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# Kansas City

## Confocal Laser Endomicroscopy

**Policy Number:** 2.01.87

**Last Review:** 9/2014

**Origination:** 3/2013

**Next Review:** 3/2015

### **Policy**

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Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for confocal laser endomicroscopy. This is considered investigational.

### **When Policy Topic is covered**

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Not Applicable

### **When Policy Topic is not covered**

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Use of confocal laser endomicroscopy is considered **investigational**.

### **Description of Procedure or Service**

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Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows *in vivo* microscopic imaging of cells during endoscopy. CLE is proposed for a variety of purposes, especially as a real-time alternative to histology during colonoscopy and for targeting areas to undergo biopsy in patients with inflammatory bowel disease and Barrett's esophagus.

### **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. According to the American Society for Gastrointestinal Endoscopy (ASGE), (1) with CLE, light from a low-power laser illuminates 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 the U.S. 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 probe-based system; the probe is placed through the biopsy channel of a conventional endoscope. The depth of view is up to 250  $\mu\text{m}$  with the endoscopic system and about 120  $\mu\text{m}$  with the probe-based system. A limited area can be examined; no more than 700  $\mu\text{m}$  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 histological evaluation. This would reduce risks

associated with biopsy and reduce the number of biopsies and histological evaluations. Another key potential application of CLE technology is targeting areas for biopsy in patients with Barrett's esophagus undergoing surveillance endoscopy. This is an alternative to conducting random biopsies during surveillance and has the potential to reduce the number of biopsies and/or improve the detection of 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 previously, 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. (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 confocal laser endomicroscopy devices have been cleared for marketing by the FDA. These include:

Cellvizio (Mauna Kea Technologies; Paris, France): This is a confocal microscopy 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 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.

Confocal Video Colonoscope (Pentax Medical Company: Montvale, NJ): This 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 FDA materials, the intended use of the device is to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract.

## **Rationale**

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### **Literature Review**

This policy was created with a search of the MEDLINE database through November 2012. The policy was updated with a search of the literature through December 4, 2013. Following is a summary of the key literature.

### **Colorectal lesions**

*What is the diagnostic accuracy of confocal laser endomicroscopy compared with biopsy with histology for analysis of colorectal lesions?*

Several systematic reviews of studies evaluating the diagnostic accuracy of confocal laser endomicroscopy (CLE) compared to a reference standard have been published. In 2013, Su et al reviewed studies on the efficacy of CLE for discriminating colorectal neoplasms from non-neoplasms,(4) Studies needed to use histologic biopsy as the reference standard and in which the pathologist and endoscopist were blinded to each other's findings. Included studies also used a standardized CLE classification system. Patient populations in included studies were individuals at increased risk of colorectal cancer due to personal or family history, patients with previously identified

polyps, and/or patients with inflammatory bowel disease (IBD). Two reviewers independently assessed the quality of individual studies using the modified Quality Assessment Of Diagnostic Accuracy Studies (QUADAS) tool, and studies considered to be at high risk of bias were excluded from further consideration.

A total of 15 studies with 719 adult patients were found to be eligible for the systematic review. All were single-center trials and 2 were available only as abstracts. In all the studies, suspicious lesions were first identified by conventional white-light endoscopy with or without chromoendoscopy and then further examined by CLE. A pooled analysis of the 15 studies found an overall sensitivity of CLE of 94% (95% confidence interval [CI], 0.88 to 0.97) and specificity of 95% (95% CI, 0.89 to 0.97), compared to histology. Six of the studies included patients at increased risk of colorectal cancer (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 was 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 specificity was 85% (95% CI, 78% to 90%). For patients with IBD, the pooled sensitivity was 83% (95% CI, 70% to 92%) and specificity was 90% (95% CI, 87% to 93%). In other predefined subgroup analyses, the summary sensitivity and specificity was significantly higher ( $p < 0.001$ ) in studies of endoscopy-based CLE (97% and 99%, respectively) than studies of probe-based CLE (87% and 82%, respectively). In addition, the summary sensitivity and specificity was significantly higher ( $p < 0.01$ ) with real-time CLE in which the macroscopic endoscopy findings were known (96% and 97%, respectively) than with blinded CLE in which recorded confocal images were subsequently analyzed without knowledge of macroscopic endoscopy findings (85% and 82%, respectively).

Another systematic review was published in 2013 by Dong et al.(5) The investigators included studies that assessed the diagnostic accuracy of CLE compared with conventional endoscopy. They did not explicitly state that the reference standard was histologic biopsy, but this was the implied reference standard. A total of 6 studies were included in a meta-analysis. All of the studies were prospective, and at least 5 included blinded interpretation of CLE findings (in one study, it was unknown 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%). The authors 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 a sufficient number 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 systematic review by Wanders et al searched for studies that reported diagnostic accuracy of studies on any of several new technologies used to differentiate between colorectal neoplasms and non-neoplasms.(6) To be included in the review, studies needed 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 were identified that included an analysis of CLE. A pooled analysis of study findings 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%). A 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 studies on probe-based CLE were pooled, the sensitivity was 91.5% (86.0% to 97.0%) and the specificity was 80.9 (95% CI, 69.4% to 92.4%). Representative diagnostic accuracy studies are described below.

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 postpolypectomy, 2 had a family history of colorectal cancer, 3 had IBD and 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, 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 (which is adapted from the Mainz classification system). The polyps were then underwent biopsy or were removed and histopathologic diagnosis was determined. Real-time CLE diagnosis correctly identified 109 of 115 (95%) adenomas or hyperplastic polyps. Four adenomas were misdiagnosed by CLE as hyperplastic polyps (2 were tubulous adenomas and 2 were tubulovillous adenomas) and 2 hyperplastic polyps were misdiagnosed as adenomas. The overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CLE diagnosis was 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, the CLE diagnosis had a sensitivity of 90.3% and specificity of 95.7%, and for polyps 10 mm and larger, sensitivity was 97.1% and specificity was 100%.(7)

In 2010, Buchner et al at Mayo Clinic published findings on 75 patients who had a total of 119 polyps.(8) Patients were eligible for study 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 system and a probe-based CLE system. Intravenous fluorescein sodium was administered after the first polyp was identified. Following the imaging techniques, the appropriate intervention, ie, polypectomy, biopsy, or endoscopic mucosal resection, of lesions were 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 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 (58 tubular adenomas, 15 tubulovillous adenomas and 4 adenocarcinomas). 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 Mayo Clinic study was published in 2012 by Shadid et al.(9) The focus of the study was to compare 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 a total of 154 colorectal lesions. Eligibility criteria were similar to the Buchner et al study (see above); the included patients undergoing surveillance or screening colonoscopy. Patients underwent 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 time of 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. The CLE images were then de-identified and then 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 and 2 adenocarcinomas). Overall, there was not a statistically significant difference in the diagnostic accuracy of real-time CLE diagnosis and blinded offline CLE diagnosis (ie, confidence intervals overlapped). The sensitivity, specificity, PPV and NPV for real-time CLE diagnosis was 81%, 76%, 87%, and 79%, respectively. For offline diagnosis, these numbers were 88%, 77%, 81% and 85%, respectively. However, in the subgroup of 107 smaller polyps, less than 10 mm in size, the accuracy of real-time CLE was significantly lower than offline CLE. For the smaller polyps, sensitivity, specificity, PPV and NPV of real-time CLE was 71%, 83%, 78%, and 78% and for offline CLE was 86%, 78%, 76%, and 87%, all respectively. For larger polyps, in contrast, there was a nonsignificant trend in favor of better diagnostic accuracy with real-time compared to offline CLE.

A 2011 study by Hlavaty et al in Slovakia included patients with ulcerative colitis or Crohn disease.(10) Thirty patients were examined with standard white-light colonoscopy, chromoendoscopy and an endoscopy-based CLE system. An additional 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 underwent biopsy and, additionally, 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 who was blinded to the CLE diagnosis. Diagnostic accuracy of CLE was calculated for examinable lesions only. Compared to histologic diagnosis, the sensitivity of CLE for diagnosing low-grade and high-grade intraepithelial neoplasia was 100%, the specificity was 98.4%, the PPV was 66.7%, and the NPV was 100%. However, whereas CLE was able to examine 28 of 30 (93%) flat lesions, it could examine only 40 of 70 (57%) protruding polyps. Moreover, 6 of 10 (60%) 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, see in Policy 2.01.84) was similar to that of CLE. The sensitivity, specificity, PPV and NPV of chromoendoscopy was 100%, 97.9%, 75%, and 100%, respectively.

## Section Summary

Multiple studies have evaluated the accuracy of confocal laser endoscopy compared with 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 specificity ranged from 88% to 95%. Although the reported diagnostic accuracy tended to be relatively high, it is not clear whether the accuracy is high enough to replace biopsy/polypectomy and histologic analysis.

## Barrett esophagus

*What is the evidence that CLE with targeted biopsy can:*

- *distinguish BE without dysplasia from Barrett esophagus (BE) with low- and high-grade dysplasia,*
- *lead to fewer biopsies of benign tissue compared with surveillance with random biopsies?*

The American Gastroenterological Association (AGA) recommends that patients with BE who do not have dysplasia undergo endoscopic surveillance every 3 to 5 years.(11) They further recommend that random 4-quadrant biopsies every 2 cm be taken with white-light endoscopy in patients without known dysplasia.

The ideal study to answer the above question would include an unselected clinical population of patients with BE presenting for surveillance and would randomly assign patients to CLE with targeted biopsy or a standard biopsy protocol without CLE. Relevant outcomes include diagnostic accuracy for detecting dysplasia, the detection rate for dysplasia, and the number of biopsies. Several studies with most or all of these elements of study design were identified, including randomized controlled trials (RCTs). A description of representative randomized studies is included below.

In 2013, Canto et al published findings from a single-blind multicenter RCT conducted at academic centers with experienced endoscopists.(12) The trial included consecutive patients undergoing endoscopy for routine surveillance of BE 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 of the entire length of the BE for patients undergoing surveillance and every 1 cm in patients with suspected neoplasia. In the CLE group, biopsy specimens were obtained only when there was CLE evidence of neoplasia. The final pathology 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 alone and 95% with white-light endoscopy plus CLE. Specificity was 98% with white-light endoscopy alone and 92%

with white-light endoscopy plus CLE. When the analysis was done on a per-biopsy specimen basis, when CLE was added, the sensitivity was substantially higher and the specificity was slightly lower. The median number of biopsies per patient was significantly higher in the white-light endoscopy group compared with the group that also received CLE (4 vs 2,  $p<0.001$ ).

The investigators conducted an analysis of the number of cases in which CLE resulted in a different diagnosis. Thirty-two of 94 (34%) patients in the white-light plus CLE group had a correct change in dysplasia grade after CLE compared to the initial endoscopic findings. Six of the 32 (19%) 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 of 94 (65%) patients in the white-light endoscopy plus CLE group had concordant diagnoses with the 2 techniques. The study was conducted at academic centers and used endoscopy-based CLE. Findings may not be generalizable to other clinical settings or to probe-based CLE.

In 2011, Sharma et al published an international, multicenter RCT that included 122 consecutive patients presenting for surveillance of BE or endoscopic treatment of high-grade dysplasia or early carcinoma.(13) Patients were randomly assigned to receive, in random order, both standard white-light endoscopy and narrow-band imaging. Following these 2 examinations, which were done in a blinded fashion, the location of lesions was unblinded and, subsequently, all patients underwent probe-based CLE. All examinations involved presumptive diagnosis of suspicious lesions. Also, in both groups, after all evaluations were performed, there were biopsies of all suspicious lesions, as well as biopsies of random locations (4 quadrants every 2 cm). Histopathologic analysis was the reference standard. Twenty-one patients were excluded from the analysis. Of the remaining 101 patients, 66 (65%) were found on histopathologic analysis to have no dysplasia, 4 (4%) had low-grade dysplasia, 6 (6%) had high-grade dysplasia and 25 (25%) had early carcinoma. The sensitivity of CLE with white-light endoscopy for detecting high-grade dysplasia 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, the specificity of CLE and white-light endoscopy was significantly lower than white-light endoscopy alone : 92.7% (95% CI, 90.8% to 94.6%) versus 87.8% (95% CI, 85.5% to 90.1%;  $p<0.001$ ). For white-light endoscopy alone, the PPV was 42.7% (32.8% to 52.6%) and the 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 the NPV was 94.6% (95% CI, 92.9% to 96.2%). White-light endoscopy alone missed 79 of 120 (66%) areas with high-grade dysplasia or early carcinoma and white-light endoscopy with CLE missed 38 (32%) areas. On a per-patient basis, 31 patients were diagnosed with high-grade dysplasia or early carcinoma. White-light endoscopy alone failed to identify 4 of these patients (sensitivity, 87%), whereas white-light endoscopy and CLE failed to identify 2 patients (sensitivity, 93.5%).

Another RCT was published in 2012 by Bertani et al in Italy; this was a single-center study.(14) The study compared the dysplasia detection rate of biopsies obtained by standard white-light endoscopy only to the detection rate with standard endoscopy followed by probe-based CLE in patients with BE who were enrolled in a surveillance program. One hundred consecutive patients were included, and 50 were randomly assigned to each group. In both groups, targeted biopsies of suspicious lesions and random 4-quadrant biopsies (1 biopsy every 1 cm) were taken. The authors described the criteria they used for classifying CLE images as dysplastic or neoplastic. According to histopathologic analysis, the reference standard, high-grade dysplasia, was diagnosed in 3 patients and low-grade dysplasia was diagnosed in 16 patients, for an overall detection rate of 19 in 100 (19%) cases. Five cases were in the standard endoscopy group (1 case of high-grade dysplasia and 4 cases of low-grade dysplasia) and 14 were in the CLE group (2 cases of high-grade dysplasia and 12 cases of low-grade dysplasia). No suspicious lesions were identified in the standard endoscopy group and thus, only random biopsies were performed. In the CLE group, no suspicious lesions were identified when patients were initially evaluated with standard endoscopy but CLE detected areas suspicious for neoplasia in 21 of 50 (42%) of patients. All the cases of dysplasia were in patients with areas suspicious for neoplasia at CLE but not standard endoscopy. The sensitivity, specificity, PPV and NPV of probe-based CLE for detecting dysplasia were 100%, 83%, 67%, and 100%, respectively. Overall, the mean number of biopsies did

not differ between groups (mean of 6.6 per patient in the standard endoscopy group and 6.1 in the CLE group,  $p=0.77$ ), so the increased detection rate in the CLE group cannot be explained by a larger number of biopsies.

A single-center crossover RCT was published in 2009 by Dunbar et al.(15) This study was able to evaluate whether CLE can reduce the biopsy rate. 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 and 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 compared to standard endoscopy (mean of 9.8 biopsies vs 23.9 biopsies per patient,  $p=0.002$ ). Although there were fewer biopsies, the mean number of biopsy specimens showing high-grade dysplasia or cancer was similar in the 2 groups: 3.1 during CLE and 3.7 during standard endoscopy, respectively. 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 were found to have high-grade dysplasia 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 ( $p<0.001$ ).

In 2013, a meta-analysis by Wu et al of observational studies and RCTs focused on the diagnostic accuracy of CLE for detecting neoplasia in BE patients.(16) In a pooled analysis of data from 4 studies that reported per-patient accuracy of CLE, the pooled sensitivity for detection of neoplasia was 89% (95% CI, 0.80% to 0.95%), and the pooled specificity was 75% (95% CI, 69% to 81%). Seven studies reported per-location accuracy of CLE. The pooled sensitivity for CLE was 70% (95% CI, 65% to 74%) and the pooled specificity was 91% (95% CI, 90% to 92%). This study did not address other outcomes such as number of biopsies and did not compare CLE for detection of neoplasia in patients with BE with white-light endoscopy.

## Section Summary

Several RCTs and a meta-analysis of RCTs and observational studies suggest that CLE has high accuracy for identifying dysplasia in patients with BE. The sensitivity of CLE in these studies was higher than for white-light endoscopy alone, but the specificity was not consistently higher. There are limited data comparing standard protocols using random biopsies to protocols using CLE and targeted biopsies, so data are inconclusive regarding 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 use a consistent approach to classifying lesions viewed using CLE as dysplastic.

## Other potential applications of CLE

Preliminary studies have been published evaluating CLE for diagnosing a variety of conditions including lung cancer,(17) bladder cancer,(18,19) gastric cancer,(20-23) and bile duct malignancies.(24) There are insufficient studies to determine the accuracy of CLE for these applications and their potential role in clinical care in the United States.

## Ongoing Clinical Trials

Confocal Laser Endomicroscopy for the Diagnosis of Gastric Intestinal Metaplasia, Intraepithelial Neoplasia, and Carcinoma (NCT01642797)(25): This double-blind randomized trial will include approximately 242 patients with *Helicobacter pylori* infection, gastric intestinal metaplasia, low-grade

intraepithelial neoplasia or atrophic gastritis. Patients will receive either CLE with targeted biopsy or standard white-light endoscopy with standard biopsy. The primary outcome measure is the diagnostic yield for identifying gastric intestinal metaplasia, intraepithelial neoplasia and carcinoma.

## Summary

Confocal laser endomicroscopy (CLE) is a device that allows *in vivo* microscopic imaging of cells during endoscopy. For patients undergoing screening or surveillance colonoscopy, multiple studies have evaluated the diagnostic accuracy of CLE. While the reported sensitivity and specificity in these studies is high, it may not be sufficiently high to replace biopsy/polypectomy and histopathologic analysis. Therefore, this evidence is not sufficient to conclude that CLE improves outcomes when used as an adjunct to colonoscopy.

Several studies have evaluated CLE for identifying areas of dysplasia and targeting biopsies in patients undergoing surveillance for Barrett esophagus. Evidence from RCTs supports that CLE is more sensitive than white-light endoscopy for identifying areas of dysplasia. However, this evidence is insufficient to determine the impact of this technology on health outcomes in this population, particularly outside of the research setting. National guidelines continue to recommend 4-quadrant random biopsies for patients with Barrett esophagus undergoing surveillance. There are less data on the use of CLE in nongastrointestinal conditions such as lung or bladder cancer. Thus, use of CLE with endoscopy is considered investigational for all indications.

## Practice Guidelines and Position Statements

In 2006 (reaffirmed in 2011), the American Society for Gastrointestinal Endoscopy published a guideline on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.<sup>(26)</sup> The guideline included the following statements on surveillance of patients with Barrett esophagus:

- “The cost effectiveness of surveillance in patients without dysplasia is controversial. Surveillance endoscopy is appropriate for patients fit to undergo therapy, should endoscopic/histologic findings dictate. For patients with established Barrett’s esophagus of any length and with no dysplasia, after 2 consecutive examinations within 1 year, an acceptable interval for additional surveillance is every 3 years.”
- “Patients with high-grade dysplasia are at significant risk for prevalent or incident cancer. Patients who are surgical candidates may elect to have definitive therapy. Patients who elect surveillance endoscopy should undergo follow-up every 3 months for at least 1 year, with multiple large capacity biopsy specimens obtained at 1 cm intervals. After 1 year of no cancer detection, the interval of surveillance may be lengthened if there are no dysplastic changes on 2 subsequent endoscopies performed at 3-month intervals. High-grade dysplasia should be confirmed by an expert GI pathologist.”
- “Surveillance in patients with low-grade dysplasia is recommended. The significance of low-grade dysplasia as a risk factor for cancer remains poorly defined; therefore, the optimal interval and biopsy protocol has not been established. A follow-up EGD (*screening esophagogastroduodenoscopy*) (i.e., at 6 months) should be performed with concentrated biopsies in the area of dysplasia. If low-grade dysplasia is confirmed, then one possible management scheme would be surveillance at 12 months and yearly thereafter as long as dysplasia persists.”

In 2011, the American Gastroenterological Association published a position statement on the management of Barrett esophagus.<sup>(11)</sup> The statement included the following recommendations regarding endoscopic surveillance of Barrett esophagus:

The guideline developers suggest that endoscopic surveillance be performed in patients with Barrett esophagus (weak recommendation, moderate-quality evidence).



The guideline developers suggest the following surveillance intervals (weak recommendation, low-quality evidence):

- No dysplasia: 3 to 5 years
- Low-grade dysplasia: 6 to 12 months
- High-grade dysplasia in the absence of eradication therapy: 3 months

For patients with Barrett esophagus who are undergoing surveillance, the guideline developers recommend:

- Endoscopic evaluation be performed using white light endoscopy (strong recommendation, moderate-quality evidence).
- 4-quadrant biopsy specimens be taken every 2 cm (strong recommendation, moderate-quality evidence).
- Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist (strong recommendation, moderate-quality evidence).
- 4-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia (strong recommendation, moderate-quality evidence).

The guideline developers suggest against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett esophagus at this time (weak recommendation, low-quality evidence).

### **Medicare National Coverage**

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

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#### **Billing Coding/Physician Documentation Information**

<b>43206</b>	Esophagoscopy, flexible, transoral; with optical endomicroscopy
<b>43252</b>	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
<b>88375</b>	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

The interpretation and report of optical endomicroscopic image(s) would be reported with the following code:

88375: Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session.

Code 88375 cannot be reported in conjunction codes 43206 and 43252.

#### **Additional Policy Key Words**

N/A

#### **Policy Implementation/Update Information**

3/1/13	New policy; considered investigational.
9/1/13	No policy statement changes.
3/1/14	No policy statement changes.
9/1/14	No policy statement changes. Added Billing and Coding Information section. Added CPT: 43206, 43252, 88375.

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