
Medical Policy



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***Current Policy Effective Date: 7/1/25**

(See policy history boxes for previous effective dates)

Title: Confocal Laser Endomicroscopy

Description/Background

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 is 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. One is an endoscope-based system in which a confocal probe is 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 μm 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 the 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 immediately characterize the cellular structure of lesions. CLE 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 left in place 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 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 not currently an internationally accepted classification system for colorectal lesions, 2 systems have been developed that have been used in a number of studies conducted in different countries. They are 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 potential issue is the learning curve for obtaining high-quality images and classifying lesions. Several recent studies, however, have found that the ability to acquire high-quality images and interpret them accurately can be learned relatively quickly; these studies were limited to colorectal applications of CLE.(3,4)

Regulatory Status

Two CLE devices, listed below, 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 documents, the device is intended for confocal laser imaging of the internal microstructure of tissues in the anatomical 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 of 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 mini probes 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-3S7OCILK 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 materials, 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 US Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	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

Medical Policy Statement

Confocal laser endomicroscopy is not an established procedure. Its safety and effectiveness have not been scientifically determined. Therefore, confocal laser endomicroscopy is experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

43206

43252

88375

0397T

**Established codes may be considered experimental/investigational for the purpose of this policy.

Rationale

Evidence reviews 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 review.

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 CLD 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 of studies 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. Individuals had to be at increased risk of colorectal cancer (CRC) due to personal or family history, have previously identified polyps, and/or have inflammatory bowel disease (IBD). 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 eligible for the systematic review. All were single-center trials and two 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 individuals at increased risk of CRC who were undergoing surveillance endoscopy; 5 studies included individuals with colorectal polyps and four studies included individuals with IBD. 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 individuals 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 individuals with IBD, 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 ($p<0.001$) 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 ($p<0.01$) 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 compared 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 one 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 four 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 diagnostic accuracy of studies on any 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, 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 individuals who had polyps found during CLE (one patient was excluded from the analysis).(8) All individuals had an indication for colonoscopy (19 were undergoing surveillance after polypectomy, 2 had a family history of CRC, three had IBD, 91 were seeking a diagnosis). All individuals first underwent white-light colonoscopy. Endoscopy-based CLE was used on the first polyp identified during withdrawal of the endoscope (i.e., one polyp per patient was analyzed). Intravenous fluorescein sodium was used. 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 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 (two were tubulous adenomas, two were tubulovillous adenomas) and two 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 <10 mm, CLE diagnosis had a sensitivity of 90.3% and a specificity of 95.7%; for polyps >10 mm, sensitivity was 97.1% and specificity was 100%.

Buchner et al (2010) published findings on 75 individuals who had a total of 119 polyps.(9) Individuals 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. Intravenous fluorescein sodium was administered after the first polyp was identified. After the imaging techniques, the appropriate intervention (i.e., polypectomy, biopsy, endoscopic mucosal resection [EMR]) 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 histology diagnosis and 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⁾ It 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 individuals with a total of 154 colorectal lesions. Eligibility criteria were similar to the Buchner et al (2010) study (previously discussed) selected individuals were undergoing surveillance or screening colonoscopy. Individuals had a white-light colonoscopy and identified polyps were also evaluated with virtual chromoendoscopy and probe-based CLE. Intravenous fluorescein sodium was administered after the first polyp was identified. 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. At 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., confidence intervals 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, 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 individuals with ulcerative colitis or Crohn disease.⁽¹¹⁾ Thirty individuals were examined with standard white-light colonoscopy, chromoendoscopy and an endoscopy-based CLE system. An additional 15 individuals 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 underwent biopsy and, additionally, random biopsies were taken from four quadrants every 10 cm per the standard surveillance colonoscopy protocol. All specimens underwent histologic analysis by a gastrointestinal pathologist who was blinded to CLE diagnosis. Diagnostic accuracy of CLE was calculated for examinable lesions only. Compared with histologic diagnosis, 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 (considered investigational) was similar to that of CLE. Sensitivity, specificity, PPV and NPV of chromoendoscopy was 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 individuals 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 individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

In individuals at average risk of CRC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of CLE on subsequent development of CRC or on CRC 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 indirect 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 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

Clinical Context and Test Purpose

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

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).

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 individuals 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 4-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 individuals with BE, using histopathologic analysis as the criterion standard.(15) Studies were not required to compare CLE to 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.

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 individuals 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 individuals 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 individuals referred for surveillance of nondysplastic BE or flat dysplasia at 2 high-volume tertiary centers in the United Kingdom.(17) A total of 154 individuals 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 individuals withdrew consent. A total of 134 individuals 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 individuals with BE who were undergoing ablation. After an initial attempt at ablation, individuals 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 individuals, 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 individuals 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 individuals undergoing endoscopy for routine BE surveillance or for suspected or known neoplasia. Individuals 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 individuals undergoing surveillance and every 1 cm for individuals 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 prebiopsy 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<0.001).

The investigators analyzed the number of cases in which CLE resulted in a different diagnosis. Thirty-two (34%) of 94 individuals 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 individuals had lesions, and the remaining 26 did not. In 21 of the 26 individuals without lesions, CLE changed the plan from biopsy to no biopsy. The remaining 62 (65%) of 94 individuals 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 individuals presenting for surveillance of BE or endoscopic treatment of HGD or early carcinoma.(21) Individuals 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 individuals 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 individuals were excluded from the analysis. Of the remaining 101 individuals, 66 (65%) were found on histopathologic analysis to have no dysplasia, 4 (4%) had LGD, 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%; $p=0.002$). 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%; $p<0.001$). 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 individuals were diagnosed with HGD or early carcinoma. White-light endoscopy alone failed to identify 4 of these individuals (sensitivity, 87%), whereas white-light endoscopy plus CLE failed to identify 2 individuals (sensitivity, 93.5%).

A single-center crossover RCT was published by Dunbar et al (2009).(22) Forty-six individuals 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 individuals 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; $p=0.002$). Although there were fewer biopsies, the mean number of biopsy specimens showing HGD, or cancer was similar in the two 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 individuals undergoing BE for surveillance had HGD or cancer. The mean number of mucosal specimens obtained for individuals in this group was 12.6 with white-light endoscopy and 1.7 with CLE ($p<0.001$).

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 individuals 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 individuals 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. Individuals 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 individuals (57.6%) using CLE compared to 46 individuals (27%) using the Seattle Protocol ($p<0.0001$). Dysplasia was identified in 6 individuals using CLE compared to 2 individuals using the Seattle Protocol (both of which were also identified via CLE). Confocal laser endomicroscopy also identified significantly more individuals with intestinal metaplasia compared to the Seattle Protocol among those with visible columnar lined esophagus (75 vs. 31 individuals, respectively; $p<0.0001$), but not among those without columnar lined esophagus (24 vs. 15 individuals; $p=0.067$). Identification of intestinal metaplasia was not found to be significantly different when comparing CLE to expert review.

Other

Literature where authors were found to favor the use of CLE for the detection of neoplasia in Barrett's Esophagus were found to contain non-randomized, single center studies, small sample sizes, inconsistent blinding, conflicts of interest, quoted outdated position statements, or didn't prove to be better than the gold standard.(60-62)

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 individuals 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 individuals 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 LGD 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 (BE)

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 individuals with BE undergoing surveillance. One single 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 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 review.

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).

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 EMR of gastrointestinal lesions.(18) After examining full-text articles, 3 studies (1 RCT, 2 prospective, nonrandomized comparative studies) met the eligibility criteria. Studies included individuals 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 individuals 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 individuals 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 review.

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).

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).

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 studies testing diagnostic accuracy, are insufficient to determine the accuracy of CLE and its potential role in clinical care for individuals 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 individuals 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 individuals 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 individuals 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 CLE as an adjunct to colonoscopy, the evidence includes multiple diagnostic accuracy studies. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. In 3 published systematic reviews, pooled estimates of 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 about the use of this technology in 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 who are undergoing surveillance and receive CLE with targeted biopsy, the evidence includes several randomized controlled trials (RCTs) and meta-analyses. The relevant outcomes are overall survival, 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 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 individuals with Barrett esophagus undergoing surveillance. One single 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 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 overall survival, disease-specific survival, test validity, and resource utilization. The evidence is insufficient to determine that the technology results in an improvement in the 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 includes a small number of diagnostic accuracy studies. The relevant outcomes are overall survival, 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.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Gastrointestinal Endoscopy

The American Society for Gastrointestinal Endoscopy (2006; reaffirmed in 2011) published guidelines on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.⁽⁵³⁾ 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 BE which recommends against routine use of CLE compared with white-light endoscopy with Seattle protocol biopsy sampling in individuals 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.”⁽⁵⁴⁾

In 2014, the ASGE published a technology status evaluation on confocal laser endomicroscopy.⁽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 ... 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.”⁽⁵⁵⁾ 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.(56)

American Gastroenterological Association

The American Gastroenterological Association (2011) published a position statement on the management of Barrett esophagus.(1) The statement included the following recommendations on endoscopic surveillance of Barrett esophagus (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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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. • 4-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia."	Strong (for all)	Moderate (for all)
"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.(57) 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 individuals undergoing surveillance.

In 2022, the AGA published a clinical practice update on new technology for surveillance and screening in BE.(58) The article makes the following best practice advice statement 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."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The 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 review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04154683	Diagnostic Performance of Optical Biopsy by Cellvizio® in Gynecological Surgery (GYNECOPTIC)	100	Jun 2023
NCT03492151	Confocal Laser Endomicroscopy as an IMaging Biomarker for the Diagnosis of Pancreatic Cystic Lesions (CLIMB)	500	Dec 2024
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 2024
NCT06289803	The Application of Probe Confocal Laser Endomicroscopy in Pancreatic Tumor Surgery	200	Jun 2025
NCT01034670	Advanced Gastrointestinal Endoscopic Imaging	500	Dec 2025
NCT06152783	Confocal Laser Microendoscopy (CellTouch) for the Diagnosis of Early Gastric Cancer: A Multicenter Clinical Study	578	Nov 2024
NCT06389448	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.

Government Regulations

National:

There is no National Coverage Determination on this topic. Medicare lists fees for procedure codes 43206, 43252, and 88375. Procedure code 0397T is contractor priced.

Local:

There is no Local Coverage Determination on this topic. The Wisconsin Physician Services Insurance Corporation, the contractor for Michigan does not list 0397T as a covered procedure in its local coverage determination addressing Category III Codes (L35490). Effective date: 4/27/23

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Endoscopic Radiofrequency Ablation or Cryoablation for Barrett’s Esophagus
- Virtual Colonoscopy/CT Colonography

References

1. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* Mar 2011;140(3):1084–1091. PMID 21376940
2. Salvatori F, Siciliano S, Maione F et al. Confocal Laser Endomicroscopy in the Study of Colonic Mucosa in IBD Patients: A Review. *Gastroenterol Res Pract* 2012; 2012:525098.
3. Neumann H, Vieth M, Atreya R et al. Prospective evaluation of the learning curve of confocal laser endomicroscopy in patients with IBD. *Histol Histopathol* 2011; 26(7):867-72.
4. Buchner AM, Gomez V, Heckman MG et al. The learning curve of in vivo probe-based confocal laser endomicroscopy for prediction of colorectal neoplasia. *Gastrointest Endosc* 2011; 73(3):556-60.
5. Su P, Liu Y, Lin S et al. Efficacy of confocal laser endomicroscopy for discriminating colorectal neoplasms from non-neoplasms: a systematic review and meta-analysis. *Colorectal Dis* 2012 [Epub ahead of print].
6. Dong YY, Li YQ, Yu YB, et al. Meta-analysis of confocal laser endomicroscopy for the detection of colorectal neoplasia. *Colorectal Dis*. Sep 2013;15(9):e488-495. PMID 23810105
7. Wanders LK, East JE, Uitentuis SE, et al. Diagnostic performance of narrowed spectrum endoscopy, autofluorescence imaging, and confocal laser endomicroscopy for optical diagnosis of colonic polyps: a meta-analysis. *Lancet Oncol*. Dec 2013;14(13):1337-1347. PMID 24239209
8. Xie XJ, Li CQ, Zuo XL et al. Differentiation of colonic polyps by confocal laser endomicroscopy. *Endoscopy* 2011; 43(2):87-93.
9. Buchner AM, Shahid MW, Heckman MG et al. Comparison of probe-based confocal laser endomicroscopy with virtual chromoendoscopy for classification of colon polyps. *Gastroenterology* 2010; 138(3):834-42.
10. Shahid MW, Buchner AM, Raimondo M et al. Accuracy of real-time vs. blinded offline diagnosis of neoplastic colorectal polyps using probe-based confocal laser endomicroscopy: a pilot study. *Endoscopy* 2012; 44(4):343-8.
11. Hlavaty T, Huorka M, Koller T et al. Colorectal cancer screening in patients with ulcerative and Crohn's colitis with use of colonoscopy, chromoendoscopy and confocal endomicroscopy. *Eur J Gastroenterol Hepatol* 2011; 23(8):680-9.
12. Qumseya B, Sultan S, Bain P, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. *Gastrointest Endosc*. Sep 2019; 90(3): 335-359.e2. PMID 31439127
13. Chauhan SS, Dayyeh BK, Bhat YM, et al. Confocal laser endomicroscopy. *Gastrointest Endosc*. Dec 2014; 80(6): 928-38. PMID 25442092
14. DeMeester S, Wang K, Ayub K, et al. High-definition probe-based confocal laser endomicroscopy review and meta-analysis for neoplasia detection in Barrett's esophagus. *Techniques and Innovations in Gastrointestinal Endoscopy*. 2022;24(4):340-350. <https://doi.org/10.1016/j.tige.2022.06.001>.
15. Xiong YQ, Ma SJ, Zhou JH, et al. A meta-analysis of confocal laser endomicroscopy for the detection of neoplasia in patients with Barrett's esophagus. *J Gastroenterol Hepatol*. Jun 2016;31(6):1102-1110. PMID 26676646

16. Gupta A, Attar BM, Koduru P, et al. Utility of confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett's esophagus: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. Apr 2014;26(4):369-377. PMID 24535597
17. Vithayathil M, Modolell I, Ortiz-Fernandez-Sordo J, et al. Image-Enhanced Endoscopy and Molecular Biomarkers vs Seattle Protocol to Diagnose Dysplasia in Barrett's Esophagus. *Clin Gastroenterol Hepatol*. Feb 17 2022. PMID 35183768
18. Ypsilantis E, Pissas D, Papagrigroriadis S, et al. Use of Confocal Laser Endomicroscopy to Assess the Adequacy of Endoscopic Treatment of Gastrointestinal Neoplasia: A Systematic Review and Meta-Analysis. *Surg Laparosc Endosc Percutan Tech*. Jun 6 2014. PMID 24910941
19. Wallace MB, Crook JE, Saunders M, et al. Multicenter, randomized, controlled trial of confocal laser endomicroscopy assessment of residual metaplasia after mucosal ablation or resection of GI neoplasia in Barrett's esophagus. *Gastrointest Endosc*. Sep 2012;76(3):539-547 e531. PMID 22749368
20. Canto MI, Anandasabapathy S, Brugge W, et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). *Gastrointest Endosc*. Nov 9, 2013. PMID 24219822
21. Sharma P, Meining AR, Coron E, et al. Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc*. Sep 2011;74(3):465-472. PMID 21741642
22. Dunbar KB, Okolo P, 3rd, Montgomery E, et al. Confocal laser endomicroscopy in Barrett's esophagus and endoscopically inapparent Barrett's neoplasia: a prospective, randomized, double-blind, controlled, crossover trial. *Gastrointest Endosc*. Oct 2009;70(4):645-654. PMID 19559419
23. Richardson C, Colavita P, Dunst C, et al. Real-time diagnosis of Barrett's esophagus: a prospective, multicenter study comparing confocal laser endomicroscopy with conventional histology for the identification of intestinal metaplasia in new users. *Surg Endosc*. May 2019; 33(5): 1585-1591. PMID 30203202
24. Sorokina A, Danilevskaya O, Averyanov A, et al. Comparative study of ex vivo probe-based confocal laser endomicroscopy and light microscopy in lung cancer diagnostics. *Respirology*. Aug 2014;19(6):907-913. PMID 24909555
25. Wellikoff AS, Holladay RC, Downie GH, et al. Comparison of in vivo probe-based confocal laser endomicroscopy with histopathology in lung cancer: A move toward optical biopsy. *Respirology*. Aug 2015;20(6):967-974.
26. Fuchs FS, Zirlik S, Hildner K et al. Confocal laser endomicroscopy for diagnosing lung cancer in vivo. *Eur Resp J* 2012 [Epub ahead of print].
27. Wu J, Wang YC, Luo WJ, et al. Diagnostic Performance of Confocal Laser Endomicroscopy for the Detection of Bladder Cancer: Systematic Review and Meta-Analysis. *Urol Int*. 2020; 104(7-8): 523-532. PMID 32554957
28. Beji S, Wrist Lam G, Ostergren PB, et al. Diagnostic value of probe-based confocal laser endomicroscopy versus conventional endoscopic biopsies of non-muscle invasive bladder tumors: a pilot study. *Scand J Urol*. Feb 2021;55(1): 36-40. PMID 33153363
29. Liem EIML, Freund JE, Savci-Heijink CD, et al. Validation of Confocal Laser Endomicroscopy Features of Bladder Cancer: The Next Step Towards Real-time Histologic Grading. *Eur Urol Focus*. Jan 15 2020;6(1): 81-87. PMID 30033066
30. Nathan CA, Kaskas NM, Ma X, et al. Confocal Laser Endomicroscopy in the Detection of Head and Neck Precancerous Lesions. *Otolaryngol Head Neck Surg*. Apr 3 2014;151(1):73-80. PMID 24699456

31. Moore C, Mehta V, Ma X, et al. Interobserver agreement of confocal laser endomicroscopy for detection of head and neck neoplasia. *Laryngoscope*. Sep 15, 2015
32. Dittberner A, Ziadat R, Hoffmann F, et al. Fluorescein-Guided Panendoscopy for Head and Neck Cancer Using Handheld Probe-Based Confocal Laser Endomicroscopy: A Pilot Study. *Front Oncol*. 2021; 11: 671880. PMID 34195078
33. Liu J, Li M, Li Z, et al. Learning curve and interobserver agreement of confocal laser endomicroscopy for detecting precancerous or early-stage esophageal squamous cancer. *PLoS One*. 2014;9(6):e99089. PMID 24897112
34. Guo J, Li CQ, Li M, et al. Diagnostic value of probe-based confocal laser endomicroscopy and high-definition virtual chromoendoscopy in early esophageal squamous neoplasia. *Gastrointest Endosc*. Jun 2015;81(6):1346-1354.
35. Liu T, Zheng H, Gong W, et al. The accuracy of confocal laser endomicroscopy, narrow band imaging, and chromoendoscopy for the detection of atrophic gastritis. *J Clin Gastroenterol*. May-Jun 2015;49(5):379-386. PMID25485568
36. Park CH, Kim H, Jo JH, et al. Role of probe-based confocal laser endomicroscopy-targeted biopsy in the molecular and histopathological study of gastric cancer. *J Gastroenterol Hepatol*. Jan 2019; 34(1): 84-91. PMID 30221400
37. He XK, Liu D, Sun LM. Diagnostic performance of confocal laser endomicroscopy for optical diagnosis of gastric intestinal metaplasia: a meta-analysis. *BMC Gastroenterol*. Sep 05, 2016;16:109. PMID 27596838
38. Qian W, Bai T, Wang H, et al. Meta-analysis of confocal laser endomicroscopy for the diagnosis of gastric neoplasia and adenocarcinoma. *J Dig Dis*. Jun 2016;17(6):366-376. PMID 27129127
39. Schueler SA, Gamble LA, Curtin BF, et al. Evaluation of confocal laser endomicroscopy for detection of occult gastric carcinoma in CDH1 variant carriers. *J Gastrointest Oncol*. Apr 2021; 12(2): 216-225. PMID 34012620
40. Kollar M, Krajciova J, Prefertusova L, et al. Probe-based confocal laser endomicroscopy versus biopsies in the diagnostics of oesophageal and gastric lesions: A prospective, pathologist-blinded study. *United European Gastroenterol J*. May 2020; 8(4): 436-443. PMID 32213027
41. Canakis A, Deliwala SS, Kadiyala J, et al. The diagnostic performance of probe-based confocal laser endomicroscopy in the detection of gastric cancer: a systematic review and meta-analysis. *Ann Gastroenterol*. Sep-Oct 2022; 35(5): 496-502. PMID 36061161
42. Facciorusso A, Buccino VR, Sacco R. Needle-based confocal laser endomicroscopy-targeted biopsy in the molecular and in pancreatic cysts: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2018. Sep 2020; 32(9): 1084-1090. PMID 32282543
43. Krishna SG, Hart PA, Malli A, et al. Endoscopic Ultrasound-Guided Confocal Laser Endomicroscopy Increases Accuracy of Differentiation of Pancreatic Cystic Lesions. *Clin Gastroenterol Hepatol*. Feb 2020; 18;34(1).(2): 432-440.e6. PMID 31220640
44. Hao S, Ding W, Jin Y, et al. Appraisal of EUS-guided needle-based confocal laser endomicroscopy in the diagnosis of pancreatic lesions: A single Chinese center experience. *Endosc Ultrasound*. May-Jun 2020; 9(3): 180-186. PMID 32584313
45. Nakaoka K, Hashimoto S, Kawabe N, et al. Probe-based confocal laser endomicroscopy for the diagnosis of pancreatic ductal structures. *J Gastroenterol Hepatol*. Jan 2021; 36(1): 118-124. PMID 32433791
46. Kovacevic B, Antonelli G, Klausen P, et al. EUS-guided biopsy versus confocal laser endomicroscopy inpatients with pancreatic cystic lesions: A systematic review and meta-analysis. *Endosc Ultrasound*. Jul-Aug 2021; 10(4): 270-279. PMID 34290168

47. Konjeti VR, McCarty TR, Rustagi T. Needle-based Confocal Laser Endomicroscopy (nCLE) for Evaluation of Pancreatic Cystic Lesions: A Systematic Review and Meta-analysis. *J Clin Gastroenterol.* Jan 01 2022; 56(1): 72-80. PMID 33252557
48. De Palma GD, Esposito D, Luglio G, et al. Confocal laser endomicroscopy in breast surgery: a pilot study. *BMC Cancer.* 2015;15:252. PMID 25885686
49. Slivka A, Gan I, Jamidar P, et al. Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary strictures: results of a prospective multicenter international study. *Gastrointest Endosc.* Feb 2015;81(2):282-290. PMID 25616752
50. Martinek J, Kollar M, Krajciová J, et al. Confocal laser endomicroscopy in diagnosing indeterminate biliary strictures and pancreatic lesions a prospective pilot study. *Rozhl Chir.* 2020; 99(6): 258-265. PMID 32736480
51. Han S, Kahaleh M, Sharaiha RZ, et al. Probe-based confocal laser endomicroscopy in the evaluation of dominant strictures in patients with primary sclerosing cholangitis: results of a U.S. multicenter prospective trial. *Gastrointest Endosc.* Sep 2021; 94(3): 569-576.e1. PMID 33798541
52. Mi J, Han X, Wang R, et al. Diagnostic accuracy of probe-based confocal laser endomicroscopy and tissue sampling by endoscopic retrograde cholangiopancreatography in indeterminate biliary strictures: a meta-analysis. *Sci Rep.* May 04 2022; 12(1): 7257. PMID 35508585
53. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc.* Apr 2006;63(4):570-580. PMID 16564854
54. Evans JA, Early DS, Fukami N et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest. Endosc.*, 2012 Nov 21;76(6). PMID 23164510.
55. Chandrasekhara V, Chathadi KV, Acosta RD, et al. The role of endoscopy in benign pancreatic disease. *Gastrointest Endosc.* Aug 2015; 82(2): 203-14. PMID 26077456
56. Muthusamy VR, Chandrasekhara V, Acosta RD, et al. The role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms. *Gastrointest Endosc.* Jul 2016; 84(1): 1-9. PMID 27206409
57. Wani S, Rubenstein JH, Vieth M, et al. Diagnosis and Management of Low-Grade Dysplasia in Barrett's Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association. *Gastroenterology.* Nov 2016; 151(5): 822-835. PMID 27702561
58. Muthusamy, V.R., Wani, S., Gyawali, C.P., et al. AGA Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review. *Clinical Gastroenterology and Hepatology* 2022;20:2696–2706. PMID 35788412
59. Davidson KW, Barry MJ, Mangione CM, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* May 18 2021; 325(19): 1965-1977. PMID 34003218
60. DeMeester, S., Samarasena, J., et al. High definition probe-based confocal laser endomicroscopy review and meta-analysis for neoplasia detection in Barrett's esophagus. *Techniques and Innovations in Gastrointestinal Endoscopy.* 2022. <https://doi.org/10.1016/j.tige.2022.06.001>.
61. Richardson, C., Colavita, P., Dunst, C., et al. Real-time diagnosis of Barrett's esophagus: a prospective, multicenter study comparing confocal laser endomicroscopy with conventional histology for the identification of intestinal metaplasia in new users. (2019). *Surgical endoscopy*, 33(5), 1585–1591. <https://doi.org/10.1007/s00464-018-6420-9>

62. Al-Mansour M, et al. SAGES TAVAC safety and efficacy analysis confocal laser endomicroscopy. Surg Endosc. 2020 May;35(5):2091-2103.
<https://doi.org/10.1007/s00464-020-07607-3>.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/16/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/14	12/10/13	1/6/14	Joint policy established
5/1/15	2/17/15	2/27/15	Routine maintenance Added procedure codes 43206 and 43252 Updated references and rationale
7/1/16	4/19/16	4/19/16	Routine maintenance Added procedure code 0397T References and rationale updated
3/1/17	12/13/16	12/13/16	Routine maintenance Added ASGS position statement References and rationale updated
3/1/18	12/12/17	12/12/17	Routine maintenance
3/1/19	12/11/19	12/11/19	Routine maintenance
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Updated rationale; added references 5, 6, 22, 26, 34, 37-39 and 44. No change in policy status.
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (slp) Vendor managed: N/A
7/1/24	4/16/24		Routine maintenance (slp) Vendor managed: N/A
7/1/25	4/15/25		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 2nd Qtr. 2026

**BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CONFOCAL LASER ENDOMICROSCOPY**

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.