# AFS Letter to Insurers: Confocal Laser Endomicroscopy for Barrett's Diagnosis and Surveillance- 2025 Update

**Key Points-**

• Probe based Confocal Endomicroscopy (pCLE), available in the US as Cellvizio (Mauna Kea Technologies Inc.) has significantly greater sensitivity and specificity compared to Seattle protocol biopsies in the diagnosis of Barrett's esophagus and dysplasia detection.

• Broad payor coverage for pCLE is essential to ensure accurate diagnosis, treatment, and surveillance of patients with Barrett's esophagus, potentially improving patient outcomes and reducing costs.

**Introduction-**

Gastroesophageal reflux disease (GERD) affects nearly 15% of the US population and Westernized countries. The diagnosis of GERD is associated with a 10-15% risk of developing Barrett's esophagus (BE). Compared to the general population, patients with BE have a 30-50% increased risk of developing esophageal adenocarcinoma. Despite advances in medical therapy to suppress gastric acid exposure in the esophagus, the occurrence rates of esophageal adenocarcinoma as a result of GERD continues to be of great concern and has risen 600% since 1975. Barrett's esophagus is the number one risk factor for the development of esophageal adenocarcinoma. Intestinal metaplasia of the esophagus, or Barrett's esophagus, is the result of damage caused by GERD. Despite these alarming numbers regarding the rise of esophageal cancer, Barrett's esophagus continues to be an underdiagnosed and undertreated condition.

The development of BE occurs when normal squamous epithelium is replaced with specialized columnar epithelium with intestinal type goblet cells. This transformation to metaplastic columnar cells is in response to esophageal damage due to GERD. The presence of goblet cells defines BE and is considered a risk factor for cancer.

Current American Society of Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) guidelines recommend that tissue samples be obtained to confirm endoscopically suspected Barrett's esophagus for diagnosis and surveillance. The goal of diagnosis and surveillance is to identify pre-cancerous changes, called dysplasia, so that additional therapy can be provided to prevent progression to esophageal cancer. The Seattle Protocol for BE recommends four-quadrant random biopsies at 1-2-cm intervals (1-cm intervals if suspected high-grade intraepithelial neoplasia).[1] This random biopsy protocol can be time consuming, expensive, and prone to sampling error, as very little of the esophageal surface area is actually sampled.

Unfortunately, this "Gold Standard" of random 4-quadrant biopsies suffers from multiple problems. First, the Seattle protocol is often not strictly followed, leading to inadequate sampling by endoscopists. Second, the sampling error is significant, as forcep biopsies cover only a fraction of total surface area of concern. This is exacerbated with increased length of Barrett's Esophagus. Finally, there is considerable intra-observer variability among pathologists when diagnosing Barrett's esophagus and, in particular, dysplasia. This variability contributes to diagnostic uncertainty, often necessitating additional tests, biopsies, and increased costs.

Diagnosis of BE remains challenging. The AGA white paper addresses this issue by stating, "BE (specifically shorter disease) is often misdiagnosed during endoscopy. This misdiagnosis is often attributed to 1 of 2 reasons: (1) inability to differentiate columnar mucosa of the proximal stomach (cardia) from metaplastic epithelium in the distal esophagus or (2) lack of goblet cells in biopsies obtained from columnar lined epithelium in the esophagus." [1]

Probe-based Confocal Laser Endomicroscopy (pCLE) generates functional and dynamic cellular images, providing physicians with a microscopic view of tissue, in vivo in real time, and in a minimally invasive manner. This provides endoscopists with dynamic microscopic views of gastrointestinal mucosa, allowing for real-time diagnosis of intestinal metaplasia. It also allows a greater esophageal surface area to be examined as compared to the random tissue biopsy method. pCLE allows for directed tissue biopsies when clinically appropriate of specific high-risk areas of the esophageal mucosa. pCLE also provides real-time tissue diagnosis, aids in targeted sampling. Additionally, there is the option for treatment via endoscopic eradication therapy of highly suspicious areas without the need to wait for tissue biopsy results. Finally, this technology is versatile and has FDA indications for use in the esophagus, biliary/pancreatic tree, respiratory tract, small/large intestine, and the genitourinary system.

**Clinical Evidence-**

Multiple published studies provide evidence that the addition of pCLE and or endoscopic based confocal laser endomicroscopy (eCLE) (no longer commercially available) to standard endoscopic imaging techniques and biopsies is of high value to both patients and payors.

• pCLE significantly increases the diagnostic yield of Barrett's, dysplastic Barrett's, and esophageal cancer compared with Seattle protocol tissue biopsies. This has been repeated in multiples studies over many years. Early studies showed significantly increased sensitivity and specificity of pCLE in the detection of non-dysplastic Barrett's. Dunbar, Richardson[2,3] and others have consistently shown a 200% increase in diagnostic yield with endoscopic based CLE (eCLE) and pCLE Likewise, studies are consistent in showing the same superiority detecting dysplastic lesions in patients undergoing surveillance endoscopy for known BE. Sharma[4] showed a doubling in detection of dysplastic Barrett's with pCLE vs the gold standard in a prospective randomized trial. These results, and those of several other investigators, are summarized in a recent meta-analysis by DeMeester[5] and colleagues where they demonstrated the relative increase in neoplasia detection using pCLE compared with the Seattle protocol randomized biopsies was 243% (95% CI 122%-482%; I2 statistic = 0%). This consistency of the relative increase in diagnostic yield of pCLE stands in direct contradistinction to that of the traditional endoscopy and biopsy. This is especially true when considering the known discrepancies

between community and expert endoscopists when performing the gold standard 4-quadrant random biopsies.

• pCLE has been shown to be easy to learn and use. New technology, while potentially superior to an established 'gold-standard', must be easy to learn and incorporate among a wide range of endoscopists.  pCLE has been shown in numerous studies to be easy to perform with almost no learning curve.  Additionally, it shows high intra-observer agreement with a kappa as high as .86 vs the low kappa of pathologists with rates as low as .22 when it comes to the detection of low-grade dysplasia in Barrett's. Richardson[3], Dunbar[2], Wallace[6].

• pCLE potentially decreases the number of biopsies needed during endoscopic evaluation, based on early studies with eCLE. This observation in multiple trials has significant implications for patients in terms of potential for harm as well as for value-oriented organizations and payors. The costs associated with additional (especially low yield/ non-therapeutic) biopsies can be immense.  Decreased need for cold-forcep biopsies range in trials from 60-80%. Dunbar[2], Cantu[7].

• pCLE leads to more accurate and timely diagnosis. The ability to make diagnostic and therapeutic decisions in real-time is a distinct and unique advantage to pCLE over tissue biopsies.  This is especially true in detecting dysplastic Barrett's leading to earlier detection, less invasive and costly treatment, definitive treatment that can be rendered during a single endoscopic session and potentially decreasing the progression rates to invasive esophageal cancer.  The missed opportunity is summed up in the fact that up 25-33% of patients with even high-grade dysplasia and esophageal cancer are missed on the initial endoscopy.

Conclusion- All providers from primary care to foregut specialists are critical to reversing the exponential rise in esophageal cancer. This begins with properly identifying those patients at risk for Barrett's esophagus, accurately diagnosing and surveying them, and then ideally performing endoscopic treatment prior to progression to esophageal cancer.

To appropriately diagnose and treat patients there are multiple studies that are required to perform that comprehensive assessment. Key elements include a properly performed endoscopy, use of narrow band imaging, classifying the Prague Classification to characterize the columnar lined esophagus, accurately ruling in or out Barrett's esophagus and identification and treatment of high-risk lesions.

Cellvizio's® pCLE platform is an important adjunct for patients with Barrett's esophagus. pCLE also fills a therapeutic gap in that patients with dysplasia or non-invasive cancers can be potentially treated during a single  endoscopic session.  Clinicians and patients alike deserve access to Cellvizio® (pCLE) to obtain a comprehensive assessment of the extent of disease and to make real-time therapeutic treatment decisions. Employing pCLE has the additional advantage of being cost effective by potentially decreasing the number of low-yield biopsies. In addition to improving diagnostic yield, pCLE can also be used to map an area of Barrett's esophagus prior to treatment and evaluate completeness of therapy during follow-up endoscopy.

Foregut specialists and the available medical literature consistently question the 'gold-standard' for the diagnosis and treatment of Barrett's esophagus. Seattle protocol is characterized by poor compliance, lack of accuracy, and high cost. Accurate diagnosis of tissue in patients suffering from Barrett's esophagus is paramount in that medical, endoscopic, and surgical management choices are determined by it.

**References-**

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