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Dear Ms. Mills:

On behalf of the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE), representing over 16,000 physicians and scientists who are involved in research, clinical practice, and education on disorders of the digestive system, we are pleased to provide these comments to the California Technology Assessment Forum (CTAF) with respect to your review of PillCam ESO Capsule for the Diagnosis of Esophageal Disease, which is scheduled to be discussed at the upcoming CTAF meeting on October 15, 2008.

The PillCam ESO is being investigated for use in evaluating patients with esophageal varices. The potential advantages of capsule endoscopy (CE) over esophagogastroduodenoscopy (EGD) include the ability to avoid sedation in patients with liver cirrhosis, and the ability to perform capsule endoscopy during the office visit.

In a pilot study of 32 patients with cirrhosis, the PillCam ESO was compared with EGD in detecting esophageal varices and portal hypertensive gastropathy. Eisen et al. (2006) performed CE on 32 patients with cirrhosis who had prior endoscopic confirmation of esophageal varices and were undergoing clinically indicated EGD for screening or surveillance for esophageal varices. EGD was performed the same day following CE. The gold standard for all findings was the upper endoscopic findings. Accuracy was assessed for two findings, the presence or absence of esophageal varices and the presence or absence of portal hypertensive gastropathy. Twenty-three patients had esophageal varices at both EGD and PillCam ESO evaluation. The overall concordance between PillCam ESO and EGD was 96.9% for the diagnosis of esophageal varices and 90.6% for portal hypertensive gastropathy. For the detection of esophageal varices, PillCam ESO capsule endoscopy had a sensitivity of 100%, a specificity of 89%, a positive likelihood ratio of 9.1, and a negative likelihood ratio of 0.0, in comparison with EGD. In one patient, PillCam ESO detected small varices that were not seen at EGD. For the detection of portal

hypertensive gastropathy, PillCam ESO capsule endoscopy had a sensitivity of 100%, a specificity of 77%, a positive likelihood ratio of 4.3, and a negative likelihood ratio of 0.0, in comparison with EGD. The authors noted the patients who were enrolled in this study comprised a selected sample group of patients who were undergoing clinically indicated screening or surveillance exams for esophageal varices. The study was not designed or powered to assess the accuracy of grading the size of varices. The authors stated there are several issues that must be addressed before CE can be broadly recommended as an alternative screening tool. Endoscopists generally use insufflation to better appreciate the “true” size of varices in the esophagus, which is not possible with capsule endoscopy. Another issue is the presence or absence of gastric varices and the ability of the PillCam ESO capsule to visualize this reliably. The authors stated that further studies will need to address the above issues and show the value of the method in low prevalence populations for distinguishing between low-grade and high-grade varices requiring prophylactic therapy.

Lapalus et al. (2006) evaluated 20 patients with recently diagnosed cirrhosis who underwent EGD and CE on the same day. The procedures were carried out for screening purposes in all of the patients. There was complete diagnostic agreement regarding the absence or presence of esophageal varices in 17 of the 20 patients (85%). The three patients in whom there was a discrepancy between the two procedures were diagnosed with grade 1 varices on EGD and no varices on capsule endoscopy. The sensitivity of capsule endoscopy for detecting esophageal varices in comparison with EGD as the gold standard was 81.25% (13 of 16), with a 100% positive predictive value, a specificity of 100% (12 of 12), and a negative predictive value of 57.1% (four of seven). All 20 patients were adequately classified for the indication of beta-blocker treatment or band ligation (varices larger than grade 1 and/or red signs) with the capsule endoscopy examination. Regarding gastric varices, one patient presented with gastric varices that were diagnosed with both EGD and capsule endoscopy. Portal hypertension gastropathy was diagnosed with EGD in 16 of 21 patients and with capsule endoscopy in 13 of 20 patients. The four patients in whom there was a discrepancy were diagnosed as having gastropathy on EGD but not on capsule endoscopy in three cases, or as having gastropathy on capsule endoscopy but not on EGD in one case. The authors stated that CE was feasible, safe, and accurate.

De Franchis, et al. (2008) reported on a multicenter clinical trial comparing capsule endoscopy to EGD in detecting esophageal varices. This trial was first reported in abstract form (*Gastrointest Endosc.* 2007;65(5):AB107). The study was designed as an equivalence study, assuming that a difference of <10% between capsule endoscopy and EGD in diagnosing esophageal varices would demonstrate equivalence. Patients who were undergoing clinically indicated EGD for screening or surveillance of esophageal varices were asked to undergo capsule endoscopy prior to the EGD. EGD was performed within 48 hours of capsule endoscopy. A second investigator read each capsule endoscopy study, blinded to patient history and EGD results. Two hundred eighty five patients underwent capsule endoscopy and EGD, 61 percent of whom underwent the procedures for screening, and the remainder for surveillance of known esophageal varices. Sensitivity, specificity, positive predictive value and negative predictive value for capsule endoscopy compared to EGD were 84%, 88%, 92%, and 77%, respectively. The overall agreement for detecting varices was 85.8%, where kappa score of 0.73 denoted substantial agreement. There was complete agreement on variceal grade in 227 of 288 cases (79%). In four cases, capsule endoscopy did not detect esophageal varices that were considered medium/large

on EGD, and EGD did not detect two cases of medium/large esophageal varices seen on capsule endoscopy. In differentiating between two patient management alternatives (i.e., medium/large varices which requires treatment and small varices or no varices which requires monitoring), sensitivity, specificity, positive predictive value and negative predictive value for capsule endoscopy compared to EGD were 78%, 96%, 87% and 92%, respectively. The overall agreement of treatment decisions based on esophageal varices size was 91% with a kappa score of 0.77 denoting substantial agreement. Kappa statistics were calculated for the diagnosis of varices with three different conventions: presence or absence of varices; variceal grade (none, small, or medium / large), and differentiation of medium / large varices from all other variceal grades. In clinical practice, the last distinction determines whether or not patients receive chronic therapy for primary prevention of variceal bleeding.

Guidelines on the prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis from the American Association for the Study of Liver Diseases state the frequency of surveillance endoscopies in patients with no or small varices depends upon their natural history (Garcia-Tsao, et al., 2007). Upper endoscopy should be performed once the diagnosis is established. In patients with compensated cirrhosis who have no varices on screening endoscopy, upper endoscopy should be repeated in 2 to 3 year intervals. In those who have small varices, upper endoscopy should be repeated in 1 to 2 years. In the presence of decompensated cirrhosis, upper endoscopy should be repeated at yearly intervals.

Based on these studies, we note that CTAF criteria #1-5 are met for selected patients with esophageal varices who are unable or unwilling to undergo upper gastrointestinal endoscopy. The PillCam™ received clearance from the FDA in August 2001 for use as an adjunctive method of evaluating small-bowel abnormalities in persons with unexplained or recurrent GI bleeding who have undergone conventional endoscopy and/or other diagnostic procedures that failed to locate the source of bleeding. The FDA has classified Ingestible Telemetric Gastrointestinal Capsule Imaging System as class II devices (product code 78NZE and 78NS1) that were reviewed by the FDA's Gastroenterology Panel. In October 2004, the FDA granted marketing clearance for the PillCam ESO video capsule for visualization of the esophageal mucosa.

The scientific evidence as described above permits conclusions concerning the effectiveness of this technology regarding health outcomes. The PillCam ESO provides a safe and reasonable diagnostic alternative for the evaluation and monitoring of esophageal varices in patients who are unwilling to undergo upper gastrointestinal endoscopy or those with hepatic dysfunction in whom there is an increased risk from sedation.

Capsule endoscopy has also been proposed as a method for the evaluation of patients with Barrett's esophagus. The American College of Gastroenterology (ACG) (2008) recommends that patients with long-standing GERD symptoms, particularly those 50 years of age and older, undergo an upper endoscopy for evaluating the mucosa for esophagitis. Approximately 20 percent of U.S. adults have symptoms of GERD at least once a week; however, a subgroup of patients with GERD develops severe complications that include erosive esophagitis, stricture formation, Barrett's esophagus, and adenocarcinoma of the esophagus. The ACG states that "patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy." More importantly, the ACG guidelines state that the

diagnosis of Barrett's esophagus requires biopsy to determine whether intestinal metaplasia is present. Tissue acquisition can be performed during conventional endoscopy for biopsy.

In a feasibility study, Eliakim, et al. (2004) compared the PillCam ESO to conventional upper endoscopy as the gold standard for detection of esophageal pathologies in patients with suspected disorders of the esophagus (n=17). Esophageal pathology was found in twelve of the patients by conventional upper endoscopy and with the PillCam ESO. An additional pathology that was found with the PillCam ESO was considered a false-positive. The authors concluded that this pilot study provides evidence that the esophageal capsule is an accurate, convenient, safe and well-tolerated method to screen patients for significant esophageal disorders; however, the authors stated that further, large-scale studies are necessary to fully assess this diagnostic tool.

A prospective multicenter study comparing the diagnostic accuracy of PillCam ESO esophageal CE to that of conventional upper endoscopy was conducted in 106 patients with chronic gastroesophageal reflux diseases (93 GERD; 13 Barrett) (Eliakim, et al., 2005). Patients underwent CE followed by EGD. CE videos were evaluated by an investigator blinded to EGD findings. A blinded adjudication committee reviewed all discrepant findings between CE and EGD. The gold standard in this study was defined as either the findings noted at the time of the EGD or the decision of the adjudication committee following review of the endoscopic findings, photographs, and CE results. The PillCam ESO identified esophageal abnormalities in 61 of the 66 patients with positive esophageal findings (sensitivity, 92%; specificity, 95%). In patients diagnosed with Barrett's esophagus based on the gold standard, the CE demonstrated a sensitivity of 97%, specificity of 99%, PPV of 99%, and an NPV of 97%. In patients diagnosed with esophagitis based on the gold standard, the CE demonstrated a sensitivity of 89% in detecting esophagitis and an NPV of 94% for ruling out esophagitis. Specificity and PPV were estimated as 99% and 97%, respectively. The authors concluded that CE using PillCam ESO is "a simple, safe, and accurate method for the diagnosis of esophageal mucosal disease and is well-tolerated by patients." They noted that future generations of esophageal capsules with higher frame speed are in trials, and CE using the esophageal capsule may become the primary diagnostic modality for the evaluation of patients with esophageal disease.

Delvaux et al. (2007) prospectively evaluated the diagnostic yield of esophageal CE to detect esophageal lesions in 98 patients with an indication of EGD, and to compare it with the results of EGD, which was used as the gold standard. All patients were investigated by both methods, and the procedures were read in a blinded way. The study included an artificially enriched population to reach a prevalence of about 66% of esophageal lesions. Patients with symptoms suggesting rather a gastric or duodenal origin were additionally recruited as expected negative controls within the limit of 33% of the inclusions. Results showed the EGD was described as entirely normal at the level of the esophagus in 34 patients (35.4%), and showed 86 lesions among the 62 remaining patients (reflux esophagitis in 28, hiatus hernia in 21, esophageal varices in 21, Barrett's esophagus in 11, and miscellaneous in five). Capsule recording was reported to be normal in 36 patients and to show at least one significant finding in 60. The positive predictive value of capsule endoscopy was 80.0%. and the negative predictive value was 61.1%. Overall agreement per patient was moderate between EGD and capsule endoscopy for the per-patient ($\kappa=0.42$) and per-findings ($\kappa=0.40$) analyses. Interobserver agreement between capsule endoscopy readings was moderate for findings ($\kappa=0.39$) and quality assessment

(kappa=0.24). The authors note that low diagnostic specificity and levels of agreement observed may be explained by the moderate quality of the capsule recordings obtained; only 72% of the recordings were considered of at least moderate quality and regarded as allowing a fair diagnosis, with 25% of the recordings considered of poor quality. The authors concluded that large comparative studies will be needed in nonspecialized units to further evaluate esophageal capsule endoscopy.

Lin et al. (2007) prospectively evaluated the accuracy of esophageal CE compared with EGD for the identification of biopsy-proven Barrett's esophagus. Included were 90 patients scheduled for upcoming EGD for the indications of chronic gastroesophageal reflux symptoms (n=66, screening group) or Barrett's esophagus (n=24, surveillance group). There was oversampling of surveillance patients to increase the number of subjects with Barrett's esophagus to encourage calculation of sensitivity and specificity with higher accuracy. There were 18 patients with true Barrett's esophagus in the surveillance group because biopsy specimens did not demonstrate intestinal metaplasia in six surveillance patients, whereas three patients (4.5%) had true Barrett's esophagus in the screening group. Esophageal CE identified 14 of 21 patients with true Barrett's esophagus (sensitivity, 67%) and 58 of 69 patients without Barrett's esophagus (specificity, 84%). The positive predictive value was 22%, and the negative predictive value was 98% for Barrett's esophagus (calculated for screening patients only). The authors discuss possible study limitations. The authors noted that esophageal CE had only moderate sensitivity and specificity for identifying Barrett's esophagus and, in its present form, is not suitable as a primary screening tool for Barrett's esophagus.

Johnson (2007) noted that the findings by Lin et al (2007) are contradictory to the favorable results from the study by Eliakim et al (2005). This discrepancy is surprising because some earlier studies had been carried out with capsules that captured only 4 frames per second rather than the 14 frames per second captured by the capsule that was used in the present study. In the validation study, experts who were aware of both the endoscopy and the capsule findings adjudicated final diagnoses; as the current study did not include this protocol, its results could reflect "real-world" use more accurately. Although the convenience, safety, and patients' tolerance of CE make it an attractive tool for esophageal imaging, at present, this device probably cannot be relied on for the one-time screening to exclude Barrett's esophagus in patients with chronic GERD.

Sharma et al. (2007) prospectively evaluated the diagnostic accuracy of esophageal CE for Barrett's esophagus in 94 patients presenting with gastroesophageal reflux disease (GERD) symptoms (n=41) or for surveillance of Barrett's esophagus (n=53), and for erosive esophagitis and hiatal hernia. The gold standard in this study was the findings noted at the time of upper endoscopy (presence/absence of suspected Barrett's esophagus and grade of erosive esophagitis). Esophageal CE identified 41 of 53 patients with suspected Barrett's esophagus, with a sensitivity and specificity of 77% and 85%, respectively. The PPV and NPV were 87% and 74%, respectively. At upper endoscopy, in patients with GERD symptoms (i.e., screening for Barrett's esophagus), Barrett's esophagus was suspected in nine patients and confirmed by biopsy in six patients. In patients who underwent surveillance endoscopies, Barrett's esophagus was suspected in 44 and confirmed in 39 patients. The sensitivity, specificity, PPV, and NPV of CE for diagnosing Barrett's esophagus in patients undergoing EGD for GERD symptoms were 67%,

87%, 60%, and 90%, respectively. The sensitivity, specificity, PPV, and NPV in patients undergoing surveillance for Barrett's esophagus were 79%, 78%, 94%, and 44%, respectively. The sensitivity, specificity, PPV, and NPV for erosive esophagitis were 50%, 90%, 56%, and 88% and for hiatal hernia were 54%, 67%, 83%, and 33%, respectively. The authors discuss possible study limitations. The authors concluded that standard upper endoscopy remains the gold standard as "current diagnostic rates of esophageal CE for Barrett's esophagus are not yet accurate enough for application in clinical practice."

Qureshi et al. (2008) examined the usefulness of esophageal CE in screening for short-segment Barrett's esophagus. Twenty patients with biopsy proven short-segment Barrett's underwent esophageal CE studies which were reviewed by 2 experienced readers who were blinded as to the purpose of the study. Results showed significant inter-observer variability and a less than 50% detection rate of Barrett's esophagus. The authors concluded that esophageal CE cannot be recommended for screening for short-segment Barrett's esophagus.

The PillCam ESO technique is limited because it: (i) does not have the capability of tissue acquisition, and (ii) the rapid transit rate through the esophagus could potentially miss suspected esophageal pathologies. Although Barrett's esophagus rarely progresses to adenocarcinoma (one in 200 patients develop carcinoma per year), no studies have verified that any specific treatment or management strategy has decreased mortality rate from adenocarcinoma (Shalauta and Saad, 2004). Thus, the clinical effectiveness of the PillCam ESO as a potential screening method for suspected Barrett's esophagus is unclear. In addition, approximately 25 percent of persons with Barrett's esophagus have no symptoms of reflux. Given the high prevalence of GERD, it may be prohibitive to screen all patients with GERD symptoms for the development of Barrett's metaplasia (Shalauta and Saad, 2004).

Thus, capsule endoscopy cannot completely replace conventional endoscopy for the evaluation of diseases involving the esophagus and its clinical value as a screening technique for suspected Barrett's esophagus remains unclear. The clinical effectiveness of the PillCam ESO in screening GERD patients for suspected Barrett's esophagus to direct appropriate patients for endoscopic biopsy needs to be demonstrated by large-scale clinical trials published in the peer-reviewed medical literature.

Thank you for the opportunity to provide input to the California Technology Assessment Forum. If we can provide any additional information, please do not hesitate to contact Sheila Madhani, consultant to ASGE, at 202-833-0007 or sheila@marcassoc.com; Julie Cantor-Weinberg from ACG at 301-263-9000 or jcantorw@acg.gi.org; or Shovana Sloan from AGA at (301) 272-1601 or ssloan@gastro.org.

Sincerely



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