited by small sample sizes (for prospective studies), the lack of well-defined reference standards, blinding, and standardized follow-up.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CE is safe, has adequate diagnostic yield and is sensitive for detecting bleeding source in patients who are referred for small bowel investigation following a negative or nondiagnostic upper gastrointestinal (GI) endoscopy and colonoscopy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Inconclusive for CE’s ability to detect tumors compared to push enteroscopy, SBFT, and angiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Evidence from case series and 3 randomized studies suggests that CE has an immediate impact on patient management and overall positive impact on health outcomes comparable to push enteroscopy, SBFT, and angiography.</td>
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<tr>
<td></td>
<td></td>
<td>- Comparative effectiveness and safety of different CE systems is inconclusive.</td>
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<tr>
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<td></td>
<td>- Capsule retention was the most important complication; therefore, patients with bowel obstructions should not receive CE. For safety reasons, patients with a swallowing disorder should also not undergo CE.</td>
</tr>
<tr>
<td>Xie 2012</td>
<td>Small bowel diseases in adults: OGIB Crohn’s Disease (CD)</td>
<td>Systematic review of 14 systematic reviews and 3 health technology assessments(HTA); used evidence from 4 meta-analyses that most appropriately addressed the questions at issue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Overall quality of evidence: low, but a consistent significant diagnostic yield with CE in patients with OGIB and CD.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- OGIB-the diagnostic yield of CE is significantly higher than that of push enteroscopy and small bowel barium radiography, and not significantly different from that of double balloon enteroscopy.</td>
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<tr>
<td></td>
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<td>- OGIB-2 RCTs did not find superior outcomes using CE compared to alternatives at 1 year follow up.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CD: the diagnostic yield of CE is significantly higher than that of small bowel barium radiography, CT enterography/enteroclysis, colonoscopy</td>
</tr>
<tr>
<td>Citation</td>
<td>Indication</td>
<td>Main Points</td>
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</table>
| Hayes 2011a  | CD in adults       | Systematic review of 12 prospective blinded studies, 2 prospective unblinded studies, and 5 retrospective studies; 16 single-center studies and 3 were multicenter studies. Study n=30 to 132 patients with known or suspected CD. Studies compared CE with small bowel follow-through (SBFT), enteroclysis; push endoscopy (PE), ileocolonoscopy (IC), MRE, computed tomography enterography (CTE), CTE with enteroclysis (CT-enteroclysis), and small intestine contrast-enhanced ultrasound (SICUS).  
  - Quality of evidence: moderate.  
  - Evidence suggests CE is safe, has high diagnostic yield and is sensitive for the detection of CD (CD), and may be equivalent or superior to other small bowel investigations.  
  - CE requires prior small bowel investigation to exclude patients with bowel obstructions, limits application as a first line investigation of CD.  
  - Insufficient number of studies comparing CE with other second-line investigations of CD, such as MRE and double-balloon endoscopy, which can evaluate disease severity or taking biopsies at the time of investigation. Therefore, still unclear whether CE should be used as a second- or third-line investigation.  
  - Patient preferences: 3 preliminary studies suggest patients consider CE easy and convenient and less stressful than MRE and CTE.  
  - CE recommended to exclude CD in adult patients with suspected CD and inconclusive results on upper and lower endoscopy, and in adult patients with known CD in whom CD recurrence is suspected.  
  - CE is contraindicated in persons with gastrointestinal obstructions, strictures, or stenosis, and in patients with swallowing disorders. |
| Gilbert 2011 | Small bowel CD    | Systematic review of 22 studies for all age groups  
  - Quality of evidence: poor for comparative effectiveness with a high risk of selection and outcome bias  
  - CE for diagnosis of small bowel CD is safe based on studies with small |
### Citation | Indication | Main Points
--- | --- | ---
| Hayes 2011b | Small bowel diseases in children:  
- Suspected/existing IBD  
- OGIB and undiagnosed anemia  
- Abdominal pain, diarrhea and polyposis. | Systematic review of 14 clinical studies (6 prospective, 8 retrospective) and 1 meta-analysis  
- Overall quality of evidence: low. Only 1 study systematically compared CE with a reference standard, few studies followed up to confirm results CE, none followed patients at standard intervals. Other factors weakening the quality of the evidence included lack of blinding, lack of systematic follow-up, and small sample sizes. Only 2 studies evaluating CE exclusively in small children younger than 10 years. All other studies also enrolled adolescents and young adults up to 23 years of age. Most subjects enrolled after negative or inconclusive upper and lower endoscopy with persistent symptoms.  
- Most common diagnoses were CD (35%), polyposis (15%), identification of the source of bleeding in OGIB (13%), and malabsorption/celiac disease (2%).  
- Results suggest CE using the PillCam® system is feasible in pediatric patients with acceptable technical success rates, has good diagnostic yield for small bowel disorders, and a positive impact on patient management in children age 5 years and older.  
- The risks of endoscopic capsule placement, which was needed in all sample sizes  
- Capsule retention in up to 15% of cases; this risk can be partially, but not completely, mitigated by screening for strictures on small bowel radiology; higher rate of capsule retention and a higher rate of surgical removal of retained capsules than other indications e.g. OGIB and PJS  
- Less likely to be predictive of the absence of CD, when the CE is negative, in patient populations with negative or equivocal prior endoscopic and radiological tests  
- More likely to be predictive of the absence of CD, when the CE result is negative, when a lower threshold is used to define a positive test  
- Not to be highly predictive of the absence of CD in the largest and most applicable study  
- Likely to have at least comparable accuracy to MR  
- There were no included studies that provided evidence on the comparative accuracy of CE and CT.  
- The impact of CE findings on patient management is unknown and the resultant impact on health outcomes is uncertain.  
- Expert consensus: CE may lead to benefits that are not evident from the limited available data. In clinical practice there are a small number of patients for whom it is very difficult to reach a diagnosis of CD in whom CE may be the only option. Many new diagnoses of CD currently made via CE occur in patients who are being evaluated for OGIB. |
<table>
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<th>Citation</th>
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<th>Main Points</th>
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<tr>
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<td>children younger than 4 years old but also in some older children, is insufficiently investigated.                                                                                           • Additional evidence is needed from well-designed studies focusing on CE to determine the effectiveness and safety of small bowel endoscopy in children.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CONCLUSIONS: For CE with PillCam® SB or PillCam® SB2 recommended for children 5 years of age or older, who are able and willing to swallow the capsule, for the evaluation of known or suspected small bowel disease such as IBD, OGIB, and suspected polyposis, after negative or inconclusive results from conventional upper and lower GI endoscopy.</td>
</tr>
<tr>
<td>MSAC 2007</td>
<td>Peutz-Jeghers syndrome</td>
<td>Systematic review of 9 studies: 4 comparing CE to barium follow through; 1 comparing CE with MRI; 4 non-comparative study; plus, 3 reviews.                                                                                                                   • Quality of evidence: limited by no agreed reference standard.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CE is a safe, well-tolerated procedure compared with small bowel surveillance by barium follow-through radiography.                                                                                                                     • CE is better at detecting the number of polyps and extent of polyposis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CE is changing patient management in situations where radiographic examinations produced false negative results.                                                                                                                      • CE for small bowel surveillance of PJS is likely to be as effective and as cost-effective as small intestine x-ray.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MSAC recommends that public funding be supported for performing CE, no more than once in any two year period, for small bowel surveillance in patients diagnosed with PJS.</td>
</tr>
<tr>
<td>Rokkas 2012</td>
<td>Celiac disease</td>
<td>Meta-analysis of 6 studies of diagnostic accuracy of CE                                                                                                                                                                                                                     • Overall pooled CE Se=89% (95% CI, 82-94%), Sp=95% (95% CI, 89-98%).</td>
</tr>
<tr>
<td></td>
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<td>AUC under the weighted symmetric summary ROC=0.9584                                                                                                                                                                                                                           • Conclusions: CE is not as accurate as pathology, but could be a reasonable alternative method of diagnosing CD, especially in patients unwilling to undergo gastroscopy because of its perceived inconvenience and discomfort. However, larger, multicenter, and well-designed trials needed to further establish its role in diagnosis of CD.</td>
</tr>
<tr>
<td>El-Matary 2009</td>
<td>Celiac disease</td>
<td>Meta-analysis of 3 studies (n = 107; 63 with CD and 44 without).                                                                                                                                                                                                                • Overall pooled CE Se=83% (95% CI=71-90%), Sp=98% (95% CI=88-99.6%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No major complications reported. The costs mentioned only in one study.                                                                                                                                                                                                      • CONCLUSIONS: The overall diagnostic characteristics of CE, though good with an experienced eye, could not justify routine use as an alternative to</td>
</tr>
<tr>
<td>Citation</td>
<td>Indication</td>
<td>Main Points</td>
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<tr>
<td><em>the pathology of small-bowel biopsies. More studies are needed with proper cost-benefit analysis.</em></td>
<td></td>
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</tr>
<tr>
<td>Levesque 2010</td>
<td>CEA CD</td>
<td>Computed tomographic enterography (CTE) vs. small-bowel follow-through (SBFT) vs. [negative CTE or SBFT] + CE</td>
</tr>
<tr>
<td>• RESULTS: The cost effectiveness of strategies depends critically on the pretest probability of CD and if the terminal ileum is examined at ileocolonoscopy. With a moderate to high pretest probability of small-bowel CD, and a higher likelihood of isolated jejunal disease, follow-up evaluation with CTE has an ICER &lt; $54,000/QALY-gained over lifetime compared with SBFT. The addition of CE after ileocolonoscopy and negative CTE or SBFT costs &gt; $500,000 per QALY-gained in all scenarios, including patients with high pretest probability of disease.</td>
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<tr>
<td>Gerson 2008</td>
<td>CEA OGIB</td>
<td>Modalities: push enteroscopy, intraoperative enteroscopy, angiography, initial anterograde double-balloon enteroscopy (DBE) followed by retrograde DBE if the patient had ongoing bleeding, and CE followed by DBE guided by the CE findings.</td>
</tr>
<tr>
<td>• An initial DBE was the most cost-effective approach. The no-therapy arm cost $532 with 0.870 QALYs over a 1-year time period vs. $2407 and 0.956 QALYs for DBE, which resulted in an incremental cost-effectiveness ratio of $20,833 per QALY gained.</td>
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<tr>
<td>• Compared to the DBE approach, an initial CE was more costly and less effective. The initial DBE arm resulted in an 86% bleeding cessation rate vs. 76% for CE vs. 59% for no-therapy. The model results were robust to a wide range of sensitivity analyses.</td>
<td></td>
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<tr>
<td>• However, capsule-directed DBE may be associated with better long-term outcomes because of the potential for fewer complications and decreased utilization of endoscopic resources.</td>
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<tr>
<td>Esophageal CE</td>
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<td></td>
</tr>
<tr>
<td>Bhardwaj 2009</td>
<td>Barrett’s esophagus in patients with Gastroesophageal Reflux Disease (GERD)</td>
<td>Systematic review of 9 blinded studies (n=618 patients, range 20 to 106); 8 prospective, 1 retrospective that used esophagogastroduodenoscopy or histologically confirmed intestinal metaplasia as reference standard</td>
</tr>
<tr>
<td>• Quality of evidence: no quality assessment conducted. No evidence of publication bias</td>
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<tr>
<td>• Pooled Se of CE=77% for all studies, 78% vs. either reference standard. No statistical heterogeneity.</td>
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<tr>
<td>• Pooled Sp of CE=86% for all studies, 90% vs. esophagogastroduodenoscopy, 73% vs. histology. Statistical heterogeneity (P&lt;0.001, I²=74%).</td>
<td></td>
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<tr>
<td>Citation</td>
<td>Indication</td>
<td>Main Points</td>
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</table>
|          | CE is safe and high rate of patient preference.  
CONCLUSIONS: The modality of choice is esophagogastroduodenoscopy, prospective multicenter trials needed to address limitations of esophageal CE and evaluate modifications of the ingestion protocol to improve visualization of esophageal pathology. |
| Hayes 2008 | Esophagus: Barrett’s esophagus  
Esophagitis  
Esophageal varices | Systematic review of 6 studies (n=316)  
Quality of evidence: low, limited by the small numbers of well-designed studies and small sample sizes, lacking histologic confirmation of diagnostic accuracy of CE, instead reporting detection of pathology as an outcome.  
CE is safe and feasible. No major complications reported. One study (n=90) noted capsule retention in the esophagus of 2 patients, and 2 patients had difficulty in swallowing the capsule. High patient tolerance.  
Diagnostic yield =71% (1 study)  
Overall diagnostic performance varied, depending on pathology. Se=66%-100%, Sp=92%-99%, PPV=97%-100%, NPV=57%-99%, with EGD as the reference standard.  
Patient satisfaction significantly higher with CE than EGD  
One limitation of CE for assessment of Barrett’s esophagus is need for conventional endoscopy for biopsy confirmation.  
Esophageal varices: from two small prospective studies, CE comparable clinical validity to EGD in high prevalence populations, unclear in lower prevalence populations  
Absolute contraindications: presence of known or suspected intestinal obstruction, fistulas, or strictures, esophageal stricture, or swallowing abnormalities  
CONCLUSIONS: C rating for esophageal CE may be indicated in patients with esophageal indications who are unlikely to require biopsy for confirmation of diagnosis. |
| Gerson 2007 | CBA Barrett’s esophagus | Assuming a theoretical cohort of 10,000 patients with GERD, initial EGD cost $1988 and was associated with 18.54 life-years vs. $2392 and 18.36 life-years for the CE arm vs. $901 and 18.30 life-years for the no screening arm.  
The incremental cost effectiveness ratio of screening with EGD compared with the no screening arm was $4530 per life-year gained. The model was robust to a wide range of sensitivity analyses.  
CONCLUSIONS: Initial EGD appears more effective and less costly compared with CE under base-case conditions for patients with chronic GERD undergoing screening for BE. |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Indication</th>
<th>Main Points</th>
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</thead>
<tbody>
<tr>
<td><strong>Colon CE</strong></td>
<td></td>
<td>Systematic review of 2 prospective non-RCTs with contemporaneous controls (n=120 evaluated) comparing accuracy of CE with optical colonoscopy in detection of colorectal cancers and polyps:</td>
</tr>
</tbody>
</table>
| Ontario MAS   | Colorectal cancer screening | • Quality of evidence: moderate.  
• Colon CE has comparable yield but lower Se and Sp than colonoscopy and its accuracy in the detection of cancer has not been studied.  
• For CE detection of significant polyps (defined as >6 mm or ≥3 polyps), pooled Se= 73% (54%–87%) and pooled Sp=92% (84%–97%). Since no segmental unbinding was performed, underestimation of diagnostic accuracy is possible.  
• Higher Se, Sp, PPV, and NPV have been reported when an experienced physician interpreted the images.  
• CE is safe, acceptable to patients.  
• No adverse events related to the procedure reported by the two studies.  
• Interpretation of findings is an important aspect of capsule procedures and the learning curve is an important issue for interpretation of images. Special training required. A large number of images must be viewed.  
• Unlike colonoscopy, CE offers no therapeutic capability for detected lesions. |
| 2011          |                             |                                                                                                                                                                                                             |
| Spada 2010    | Colorectal cancer screening | Systematic review of 8 prospective diagnostic cohort studies (n=837 patients) published from 2006-2009:                                                                                                         |
|               |                             | • Quality of evidence: The reference standard (colonoscopy) was interpreted blind to the colon CE results in all but one study. Potential for publication bias.  
• The per-patient Se and Sp were calculated for polyps of any size and for significant findings (polyps, > or =6 mm in size or >3 in number)  
• Prevalence of polyps and significant findings=57% and 27.4%, respectively.  
• Se for polyps of any size and significant findings=71% and 68%, respectively; Sp for polyps of any size and significant findings=75% and 82%, respectively.  
• AUTHORS’ CONCLUSIONS: Colon CE compares with other non-invasive colorectal cancer screening strategies (but accuracy of other non-invasive strategies was not assessed in review.)  
• Future studies should elaborate a more rigorous polyp-matching algorithm between colon CE and colonoscopy to avoid incorrect |
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|               |                             |                                                                                                                                                                                                             |</p>
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| Hassan 2008 | CEA colorectal screening | Comparison of cost-effectiveness of two screening strategies using colonoscopy or CE based on a Markov process of a hypothetical population of 100,000 individuals aged 50 years and over, undergoes a 10 yearly screening procedure. Different thresholds for post capsule polypectomy referral were simulated.  
- At baseline, the incremental cost-effectiveness (compared with no screening) of colonoscopy and CE was $16,165 and $29,244 per life-year saved, respectively.  
- When equal compliance was simulated, the colonoscopy program was more effective and less costly than a strategy based on CE.  
- When initial compliance to CE 30% better than colonoscopy was simulated, CE became the more effective and more cost-effective option.  
- A 20% better compliance was sufficient when a higher accuracy of CE for polyps was assumed. A 6 mm threshold for polypectomy referral was associated with a substantial cost reduction in the CE program with only a small loss of efficacy.  
- CONCLUSIONS: The cost-effectiveness of CE depends mainly on its ability to improve compliance to CRC screening. |