Confocal Laser Endomicroscopy

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Based on review of available data, the Company considers the use of confocal laser endomicroscopy (CLE) to be **investigational.***

Background/Overview

Confocal laser endomicroscopy, also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows in vivo microscopic imaging of the mucosal epithelium during endoscopy. The process involves using 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 special resolution of CLE images.

To date, 2 types of CLE systems have been cleared by Food and Drug Administration (FDA). One is an endoscope-based system in which a confocal probe is incorporated onto the tip of a conventional endoscope. The other is a probebased 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 review articles, 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. This 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 patients with Barrett esophagus (BE) undergoing surveillance endoscopy. This is an alternative to the current standard approach recommended by the American Gastroenterological Association (AGA) which is that patients with BE who do not have dysplasia undergo endoscopic surveillance every 3 to 5 years. AGA further recommends that random 4-quadrant biopsies every 2 cm be taken with white-light endoscopy in patients 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 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. These are the Mainz criteria for endoscopy-based CLE devices and the Miami classification system for probe-based CLE devices. Lesion classification systems are less developed for nongastrointestinal lesions viewed by CLE devices, eg, 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 specific to colorectal applications of CLE.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Two CLE devices have been cleared for marketing by FDA through the 510(k) process.
Cellvizio®‡ (Mauna Kea Technologies, Paris, France) is a confocal microscopy with a fiber optic probe (ie, 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 FDA in 2006, can be used with any standard endoscope with a working channel of at least 2.8 mm. According to FDA, the device is intended for confocal laser 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 was cleared by FDA in 2015 for imaging the internal microstructure of tissues and for visualization of body cavities organs and canals during endoscopic and laparoscopic surgery. FDA product code: GCJ.

Confocal Video Colonoscope (Pentax Medical, Montvale, NJ) is an endoscopy-based CLE system. The EC-3S7OCILK system, cleared by FDA in 2004, is used with a Pentax Video Processor and with a Pentax Confocal Laser System. According to FDA, the device is intended to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract. FDA product code: GCJ/KOG (endoscope and accessories).

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes). The following is a summary of the key literature to date.

CONFOCAL LASER ENDOMICROSCOPY

Clinical Context and Test Purpose

The purposes of CLE scanning in patients with suspected or known colorectal lesions; BE who are undergoing surveillance; gastrointestinal lesions following endoscopic treatment; or suspected other conditions diagnosed by identification and biopsy of lesions (eg, lung, bladder, head and neck, esophageal, or gastric cancers) are to provide a real-time alternative to histology and assist in targeting areas for biopsy.

The question addressed in this evidence review is: Does the use of CLE improve the net health outcome in individuals with suspected or known colorectal lesions, BE who are undergoing surveillance, gastrointestinal lesions who have had endoscopic treatment, or suspected other conditions (eg, lung, bladder, head and neck, esophageal, or gastric cancers)?

The following PICOTS were used to select literature to inform this review.

Patients

The populations of interest include patients with suspected or known colorectal lesions; BE undergoing surveillance; gastrointestinal lesions who have had endoscopic treatment; and suspected other conditions diagnosed by identification and biopsy of lesions.

Interventions

The intervention of interest is CLE.

Comparators

The comparators of interest for each indication include:

- For suspected colorectal lesions: white-light colonoscopy alone or alternative adjunctive diagnostic aids
- For BE undergoing surveillance: standard endoscopy with random biopsy
- For gastrointestinal lesions following endoscopic treatment: standard endoscopy (white-light endoscopy)
- For other condition diagnosed by identification and biopsy of lesions: standard diagnostic procedures

Outcomes
For patients with suspected colorectal lesions, the outcome of interest is confirmed diagnosis. With a confirmed diagnosis, appropriate treatment options can be pursued.

For patients with BE undergoing surveillance, the outcome of interest is a reduction in the number of biopsies without compromising diagnostic accuracy.

For patients with gastrointestinal lesions following endoscopic treatment, the outcome of interest is determining whether residual disease is present following the endoscopic treatment.

For patients with other conditions diagnosed by identification and biopsy of lesions, the outcome of interest is a diagnosis confirmation to inform clinical management decisions.

Timing
For patients with suspected colorectal lesions, BE, and other conditions, the timing of CLE would be during the disease confirmation process. For patients with gastrointestinal lesions following endoscopic treatment, the timing would be following the endoscopic treatment.

Setting
The setting is a facility equipped with CLE.

Colorectal Lesions

Clinical Validity

Systematic Reviews
Several systematic reviews of studies have compared the diagnostic accuracy of CLE with a reference standard. In 2013, Su et al reviewed studies on the efficacy of CLE for discriminating colorectal neoplasms from non-neoplasms. 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 used a standardized CLE classification system. Patients 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 (total 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 patients at increased risk of CRC who were undergoing surveillance endoscopy; 5 studies included patients with colorectal polyps and 4 studies included patients 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 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 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).

Another 2013 systematic review by Dong et al included studies that compared the diagnostic accuracy of CLE with conventional endoscopy. Reviewers did not explicitly state that the reference standard was histologic biopsy, but this was the implied reference standard. Six studies were included in a meta-analysis. All were prospective, and at least five included blinded interpretation of CLE findings (in 1 study, it was unclear whether 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 2013 meta-analysis by Wanders et al searched for studies that reported the diagnostic accuracy of several new technologies used to differentiate between colorectal neoplasms and non-neoplasms. 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%).

Cohort Studies

A 2011 study by Xie et al in China included 116 consecutive patients who had polyps found during CLE (1 patient was excluded from the analysis). All patients had an indication for colonoscopy (19 were undergoing surveillance after polypectomy, 2 had a family history of CRC, 3 had IBD, 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 (ie, 1 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 a 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 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%.

In 2010, Buchner et al published findings on 75 patients who had a total of 119 polyps. 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. Intravenous fluorescein sodium was administered after the first polyp was identified. After the imaging techniques, the appropriate intervention (ie, 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 199 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. 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 was published in 2012 by Shadid et al. 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 study (previously discussed)—selected patients were undergoing surveillance or screening colonoscopy. Patients had 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 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. CLE images 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 (ie, 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 2011 study by Hlavaty et al included patients with ulcerative colitis or Crohn disease. 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 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 was similar to that of CLE. The sensitivity, specificity, PPV, and NPV of chromoendoscopy were 100%, 97.9%, 75%, and 100%, respectively.

Clinical Utility

In patients at average risk of CRC, no randomized controlled trials (RCTs) or nonrandomized comparative studies were identified that evaluated the impact of CLE on subsequent development of CRC or on CRC mortality. In addition, 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

Multiple studies have compared the accuracy of CLE with the histopathology for diagnosing colorectal lesions. 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%. Although the reported diagnostic accuracy tended to be relatively high, it is unclear whether the accuracy is high enough to replace biopsy/polypectomy and histologic analysis. Moreover, there are no controlled studies on the impact of using CLE on CRC incidence or mortality, and the available evidence is insufficient to support a chain of evidence.

Barrett Esophagus

This section addresses whether CLE can distinguish BE without dysplasia from BE with low- (LGD) and high-grade dysplasia (HGD) and/or lead to fewer biopsies of benign tissue compared with surveillance with random biopsies. The ideal study to answer this question would include an unselected clinical population of patients with BE presenting for surveillance and would randomized patients to CLE with targeted biopsy or a standard biopsy protocol without CLE. Relevant outcomes include the diagnostic accuracy for detecting dysplasia, the detection rate for dysplasia, and the number of biopsies.

Systematic Reviews

In 2014, Gupta et al published a systematic review and meta-analysis of prospective studies comparing the accuracy of CLE with targeted biopsy to standard 4-quadrant biopsy in patients with BE. Reviewers noted that, according to the Preservation and Incorporation of Valuable Endoscopic Innovation Initiative of the American Society of 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; one was a parallel-group RCT, and one was a randomized crossover study. The other six 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 adenocarcinom, 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. NPV (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 published to date is not sufficiently high for this technique to replace the standard Seattle protocol. 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.

In 2016, Xiong et al published a meta-analysis of prospective studies evaluating the diagnostic accuracy of CLE in patients with BE, using histopathologic analysis as the criterion standard. Studies were not required to compare CLE with standard 4-quadrant biopsy. Fourteen studies were included. In a pooled analysis 7 studies (n=473 patients) 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 (ie, 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 earlier).

Randomized Controlled Trials
In 2011, Sharma et al published an international, multicenter RCT that included 122 consecutive patients presenting for surveillance of BE or endoscopic treatment of HGD or early carcinoma. 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 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, 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, 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%) 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 in 2009 by Dunbar et al. 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=0.002). 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<0.001).

Another RCT was published in 2014 by Canto et al. This single-blind, multicenter trial was conducted at academic centers with experienced endoscopists. 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 (n=4) compared with the CLE group (n=2; p<0.001).

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.

Section Summary: Barrett Esophagus

Several RCTs and nonrandomized comparative studies evaluating CLE for detecting dysplasia and neoplasia in patients with BE have been published. A 2014 meta-analysis found that the pooled sensitivity, specificity, and NPV of available studies were not sufficiently high to replace the standard Seattle protocol, according to criteria adopted by the Initiative of the American Society of Gastrointestinal Endoscopy. There are limited data comparing standard protocols using random biopsies with protocols using CLE and targeted biopsies; therefore, data are inconclusive on the potential for CLE to reduce the number of biopsies in patients with BE undergoing surveillance without compromising diagnostic accuracy. Moreover, studies do not appear to have used a consistent approach to classifying lesions as dysplastic using CLE.

Adequacy of Endoscopic Treatment of Gastrointestinal Lesions
This section addresses whether the use of CLE improves the detection of residual disease compared with conventional techniques (ie, white-light endoscopy). In 2015, Ypsilantis et al 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. 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 usefulness of CLE in assessing the adequacy of endoscopic mucosal resection is weak.

The single RCT in the Ypsilantis review was published in 2012 by Wallace et al. 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.

Section Summary: Adequacy of Endoscopic Treatment of Gastrointestinal Lesions
There is insufficient evidence to demonstrate that CLE improves on standard practice for assessing the adequacy of endoscopic treatment of gastrointestinal lesions. The single RCT on this topic was stopped early because an interim analysis found that CLE did not improve on high-definition white-light endoscopy.

Other Potential Applications of CLE
Studies have evaluated CLE for diagnosing a variety of conditions, including lung cancer, bladder cancer, head and neck cancer, esophageal cancer, atrophic gastritis, gastric cancer, pancreatic cysts, breast surgery, and biliary strictures. 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.

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 overall survival, disease-specific survival, test accuracy and validity, and resource utilization. While the reported sensitivity and specificity in these studies are high, 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 (eg, the learning curve, interpretation of lesions). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Barrett esophagus who are undergoing surveillance who receive CLE with targeted biopsy, the evidence includes several RCTs and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Evidence from RCTs has suggested CLE is more sensitive 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. National guidelines continue to recommend 4-quadrant random biopsies for patients with Barrett esophagus undergoing surveillance. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have gastrointestinal lesions and have had endoscopic treatment who receive CLE to assess adequacy of endoscopic treatment, the evidence includes an RCT and a systematic review. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The 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 the effects of the technology on health outcomes.

For individuals who have a suspicion of a condition diagnosed by identification and biopsy of lesions (eg, lung, bladder, or gastric cancer) who receive CLE, the evidence includes a small number of diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. There is limited evidence on the diagnostic accuracy of CLE for these other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date:	09/17/2014
Current Effective Date:	09/19/2018
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. New policy.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
10/01/2017	Coding update: Removing ICD-9 Diagnosis codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. No change to coverage.

Confocal Laser Endomicroscopy

Policy # 00416
Original Effective Date: 09/17/2014
Current Effective Date: 09/19/2018

09/06/2018 Medical Policy Committee review
09/19/2018 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 09/2019

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0397T, 43206, 43252, 88375
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡

Confocal Laser Endomicroscopy

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