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Confocal Laser Endomicroscopy (CLE)

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Coverage

Use of confocal laser endomicroscopy **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows in vivo microscopic imaging of the mucosal epithelium during endoscopy. The process uses light from a low-power laser to illuminate tissue and, subsequently, the same lens detects light reflected from the tissue through a pinhole. The term *confocal* refers to having both illumination and collection systems in the same focal plane. Light reflected and scattered at other geometric angles that are not reflected through the pinhole is excluded from detection, which dramatically increases the resolution of CLE images.

To date, 2 CLE systems have been cleared by the U.S. Food and Drug Administration (FDA). One is an endoscope-based system with a confocal probe incorporated onto the tip of a conventional endoscope. The other is a probe-based system; the probe is placed through the biopsy channel of a conventional endoscope. The depth of view is up to 250 µm with the endoscopic system and about 120 mm with the probe-based system. A limited area can be examined; no more than 700 µm in the endoscopic-based system and less with the probe-based system. As pointed out in systematic reviews, the limited viewing area emphasizes the need for careful conventional endoscopy to target areas for evaluation. Both CLE systems are optimized using a contrast agent. The most widely used agent is intravenous fluorescein, which is FDA-approved for ophthalmologic imaging of blood vessels when used with a laser scanning ophthalmoscope.

Unlike techniques such as chromoendoscopy which are primarily intended to improve the sensitivity of colonoscopy, CLE is unique in that it is designed to characterize the cellular structure of lesions immediately. Confocal laser endomicroscopy can thus potentially be used to make a diagnosis of polyp histology, particularly in association with screening or surveillance colonoscopy, which could allow for small hyperplastic lesions to be overlooked rather than removed and sent for histologic evaluation. Using CLE would reduce risks associated with biopsy and reduce the number of biopsies and histologic evaluations.

Another potential application of CLE technology is targeting areas for biopsy in individuals with Barrett esophagus undergoing surveillance endoscopy. CLE would be proposed as an alternative to the current standard approach, recommended by the American Gastroenterological Association, which is that individuals with Barrett esophagus who do not have dysplasia undergo endoscopic surveillance every 3 to 5 years. (1) The American Gastroenterological Association has further recommended that random 4-quadrant biopsies every 2 cm be taken with white-light endoscopy in individuals without known dysplasia.

Other potential uses of CLE under investigation include better diagnosis and differentiation of conditions such as gastric metaplasia, lung cancer, and bladder cancer.

As noted, limitations of CLE systems include a limited viewing area and depth of view. Another issue is the standardization of systems for classifying lesions viewed with CLE devices. Although there is currently no internationally accepted classification system for colorectal lesions, 2 systems have been used in a number of studies conducted in different countries. These include the Mainz criteria for endoscopy-based CLE devices and the Miami classification system for probe-based CLE devices. (2) Lesion classification systems are less developed for non-gastrointestinal lesions viewed by CLE devices (e.g., those in the lung or bladder). Another challenge is the learning curve for obtaining high-quality images and classifying lesions. Several studies, however, have found that the ability to acquire high-quality images and interpret them accurately can be learned relatively quickly; these studies were specific to colorectal applications of CLE. (3, 4)

Regulatory Status
Two CLE devices have been cleared for marketing by the FDA through the 510(k) process.

Cellvizio® (Mauna Kea Technologies) is a confocal microscopy device with a fiber optic probe (i.e., a probe-based CLE system). The device consists of a laser scanning unit, proprietary software, a flat-panel display, and miniaturized fiber optic probes. The F-600 system, cleared by the FDA in 2006, can be used with any standard endoscope with a working channel of at least 2.8 mm. According to the FDA, the device is intended for imaging the internal microstructure of tissues in the anatomic tract (gastrointestinal or respiratory) that are accessed by an endoscope. The 100 series version of the system (F400-v2) was cleared by the FDA in 2015 for imaging the internal microstructure of tissues and for visualization of body cavities, organs, and canals during endoscopic and laparoscopic surgery, and has been approved for use with several miniprobes for specific indications. Confocal Miniprobes™ approved for use with the Cellvizio 100 series that are particularly relevant to this review include the GastroFlex™ and ColoFlex™ (for imaging of anatomical tracts [i.e., gastrointestinal systems] accessed by an endoscope or endoscopic accessories), and the CranioFlex™ (for visualization within the central nervous system during cranial diagnostic and therapeutic procedures such as tumor biopsy and resection). In 2020, the Cellvizio 100 series system received extended FDA approval to allow for use of fluorescein sodium as a contrast agent for visualization of blood flow for all of its approved indications. Later in 2020, the Cellvizio I.V.E. system with Confocal Miniprobes was approved by the FDA as a newer version of the previously approved 100 series system, designed to reduce the system footprint and improve device usability. The 2 devices are otherwise equivalent and are approved for the same indications. In 2022, the Cellvizio 100 series system F800 model received extended FDA approval to allow for use of indocyanine green (ICG) and pafolacianine as contrast agents. Intravenous administration of ICG is used to perform fluorescence angiography and interstitial administration of ICG is used to perform fluorescence imaging and visualization of the lymphatic system. Intravenous administration of pafolacianine is used to perform fluorescence imaging of tissues. FDA product codes: GCJ, GWG, OWN.

Confocal Video Colonoscope (Pentax Medical) is an endoscopy-based CLE system. The EC-38 70 CILK system, cleared by the FDA in 2004, is used with a Pentax Video Processor and with a Pentax Confocal Laser System. According to the FDA, the device is intended to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract. FDA product code: GCJ/FDF (endoscope and accessories). This device is no longer commercially available from the manufacturer.

Table 1. Endomicroscopy Devices Cleared by the U.S. Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) Number	Indication
Cellvizio 100 Series Confocal Laser Imaging Systems and Their Confocal Miniprobes	Mauna Kea Technologies	02/22/2019	K183640	For use in endomicroscopy

Ec-3870cilk, Confocal Video Colonoscope	Pentax Medical Company	10/19/2004	K042741	For use in endomicroscopy

Rationale

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Colorectal Lesions

Clinical Context and Test Purpose

The purpose of confocal laser endomicroscopy (CLE) scanning as an adjunct to colonoscopy in individuals with suspected or known colorectal lesions is to provide a real-time alternative to histology and assist in targeting areas for biopsy.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with suspected or known colorectal lesions.

Interventions

The test being considered is CLE as an adjunct to colonoscopy.

Comparators

The following tools and practices are currently being used to make diagnostic decisions in individuals with suspected or known colorectal lesions: white-light colonoscopy alone or colonoscopy used with alternative adjunctive diagnostic aids.

Outcomes

The general outcomes of interest are: overall survival (OS), disease-specific survival, test validity, and resource utilization.

The timing of CLE would be during the disease confirmation process.

Study Selection Criteria

For the evaluation of the clinical validity of CLE as an adjunct to colonoscopy in individuals with

suspected or known colorectal lesions, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Several systematic reviews have compared the diagnostic accuracy of CLE with a reference standard. Su et al. (2013) reviewed studies on the efficacy of CLE for discriminating colorectal neoplasms from non-neoplasms. (5) To be included in the review, studies had to use histologic biopsy as the reference standard, and the pathologist and endoscopist had to be blinded to each other's findings. Selected studies also had to use a standardized CLE classification system. Patients had to be at increased risk of colorectal cancer (CC) due to personal or family history, have previously identified polyps, and/or have inflammatory bowel disease. Two reviewers independently assessed the quality of individual studies using the modified Quality Assessment of Diagnostic Accuracy Studies tool, and studies considered at high risk of bias were excluded from further consideration.

Fifteen studies (N=719 adults) were selected. All were single-center trials, and 2 were available only as abstracts. In all studies, suspicious lesions were first identified by conventional white-light endoscopy with or without chromoendoscopy and then further examined by CLE. Meta-analysis of the 15 studies found an overall sensitivity for CLE of 94% (95% confidence interval [CI], 88% to 97%) and a specificity of 95% (95% CI, 89% to 97%) compared with histology. Six studies included patients at increased risk of CC who were undergoing surveillance endoscopy; 5 studies included patients with colorectal polyps and 4 studies included patients with inflammatory bowel disease. In a predefined subgroup analysis by indication for screening, the pooled sensitivity and specificity for surveillance studies were 94% (95% CI, 90% to 97%) and 98% (95% CI, 97% to 99%), respectively. For patients presenting with colorectal polyps, the pooled sensitivity of CLE was 91% (95% CI, 87% to 94%) and the specificity was 85% (95% CI, 78% to 90%). For patients with inflammatory bowel disease, the pooled sensitivity was 83% (95% CI, 70% to 92%) and the specificity was 90% (95% CI, 87% to 93%). In other predefined subgroup analyses, the summary sensitivity and specificity were significantly higher ($p<.001$) in studies of endoscopy-based CLE (97% and 99%, respectively) than in studies of probe-based CLE (87% and 82%, respectively). In addition, the summary sensitivity and specificity were significantly higher ($p<.01$) with real-time CLE in which the macroscopic endoscopy findings were known (96% and 97%, respectively) than in blinded CLE in which recorded confocal images were subsequently analyzed without knowledge of macroscopic endoscopy findings (85% and

82%, respectively).

A systematic review by Dong et al. (2013) included studies that compared the diagnostic accuracy of CLE with conventional endoscopy. (6) Reviewers did not explicitly state that the reference standard was a histologic biopsy, but this was the implied reference standard. Six studies were included in a meta-analysis. All were prospective, and at least 5 included blinded interpretation of CLE findings (in 1 study, it was unclear whether the interpretation was blinded). In a pooled analysis of data from all 6 studies, the sensitivity was 81% (95% CI, 77% to 85%) and the specificity was 88% (95% CI, 85% to 90%). Reviewers also conducted a subgroup analysis by type of CLE used. When findings from the 2 studies on endoscopy-based CLE were pooled, the sensitivity was 82% (95% CI, 69% to 91%) and the specificity was 94% (95% CI, 91% to 96%). Two studies may not have been sufficient to obtain a reliable estimate of diagnostic accuracy. When findings from the 4 studies on probe-based endoscopy were pooled, the sensitivity was 81% (95% CI, 76% to 85%) and the specificity was 75% (95% CI, 69% to 81%).

A meta-analysis by Wanders et al. (2013) searched for studies that reported on the diagnostic accuracy of several new technologies used to differentiate between colorectal neoplasms and non-neoplasms. (7) To be selected, studies had to use the technology to differentiate between non-neoplastic and neoplastic lesions and to use histopathology as the reference standard. Blinding was not an inclusion criterion. Eleven eligible studies identified included an analysis of CLE. Meta-analysis yielded an estimated sensitivity of 93.3% (95% CI, 88.4% to 96.2%) and a specificity of 89.9% (95% CI, 81.8% to 94.6%). Meta-analysis limited to the 5 studies that used endoscopy-based CLE found a sensitivity of 94.8% (95% CI, 90.6% to 98.92%) and a specificity of 94.4% (95% CI, 90.7% to 99.2%). When findings of the 6 probe-based CLE studies were pooled, the sensitivity was 91.5% (95% CI, 86.0% to 97.0%) and specificity was 80.9% (95% CI, 69.4% to 92.4%).

Prospective and Retrospective Studies

A study by Xie et al. (2011) in China included 116 consecutive patients who had polyps found during CLE (1 patient was excluded from the analysis). (8) All patients had an indication for colonoscopy (19 were undergoing surveillance after polypectomy, 2 had a family history of CC, 3 had inflammatory bowel disease, 91 were seeking a diagnosis). All patients first underwent white-light colonoscopy. Endoscopy-based CLE was used on the first polyp identified during withdrawal of the endoscope (i.e., 1 polyp per patient was analyzed). Real-time diagnosis of the polyp was performed based on criteria used at the study center (adapted from the Mainz classification system). The polyps were biopsied or removed, and the histopathologic diagnosis was determined. Real-time CLE diagnosis correctly identified 109 (95%) of 115 adenomas or hyperplastic polyps. Four adenomas were misdiagnosed by CLE as hyperplastic polyps (2 were tubulous adenomas, 2 were tubulovillous adenomas), and 2 hyperplastic polyps were misdiagnosed as adenomas. The overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CLE diagnosis were 93.9% (95% CI, 85.4% to 97.6%), 95.9% (95% CI, 86.2% to 98.9%), 96.9% (95% CI, 89% to 99%), and 94.8% (95% CI, 89.1% to 97.6%), respectively. For polyps less than 10 mm in size, CLE diagnosis had a sensitivity of 90.3% and a specificity of 95.7%; for polyps 10 mm or larger, sensitivity was 97.1% and specificity was

100%.

Buchner et al. (2010) published findings on 75 patients who had a total of 119 polyps. (9) Patients were eligible for participation if they were undergoing surveillance or screening colonoscopy or undergoing evaluation of known or suspected polyps identified by other imaging modalities or endoscopic resection of larger flat colorectal neoplasia. White-light colonoscopy was used as the primary screening method. When a suspicious lesion was identified, it was evaluated by virtual chromoendoscopy and a probe-based CLE system. After the imaging techniques, the appropriate intervention (i.e., polypectomy, biopsy, endoscopic mucosal resection) was performed, and all resected specimens underwent histopathologic analysis by a pathologist blinded to CLE information. Confocal images of the 119 polyps were evaluated after all procedures were completed; the evaluator was blinded to the histology diagnosis and the endoscopic appearance of the lesion. Diagnosis of confocal images used modified Mainz criteria; polyps were classified as benign or neoplastic. According to histopathologic analysis, there were 38 hyperplastic polyps and 81 neoplastic lesions. The use of CLE correctly identified 74 of 81 neoplastic polyps (sensitivity, 91%; 95% CI, 83% to 96%). In addition, CLE correctly identified 29 of 38 hyperplastic polyps (specificity, 76%; 95% CI, 60% to 89%). In contrast, virtual chromoendoscopy correctly identified 62 neoplastic polyps (sensitivity, 77%; 95% CI, 66% to 85%) and 27 hyperplastic polyps (specificity, 71%; 95% CI, 54% to 85%).

Another study from the same academic medical center as Buchner et al. (2010) was published by Shadid et al. (2012). (10) The study compared 2 methods of analyzing CLE images: real-time diagnosis and blinded review of video images after endoscopy (known as "offline" diagnosis). The study included 74 patients with 154 colorectal lesions. Eligibility criteria were similar to the Buchner et al. (2010) study (previously discussed) -- selected patients were undergoing surveillance or screening colonoscopy. Patients had a white-light colonoscopy, and identified polyps were also evaluated with virtual chromoendoscopy and probe-based CLE. At the examination, an endoscopist made a real-time diagnosis based on CLE images. Based on that diagnosis, the patient underwent polypectomy, biopsy, or endoscopic mucosal resection, and histopathologic analysis was done on the specimens. Images from CLE were deidentified and reviewed offline by the same endoscopist at least 1 month later. In the second review, the endoscopist was blinded to the endoscopic and histopathologic diagnosis. Of the 154 polyps, 74 were found by histopathologic analysis to be non-neoplastic, and 80 were neoplastic (63 tubular adenomas, 12 tubulovillous adenomas, 3 mixed hyperplastic-adenoma polyps, 2 adenocarcinomas). Overall, there was no statistically significant difference in the diagnostic accuracy between real-time CLE diagnosis and blinded offline CLE diagnosis (i.e., CIs overlapped). The sensitivity, specificity, PPV, and NPV for real-time CLE diagnosis were 81%, 76%, 87%, and 79%, respectively. For offline diagnosis, these values were 88%, 77%, 81%, and 85%, respectively. For larger polyps, there was a nonsignificant trend in favor of better diagnostic accuracy with real-time compared with offline CLE. However, in the subgroup of 107 smaller polyps (<10 mm in size), the accuracy of real-time CLE was significantly less than offline CLE. For smaller polyps, the sensitivity, specificity, PPV, and NPV of real-time CLE were 71%, 83%, 78%, and 78%, respectively; for offline CLE, they were 86%, 78%, 76%, and 87%,

respectively.

A study by Hlavaty et al. (2011) included patients with ulcerative colitis or Crohn disease. (11) Thirty patients were examined with standard white-light colonoscopy, chromoendoscopy, and an endoscopy-based CLE system. Another 15 patients were examined only with standard colonoscopy. All lesions identified by white-light colonoscopy or chromoendoscopy were examined using CLE to identify neoplasia using the Mainz classification system. Suspicious lesions were biopsied, and random biopsies were taken from 4 quadrants every 10 cm per the standard surveillance colonoscopy protocol. All specimens underwent histologic analysis by a gastrointestinal pathologist blinded to a CLE diagnosis. Diagnostic accuracy of CLE was calculated for examinable lesions only. Compared with histologic diagnosis, the sensitivity of CLE for diagnosing low-grade and high-grade intraepithelial neoplasia was 100%, specificity was 98.4%, PPV was 66.7%, and NPV was 100%. However, whereas CLE was able to examine 28 (93%) of 30 flat lesions, it could examine only 40 (57%) of 70 protruding polyps. Moreover, 6 (60%) of 10 dysplastic lesions, including 3 of 5 low-grade and high-grade intraepithelial neoplasms, were not evaluable by CLE. It is also worth noting that the diagnostic accuracy of chromoendoscopy (see evidence review 2.01.84) is similar to that of CLE. The sensitivity, specificity, PPV, and NPV of chromoendoscopy were 100%, 97.9%, 75%, and 100%, respectively.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

In patients at average risk of CC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of CLE on the subsequent development of CC or on CC mortality.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

It is not clear that the diagnostic performance of this technology is sufficient to obviate the need for biopsy of identified polyp lesions. Thus, there is insufficient evidence to support a chain of evidence to demonstrate an improvement in net health outcome.

Section Summary: Colorectal Lesions

For individuals who have suspected or known colorectal lesions who receive CLE as an adjunct

to colonoscopy, the evidence includes multiple diagnostic accuracy studies. In 3 published systematic reviews, pooled estimates of the overall sensitivity of CLE ranged from 81% to 94%, and pooled estimates of the specificity ranged from 88% to 95%. It is uncertain whether the accuracy is sufficiently high to replace biopsy/polypectomy and histopathologic analysis. Moreover, issues remain concerning the use of this technology in clinical practice (e.g., the learning curve, interpretation of lesions).

Barrett Esophagus (BE)

Clinical Context and Test Purpose

The purpose of CLE scanning with targeted biopsy in individuals with BE who are undergoing surveillance is to provide a real-time alternative to histology and assist in targeting areas for biopsy.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with BE undergoing surveillance.

Interventions

The test being considered is CLE with targeted biopsy.

Comparators

The following tools and practices are currently being used to make diagnostic decisions in individuals with BE undergoing surveillance: standard endoscopy with random biopsy. In individuals with BE undergoing surveillance, standard endoscopy is followed by random biopsy, also known as the Seattle Protocol. The Seattle Protocol involves "random 4-quadrant biopsy sampling every 1 to 2 cm starting from the top of the gastric folds up to the most proximal extent of the BE". (12)

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and resource utilization.

For individuals with BE undergoing surveillance, the timing would be during the disease confirmation process and then every 3 months to 3 years, depending on whether dysplasia has been identified. (13)

Study Selection Criteria

For the evaluation of the clinical validity of CLE with targeted biopsy in individuals with BE undergoing surveillance, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.

- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

DeMeester et al. (2022) published a meta-analysis of prospective studies and RCTs evaluating the diagnostic accuracy of probe-based CLE as an adjunct to random four-quadrant biopsies in patients with BE. (14) A total of 9 studies (N=688) were included. Results for CLE were reported in comparison to histopathological results (highest grade diagnosis detected by standard white light endoscopy targeted or random four-quadrant biopsies or from resection histopathological analysis) as the diagnostic reference. The following results were obtained for CLE for the diagnosis of high-grade dysplasia (HGD) or esophageal adenocarcinoma: pooled sensitivity, 96% (95% CI, 65% to 100%); pooled specificity, 93% (95% CI, 71% to 99%); pooled PPV, 69% (95% CI, 49% to 84%); pooled NPV, 98% (95% CI, 93% to 100%). The relative increase in neoplasia detection using CLE compared with the Seattle protocol randomized biopsies was 243% (95% CI, 122% to 482%); the absolute increase was 5% (95% CI, 1% to 9%). Dysplasia prevalence with Seattle protocol randomized biopsies was 4% (95% CI, 1% to 11%), and with CLE was 9% (95% CI, 2% to 29%).

Xiong et al. (2016) published a meta-analysis of prospective studies evaluating the diagnostic accuracy of CLE in patients with BE, using histopathologic analysis as the criterion standard. (15) Studies were not required to compare CLE with standard 4-quadrant biopsy. Fourteen studies were included. In a pooled analysis including 7 studies (n=473) reporting a per-patient analysis, the sensitivity of CLE for detecting neoplasia was 89% (95% CI, 82% to 94%) and the specificity was 83% (95% CI, 78% to 86%). The pooled positive and negative likelihood ratios were 6.53 (95% CI, 3.12 to 13.4) and 0.17 (95% CI, 0.11 to 0.29), respectively. Reviewers did not report PPV or NPV. Moreover, they provided estimates of pretest probability to aid in the interpretation of the likelihood ratios (i.e., to evaluate a person's risk level before and after getting the test). Sensitivity and specificity were similar to those calculated in the Gupta systematic review (discussed below).

Gupta et al. (2014) published a systematic review and meta-analysis of prospective studies comparing the accuracy of CLE plus targeted biopsy with standard 4-quadrant biopsy in patients with BE. (16) Reviewers noted that, according to the Preservation and Incorporation of Valuable Endoscopic Innovation Initiative of the American Society for Gastrointestinal Endoscopy, in order to replace the standard Seattle protocol, an alternative approach would need to have a per-patient sensitivity of at least 90%, specificity of at least 80%, and NPV of at least 98% for detecting HGD or esophageal adenocarcinoma compared with the current protocol.

Eight studies published through May 2014 met inclusion criteria; 1 was a parallel-group RCT, and 1 was a randomized crossover study. The other 6 were single- or double-blind

nonrandomized comparative studies. Seven studies had data suitable for pooling on a per-lesion basis; together they included 345 patients and 3080 lesions. In a meta-analysis of the diagnosis of HGD or esophageal adenocarcinoma, the pooled sensitivity was 68% (95% CI, 64% to 73%), and pooled specificity was 88% (95% CI, 87% to 89%). Four studies were included in the per-patient meta-analysis. The pooled sensitivity and specificity were 86% (95% CI, 74% to 96%) and 83% (95% CI, 77% to 88%), respectively. Negative predictive value (calculated using the sensitivity, specificity, and overall prevalence) was 96%. Thus, according to the criteria in the Preservation and Incorporation of Valuable Endoscopic Innovation Initiative, the diagnostic accuracy of CLE in the studies evaluated was not sufficiently high for this technique to replace the standard Seattle protocol. Rates of HGD and esophageal adenocarcinoma were much higher in the studies included in the meta-analysis than is generally seen in clinical practice and therefore diagnostic accuracy results should be interpreted cautiously.

Randomized Controlled Trials

Vithayathil et al. (2022) conducted a randomized crossover trial of standard high-resolution white-light Seattle protocol endoscopy or autofluorescence imaging-guided probe-based CLE in patients referred for surveillance of nondysplastic BE or flat dysplasia at 2 high-volume tertiary centers in the United Kingdom. (17) A total of 154 patients were recruited, of whom 8 were excluded based on presence of clear macroscopic lesions consistent with BE-related neoplasia upon first endoscopy. An additional patient was excluded due to a protocol breach (use of chromoendoscopy) and 11 patients withdrew consent. A total of 134 patients completed both arms of the study, with crossover occurring after a 6- to 12-week interval. Endoscopists were blinded to the endoscopy and histology results of the pretrial endoscopy and other study arm. In the per-lesion analysis, optical diagnosis by CLE had a sensitivity and specificity for high-grade dysplasia (HGD)/intramucosal cancer (IMC) of 69.2% and 73.2%, respectively. In the per-patient analysis, there was no difference in the sensitivity of CLE for dysplasia compared with Seattle protocol for HGD/IMC (76.5% for both; p=1.00) or all grades of dysplasia (74.3% vs. 80.0%, respectively; p=.48). The specificity of CLE was 60.7% for HGD and 66.7% for all grades of dysplasia. Use of a 3-biomarker panel consisting of 1 or more of optical dysplasia on CLE, aberrant p53 on immunohistochemistry, and/or aneuploidy on flow cytometry was associated with a per-patient sensitivity and specificity of 94.1% and 49.6% for HGD and 91.4% and 56.6% for all grades of dysplasia, respectively. The authors concluded that CLE has similar diagnostic accuracy for dysplasia compared with standard Seattle protocol endoscopy. In addition, the use of molecular biomarkers can further improve diagnostic accuracy. Several study limitations were noted: 1) it cannot be excluded that prior biopsy sites may have appeared as irregularities on second endoscopy due to the crossover study design, 2) sensitivity for detecting dysplasia was inconsistent across endoscopists, and 3) results may not be generalizable to general practice centers.

The single RCT in a systematic review by Ypsilantis et al. (2015; discussed further in indication 3, gastrointestinal lesions) (18) was published by Wallace et al. (2012). (19) This multicenter trial included patients with BE who were undergoing ablation. After an initial attempt at ablation, patients were randomized to follow-up with high-definition white-light endoscopy or high-definition white-light endoscopy plus CLE. The primary outcome was the proportion of

optimally treated patients, defined as those with no evidence of disease at follow-up, and those with residual disease who were identified and treated. Trial enrollment was halted after an interim analysis showed no difference between groups and higher than expected residual BE in both arms. Among the 119 patients enrolled at the interim analysis, 15 (26%) of 57 in the high-definition white-light endoscopy group and 17 (27%) of 62 in the high-definition white-light endoscopy plus CLE group were optimally treated; the difference was not statistically significant. Moreover, other outcomes were similar in the 2 groups.

Canto et al. (2014) reported on a single-blind, multicenter trial conducted at academic centers with experienced endoscopists. (20) It included consecutive patients undergoing endoscopy for routine BE surveillance or for suspected or known neoplasia. Patients were randomized to high-definition white-light endoscopy with random biopsy (n=98) or white-light endoscopy with endoscopy-based CLE and targeted biopsy (n=94). In the white-light endoscopy-only group, 4-quadrant random biopsies were taken every 1 to 2 cm over the entire length of the BE for patients undergoing surveillance and every 1 cm for patients with suspected neoplasia. In the CLE group, biopsy specimens were obtained only when there was CLE evidence of neoplasia. Final pathologic diagnosis was the reference standard. A per-patient analysis of diagnostic accuracy for diagnosing BE-related neoplasia found a sensitivity of 40% with white-light endoscopy only and 95% with white-light endoscopy plus CLE. Specificity was 98% with white-light endoscopy only and 92% with white-light endoscopy plus CLE. When the analysis was done on a per-biopsy specimen basis and when CLE was added, sensitivity was substantially higher, and specificity was slightly lower. The median number of biopsies per patient was significantly higher in the white-light endoscopy group (4 biopsies) compared with the CLE group (2 biopsies; p<.001).

The investigators analyzed the number of cases in which CLE resulted in a different diagnosis. Thirty-two (34%) of 94 patients in the white-light plus CLE group had a correct change in dysplasia grade after CLE compared with initial endoscopic findings. Six (19%) of the 32 patients had lesions, and the remaining 26 did not. In 21 of the 26 patients without lesions, CLE changed the plan from biopsy to no biopsy. The remaining 62 (65%) of 94 patients in the white-light endoscopy plus CLE group had concordant diagnoses with both techniques. Because the trial was conducted at academic centers and used endoscopy-based CLE, findings may not be generalizable to other clinical settings or to probe-based CLE.

Sharma et al. (2011) published an international, multicenter RCT that included 122 consecutive patients presenting for surveillance of BE or endoscopic treatment of HGD or early carcinoma. (21) Patients were randomized to both standard white-light endoscopy and narrow-band imaging. Following these 2 examinations, done in a blinded fashion, the location of lesions was unblinded and, subsequently, all patients underwent probe-based CLE. All examinations involved a presumptive diagnosis of suspicious lesions. Also, in both groups, after all evaluations were performed, all suspicious lesions were biopsied, as well as random locations (4 quadrants every 2 cm). The histopathologic analysis was the reference standard. Twenty-one patients were excluded from the analysis. Of the remaining 101 patients, 66 (65%) were found on histopathologic analysis to have no dysplasia, 4 (4%) had low-grade dysplasia, 6 (6%) had

HGD, and 25 (25%) had early carcinoma. Sensitivity of CLE plus white-light endoscopy for detecting HGD or early carcinoma was 68.3% (95% CI, 60.0% to 76.7%), which was significantly higher than white-light endoscopy alone (34.2%; 95% CI, 25.7% to 42.7%; p=.002). However, specificity of CLE plus white-light endoscopy was significantly lower (87.8%; 95% CI, 85.5% to 90.1%) than white-light endoscopy alone (92.7%; 95% CI, 90.8% to 94.6%; p<.001). For white-light endoscopy alone, the PPV was 42.7% (95% CI, 32.8% to 52.6%) and NPV was 89.8% (95% CI, 87.7% to 92.0%). For white-light endoscopy with probe-based CLE, the PPV was 47.1% (95% CI, 39.7% to 54.5%) and NPV was 94.6% (95% CI, 92.9% to 96.2%). White-light endoscopy alone missed 79 (66%) of 120 areas with HGD or early carcinoma, and white-light endoscopy plus CLE missed 38 (32%) of 120 areas. On a per-patient basis, 31 patients were diagnosed with HGD or early carcinoma. White-light endoscopy alone failed to identify 4 of these patients (sensitivity, 87%), whereas white-light endoscopy plus CLE failed to identify 2 patients (sensitivity, 93.5%).

A single-center crossover RCT was published by Dunbar et al. (2009). (22) Forty-six patients with BE were enrolled, and 39 (95%) completed the study protocol. Of these, 23 were undergoing BE surveillance, and 16 had BE with suspected neoplasia. All patients received endoscopy-based CLE and standard endoscopy, in random order. One endoscopist performed all CLE procedures, and another endoscopist performed all standard endoscopy procedures; endoscopists were blinded to the finding of the other procedure. During the standard endoscopy procedure, biopsies were taken of any discrete lesions followed by 4-quadrant random biopsy (every 1 cm for suspected neoplasia, every 2 cm for BE surveillance). During the CLE procedure, only lesions suspicious of neoplasia were biopsied. Endoscopists interpreted CLE images using the Confocal Barrett's Classification system, developed in a previous research study. Histopathologic analysis was the reference standard. Among the 16 study completers with suspected high-risk dysplasia, there were significantly fewer biopsies per patient with CLE (mean, 9.8 biopsies per patient) than with standard endoscopy (mean, 23.9 biopsies per patient; p=.002). Although there were fewer biopsies, the mean number of biopsy specimens showing HGD or cancer was similar in the 2 groups (3.1 during CLE vs 3.7 during standard endoscopy). The diagnostic yield for neoplasia was 33.7% with CLE and 17.2% with standard endoscopy. None of the 23 patients undergoing BE for surveillance had HGD or cancer. The mean number of mucosal specimens obtained for patients in this group was 12.6 with white-light endoscopy and 1.7 with CLE (p<.001).

Prospective Studies

Richardson et al. (2019) conducted a prospective study at 8 centers in the United States to compare probe-based CLE to conventional histology using the Seattle Protocol (random 4-quadrant biopsy) to identify intestinal metaplasia among 172 patients undergoing screening or surveillance endoscopy for BE. (23) Endoscopists recruited for the study were early users of CLE with less than 2 years of experience and no formal pathology training. All patients underwent a standardized endoscopy with white light and narrow band imaging evaluation, identification of landmarks, and recording of columnar lined esophagus visualized according to the Prague classification. Patients then received fluorescein followed by optical biopsy; images were interpreted both in real time and immediately following the procedure. After CLE images were acquired, esophageal biopsies were taken via the Seattle Protocol. Endoscopists were able to

identify intestinal metaplasia among 99 patients (57.6%) using CLE compared to 46 patients (27%) using the Seattle Protocol (p<.0001). Dysplasia was identified in 6 patients using CLE compared to 2 patients using the Seattle Protocol (both of which were also identified via CLE). Confocal laser endomicroscopy also identified significantly more patients with intestinal metaplasia compared to the Seattle Protocol among those with visible columnar lined esophagus (75 vs. 31 patients, respectively; p<.0001), but not among those without columnar lined esophagus (24 vs. 15 patients; p=.067). Identification of intestinal metaplasia was not found to be significantly different when comparing CLE to expert review.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of CLE to distinguish BE without dysplasia from BE with low-grade dysplasia or HGD were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Pooled sensitivity, specificity, and NPV of available studies were not sufficiently high to replace the standard Seattle protocol, according to the criteria adopted by the American Society for Gastrointestinal Endoscopy.

Section Summary: Barrett Esophagus

For individuals who have BE who are undergoing surveillance and receive CLE with targeted biopsy, the evidence includes several RCTs and meta-analyses. Evidence from RCTs has suggested that CLE has similar or higher sensitivity than standard endoscopy for identifying areas of dysplasia. However, a 2014 meta-analysis found that the pooled sensitivity, specificity, and NPV of available studies were not sufficiently high to replace the standard surveillance protocol. In a 2022 meta-analysis, the absolute increase in neoplasia detection using CLE compared with the Seattle protocol randomized biopsies was 5%. Additionally, dysplasia prevalence was 4% with Seattle protocol randomized biopsies and 9% with CLE. National guidelines continue to recommend 4-quadrant random biopsies for patients with BE undergoing surveillance. One RCT, which compared high-definition white-light endoscopy with high-definition white-light endoscopy plus CLE, was stopped early because an interim analysis did not find a between-group difference in outcomes.

Adequacy of Endoscopic Treatment of Gastrointestinal Lesions

Clinical Context and Test Purpose

The purpose of CLE scanning in individuals with who have had endoscopic treatment of gastrointestinal lesions is to assess the adequacy of endoscopic treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with who have had endoscopic treatment of gastrointestinal lesions.

Interventions

The test being considered is CLE to assess the adequacy of endoscopic treatment.

Comparators

The following tools and practices are currently being used to make diagnostic decisions in individuals who have had endoscopic treatment of gastrointestinal lesions: standard endoscopy.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and resource utilization.

For individuals with gastrointestinal lesions following endoscopic treatment, the timing would be following endoscopic treatment.

Study Selection Criteria

For the evaluation of the clinical validity of CLE to assess the adequacy of endoscopic treatment in individuals with gastrointestinal lesions who have had endoscopic treatment, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Ypsilantis et al. (2015) published a systematic review that included retrospective and

prospective studies reporting the diagnostic accuracy of CLE for the detection of residual disease after endoscopic mucosal resection of gastrointestinal lesions. (18) After examining full-text articles, 3 studies (1 RCT, 2 prospective, nonrandomized comparative studies) met the eligibility criteria. Studies included patients with BE, gastric neoplasia, and colorectal neoplasia. There was significant heterogeneity among studies. In a per-lesion meta-analysis, pooled sensitivity of CLE for detecting neoplasia was 91% (95% CI, 83% to 96%) and pooled specificity was 69% (95% CI, 61% to 76%). Based on the small number of studies and heterogeneity among studies, reviewers concluded that the evidence on the utility of CLE in assessing the adequacy of endoscopic mucosal resection was weak.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of CLE to improve the treatment assessment of gastrointestinal lesions were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of CLE has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Adequacy of Endoscopic Treatment of Gastrointestinal Lesions

For individuals who have gastrointestinal lesions and have had endoscopic treatment who receive CLE to assess the adequacy of endoscopic treatment, the evidence includes a systematic review that includes a single RCT and 2 prospective, nonrandomized studies.

Other Potential Applications of CLE

Clinical Context and Test Purpose

The purpose of CLE scanning in individuals with suspicion of other conditions diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer) is to provide a real-time alternative to histology and assist in targeting areas for biopsy.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with suspicion of other conditions diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer).

Interventions
The test being considered is CLE.

Comparators
The following tools and practices are currently being used to make diagnostic decisions in individuals with suspicion of other conditions diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer): standard endoscopic and other indicated diagnostic procedures.

Outcomes
The general outcomes of interest are OS, disease-specific survival, test validity, and resource utilization.

Study Selection Criteria
For the evaluation of the clinical validity of CLE in individuals with suspicion of other conditions diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer), studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Diagnostic Accuracy Studies
Studies have evaluated CLE for diagnosing a variety of conditions, including lung cancer, (24-26) bladder cancer, (27-29) head and neck cancer, (30-32) esophageal cancer, (33, 34) atrophic gastritis, (35) gastric cancer, (36-41) pancreatic cysts, (42-47) breast surgery, (48) and biliary strictures. (49-52) These studies, mostly pilot feasibility studies and diagnostic accuracy studies, are insufficient to determine the accuracy of CLE and its potential role in clinical care for patients with these conditions.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary

testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of CLE in patients with suspicion of other conditions diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer) were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of CLE has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Other Potential Applications of Confocal Laser Endomicroscopy
For individuals who have a suspicion of a condition diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer) who receive CLE, the evidence mainly consists of a small number of diagnostic accuracy studies. There is limited evidence on the diagnostic accuracy of CLE for these other indications.

Summary of Evidence
For individuals who have suspected or known colorectal lesions who receive confocal laser endomicroscopy (CLE) as an adjunct to colonoscopy, the evidence includes multiple diagnostic accuracy studies. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, and resource utilization. In 3 published systematic reviews, pooled estimates of the overall sensitivity of CLE ranged from 81% to 94%, and pooled estimates of the specificity ranged from 88% to 95%. It is uncertain whether the accuracy is sufficiently high to replace biopsy/polypectomy and histopathologic analysis. Moreover, issues remain concerning the use of this technology in clinical practice (e.g., the learning curve, interpretation of lesions). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Barrett esophagus (BE) who are undergoing surveillance and receive CLE with targeted biopsy, the evidence includes several randomized-controlled trials (RCTs) and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. Evidence from RCTs has suggested that CLE has similar or higher sensitivity than standard endoscopy for identifying areas of dysplasia. However, a 2014 meta-analysis found that the pooled sensitivity, specificity, and negative predictive value (NPV) of available studies were not sufficiently high to replace the standard surveillance protocol. In a 2022 meta-analysis, the absolute increase in neoplasia detection using CLE compared with the Seattle

protocol randomized biopsies was 5%. Additionally, dysplasia prevalence was 4% with Seattle protocol randomized biopsies and 9% with CLE. National guidelines continue to recommend 4-quadrant random biopsies for patients with BE undergoing surveillance. One RCT, which compared high-definition white-light endoscopy with high-definition white-light endoscopy plus CLE, was stopped early because an interim analysis did not find a between-group difference in outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have gastrointestinal lesions and have had endoscopic treatment who receive CLE to assess the adequacy of endoscopic treatment, the evidence includes a systematic review that includes a single RCT and 2 prospective, nonrandomized studies. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a suspicion of a condition diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer) who receive CLE, the evidence mainly consists of a small number of diagnostic accuracy studies. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. There is limited evidence on the diagnostic accuracy of CLE for these other indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Gastroenterological Association (AGA)

In 2011, the AGA published a position statement on the management of BE. (1) The statement included the following recommendations on endoscopic surveillance of BE (See Table 2).

Table 2. Recommendations on Endoscopic Surveillance of Barrett Esophagus

Recommendation	LOR	QOE
"We [the guideline developers] suggest that endoscopic surveillance be performed in patients with Barrett's esophagus."	Weak	Moderate
"We [the guideline developers] suggest the following surveillance intervals: • No dysplasia: 3-5 years • Low-grade dysplasia: 6-12 months • High-grade dysplasia in the absence of eradication therapy: 3 months"	Weak	Low
"For patients with Barrett's esophagus who are undergoing surveillance, we [the guideline developers] recommend: • Endoscopic evaluation be performed using white-light endoscopy. • 4-quadrant biopsy specimens be taken every 2 cm. • Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist.	Strong (for all)	Moderate (for all)

• 4-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia."		
"We [the guideline developers] suggest against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett's esophagus at this time."	Weak	Low

LOR: level of recommendation; QOE: quality of evidence.

In 2016, the AGA published a clinical practice update expert review on the diagnosis and management of low-grade dysplasia in BE. (53) Regarding the use of other advanced endoscopic imaging techniques, the guideline stated that the use of confocal laser endomicroscopy "cannot be recommended in the routine clinical management" of patients undergoing surveillance.

In 2022, the AGA published a clinical practice update on new technology for surveillance and screening in BE. (54) The article makes the following best practice advice statements relevant to screening and surveillance for BE:

- "Screening and surveillance endoscopic examination should be performed using high-definition white light endoscopy and virtual chromoendoscopy, with endoscopists spending adequate time inspecting the Barrett's segment."
- "Advanced imaging technologies such as endomicroscopy may be used as adjunctive techniques to identify dysplasia."

While the article did summarize data in support of innovative screening technologies such as CLE, the panelists noted that: "the use of these techniques was not required for a high-quality exam and the data to date did not support its routine use." However, the panelists also noted that "these technologies were promising and carried potential benefits in select cases and currently might be best utilized in expert centers."

American Society for Gastrointestinal Endoscopy (ASGE)

The ASGE (2006; reaffirmed in 2011) published guidelines on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract. (55) Regarding the use of confocal endoscopy as an adjunct to white-light endoscopy, the guidelines stated that this technique is "still in development."

In 2019, the ASGE published a guideline on screening and surveillance of Barrett esophagus (BE) which recommends against routine use of CLE compared with white-light endoscopy with Seattle protocol biopsy sampling in patients with BE undergoing surveillance. (12) An older guideline from the Society (2012) on the role of endoscopy in BE and other premalignant conditions of the esophagus stated the following: "Adjuncts to white-light endoscopy used to improve the sensitivity for the detection of BE and dysplastic BE include chromoendoscopy, electrical enhanced imaging, magnification, and confocal endoscopy." (56)

In 2014, the ASGE published a technology status evaluation on CLE. (13) It concluded that CLE is an emerging technology with the potential to improve patient care. However, before it can be widely accepted, further studies are needed in the following areas:

1. "[T]he applicability and practicality of CLE, especially in community settings… Although current studies of CLE seem promising, these have primarily been in academic centers, and their generalizability in nonacademic practices is unknown."
2. The "learning curve of CLE image interpretation, use of CLE devices, and additional time needed to perform the procedure…."
3. "The clinical efficacy of the technology…. compared with other available advanced imaging technologies…."
4. "Improvements in CLE imaging and image interpretation…."

The ASGE published guidelines on the role of endoscopy in benign pancreatic disease in 2015 and stated that "confocal endomicroscopy is an emerging technology that may prove useful for the evaluation of indeterminate pancreatic strictures." (57) Similarly, in the ASGE's 2016 guidelines on the role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms, they acknowledged that CLE was an emerging technique for pancreatic lesion evaluation but made no formal recommendations regarding its use. (58)

U.S. Preventive Services Task Force Recommendations

The 2021 U.S. Preventive Services Task Force recommendations on colorectal cancer screening do not mention CLE. (59)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04154683	Diagnostic Performance of Optical Biopsy by Cellvizio® in Gynecological Surgery (GYNECOPTIC)	100	Jun 2025
NCT03492151	Confocal Laser Endomicroscopy as an Imaging Biomarker for the Diagnosis of Pancreatic Cystic Lesions (CLIMB)	500	Dec 2025
NCT05556525	Needle-Based Confocal Laser Endomicroscopy With Fluorescein and Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Lung Cancer in Patients With Peripheral Pulmonary Nodules	118	May 2025

NCT06289803	The Application of Probe Confocal Laser Endomicroscopy in Pancreatic Tumor Surgery	200	Jun 2025
NCT06079970	Bronchoscopy With and Without Needle-based Confocal Laser Endomicroscopy for Peripheral Lung Nodule Diagnosis: Protocol for a Multicenter Randomized Controlled Trial (CLEVER Trial)	208	Oct 2025
NCT06152783	Confocal Laser Microendoscopy (CellTouch) for the Diagnosis of Early Gastric Cancer: A Multicenter Clinical Study	578	Nov 2024
NCT06398448	Comparison of Probe-based Confocal Laser Endomicroscopy and Traditional Endoscopic Biopsies in the Diagnosis of Gastric Cancer and Precancerous Lesions: a Prospective Multicenter Comparative Study	366	Oct 2026

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	43206, 43252, 88375, 0397T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
07/15/2025	Document updated with literature review. Coverage unchanged. No new references added; some removed.
04/01/2025	Reviewed. No changes.
03/15/2024	Document updated with literature review. Coverage unchanged. No new references added.
03/15/2023	Document updated with literature review. Coverage unchanged. References 16-17, 29, 41, 46-47, 52, 57 and 65-66 added.
04/15/2022	Document updated with literature review. Coverage unchanged. References 12, 25-26, 29, 36-41, 44-45, and 48-50 added; some updated and others removed.
02/15/2021	Reviewed. No changes.
06/15/2020	Document updated with literature review. Coverage unchanged. References 13, 21, 34, 40 and 41 added.
05/15/2018	Document updated with literature review. Coverage unchanged. References 13, 29-30 added.
04/01/2017	Reviewed. No changes.
05/15/2016	Document updated with literature review. Coverage unchanged.
06/01/2015	Reviewed. No changes.
04/15/2014	Document updated with literature review. Title changed from Confocal Laser Endomicroscopy (CLE) (Optical Endomicroscopy) to Confocal Laser Endomicroscopy (CLE). No coverage changes.
01/01/2013	New medical document. Confocal laser endomicroscopy (CLE) (optical endomicroscopy) is considered experimental, investigational and unproven for all indications.