I. Policy

Use of confocal laser endomicroscopy is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:
MP-1.118 Endoscopic Radiofrequency Ablation or Cryoablation for Barrett’s Esophagus
MP-5.045 Virtual Colonoscopy/CT Colonography

II. Product Variations

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO* BlueJourney PPO* FEP PPO**

* Refer to Novitas Solutions Local Coverage Determination (LCD) L35350 Upper Gastrointestinal Endoscopy (Diagnostic and Therapeutic).

**Refer to FEP Medical Policy Manual MP-2.01.87 Confocal Laser Endomicroscopy. The FEP Medical Policy manual can be found at: www.fepblue.org

III. 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 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 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 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 key potential application of CLE technology is targeting areas for biopsy in patients with 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 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. Lesion classification systems are less developed for non–gastrointestinal 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 limited to colorectal applications of CLE.3,4

Regulatory Status

Two confocal laser endomicroscopy (CLE) devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. They include the following.

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 documents, the device is intended for confocal laser imaging of the internal microstructure of tissues in the anatomic tract (gastrointestinal or respiratory) that are accessed by an endoscope. 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 materials, the intended use of the device is to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract. FDA product code: GCJ/KOG (endoscope and accessories).

IV. RATIONALE

The policy was most recently the literature was reviewed through October 7, 2015. Following is a summary of the key literature.

Colorectal Lesions

This section addressed 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 with 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.5 To be included in the review, studies needed to use histologic biopsy as the reference standard, and the pathologist and endoscopist needed to be 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 (CRC) 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. Meta-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 with histology. Six of the 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 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) compared with 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) compared 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. 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 1 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. 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. 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%).

Representative diagnostic accuracy studies follow.

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 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 then underwent biopsy or were 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 (2 were tubulobulbar adenomas, 2 were tubulovillous adenomas) and 2 hyperplastic polyps were misdiagnosed as adenomas. The overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CLE diagnosis 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, CLE diagnosis had a sensitivity of 90.3% and specificity of 95.7%; for polyps 10 mm and larger, sensitivity was 97.1% and specificity was 100%.8

In 2010, Buchner et al at Mayo Clinic published findings on 75 patients who had a total of 119 polyps.9 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 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, 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, 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
MEDICAL POLICY

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>CONFOCAL LASER ENDOMICROSCOPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.093</td>
</tr>
</tbody>
</table>

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. 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 (previously discussed); included patients were 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. CLE images were then 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 not a statistically significant difference between 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 were 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 less than offline CLE. For smaller polyps, sensitivity, specificity, PPV and NPV of real-time CLE was 71%, 83%, 78%, and 78%, respectively, and for offline CLE, 86%, 78%, 76%, and 87%, respectively. For larger polyps, in contrast, there was a nonsignificant trend in favor of better diagnostic accuracy with real-time compared with offline CLE.

A 2011 study by Hlavaty et al in Slovakia included patients with ulcerative colitis or Crohn disease. 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 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, see
Section Summary: Colorectal Lesions
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 unclear whether the accuracy is high enough to replace biopsy/polypectomy and histologic analysis.

Barrett Esophagus
This section addresses whether CLE can distinguish Barrett esophagus (BE) without dysplasia from BE with low- and high-grade dysplasia 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 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.

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. The authors noted that, according to the Preservation and Incorporation of Valuable Endoscopic Innovation (PIVI) Initiative of the American Society of Gastrointestinal Endoscopy (ASGE), 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 high-grade dysplasia or esophageal adenocarcinoma (HGD/EAC) compared with the current protocol.

Eight studies published through May 2014 met inclusion criteria; 1 was a parallel group randomized controlled trial (RCT), and 1 was a randomized crossover study. The other 6 were single or double-blind non-RCTs. Seven of the studies had data suitable for pooling on a per-lesion basis; together these included 345 patients and 3080 lesions. In a meta-analysis of the diagnosis of HGD/EAC, 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 PIVI Initiative, the diagnostic accuracy of CLE in the studies published to date is not sufficiently high for this technique to replace the established Seattle surveillance protocol. Moreover, the authors noted that the prevalence of high-grade dysplasia and adenocarcinoma were much higher in the studies...
Randomized Controlled Trials

The 2 RCTs included in the 2014 Gupta meta-analysis are described next.

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.\textsuperscript{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, all suspicious lesions were biopsied, as well as 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. 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\%; \textit{p}=0.002). However, 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\%; \textit{p}<0.001). For white-light endoscopy alone, PPV was 42.7\% (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 high-grade dysplasia or early carcinoma, and white-light endoscopy with CLE missed 38 areas (32\%). 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\%).

A single-center crossover RCT was published in 2009 by Dunbar et al.\textsuperscript{14} 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 with standard endoscopy (mean, 9.8 biopsies vs 23.9 biopsies per patient, \textit{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).

Another RCT was published in 2014 by Canto et al.\textsuperscript{15} This was a single-blind, multicenter trial conducted at academic centers with experienced endoscopists. It 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. 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 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, 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 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 (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 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.

**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 in available studies is not sufficiently high to replace the standard Seattle protocol, according to criteria adopted by the ASGE. There are limited data comparing standard protocols using random biopsies to protocols using CLE and targeted biopsies; therefore, 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 as dysplastic using CLE.
Assessing the Adequacy of Endoscopic Treatment of Gastrointestinal Lesions

This section addresses whether use of CLE improves the determination of residual disease compared with conventional techniques, ie, white-light endoscopy. In 2014, Ypsilantis et al published a systematic review of the literature. They included retrospective and prospective studies that reported diagnostic accuracy of CLE for the detection of residual disease after endoscopic mucosal resection (EMR) of gastrointestinal lesions. After examining full-text articles, a total of 3 studies (1 RCT and 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, the authors concluded that evidence on the usefulness of CLE in assessing the adequacy of EMR is weak.

The single RCT 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 either with high-definition white light (HDWL) endoscopy or HDWL 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. Enrollment in the study was halted after an interim analysis showed no difference between groups. Among the 119 patients who had enrolled by the time of the interim analysis, 15 (26%) of 57 in the HDWL group and 17 (27%) of 62 in the HDWL plus CLE group were optimally treated; the difference was not statistically significant. Moreover, other outcomes were similar in the 2 groups.

Section Summary: Endoscopic Treatment of Gastrointestinal Lesions

There is insufficient evidence 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 HDWL endoscopy.

Other Potential Applications of CLE

Preliminary studies have been published evaluating 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 are insufficient to determine the accuracy of CLE and its potential role in clinical care for these applications in the United States.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.
Summary of Evidence

The evidence for confocal laser endomicroscopy (CLE) in patients who have suspected or known colorectal lesions 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 about the use of this technology in practice (eg, the learning curve, interpretation of lesions). The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for CLE in patients who have Barrett esophagus and are undergoing surveillance includes several randomized controlled trials (RCTs) and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Evidence from RCTs suggests CLE is more sensitive than white-light endoscopy for identifying areas of dysplasia. However, a 2014 meta-analysis found that the pooled sensitivity, specificity, and negative predictive value of available studies are 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.

The evidence for CLE in patients who have a suspicion of a condition diagnosed by identification and biopsy of lesions (eg, lung, bladder or gastric cancer) 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 diagnostic accuracy for any of these other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

In 2006 (reaffirmed in 2011), the American Society for Gastrointestinal Endoscopy (ASGE) published a guideline on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.37 The guideline included the following statements on surveillance of patients with BE:

“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.”

The ASGE Technology Committee published a Technology Status Evaluation Report on CLE in 2014. The report concluded that CLE is an emerging technology with the potential to improve patient care. However, before the technology can be widely accepted, further studies are needed in the following areas:

- Use of CLE outside of the academic setting, particularly the applicability of the technology in community settings.
- The learning curve of CLE image interpretation and any additional time needed to perform the procedure.
- The clinical efficacy of the technology compared to other available advanced imaging technologies.
- Approaches to CLE imaging and image interpretation.

In 2011, the American Gastroenterological Association published a position statement on the management of BE. The statement included the following recommendations regarding endoscopic surveillance of BE:

- 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).

U.S. Preventive Services Task Force Recommendations

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

V. DEFINITIONS

NA

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.
VIII. Coding Information

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational, therefore not covered:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
</tr>
</thead>
<tbody>
<tr>
<td>0397T</td>
</tr>
<tr>
<td>43206</td>
</tr>
<tr>
<td>43252</td>
</tr>
<tr>
<td>88375</td>
</tr>
</tbody>
</table>

IX. References


Other

X. POLICY HISTORY

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAC 7/22/14 Consensus. No change to policy statements. References updated. Added Medicare variation referencing L34745 Upper Gastrointestinal Endoscopy (Diagnostic and Therapeutic).</td>
</tr>
<tr>
<td></td>
<td>CAC 7/21/15 Consensus review. No changes to the policy statements. References and rationale updated. Codes reviewed.</td>
</tr>
<tr>
<td></td>
<td>11/2/15 Administrative change. LCD number changed from L34745 to L35350 due to Novitas update to ICD-10</td>
</tr>
<tr>
<td></td>
<td>Administrative 1/20/16: New 2016 code (0397T) added.</td>
</tr>
<tr>
<td></td>
<td>CAC 7/26/16 Consensus review. No change to policy statements. References and rationale updated. Coding reviewed.</td>
</tr>
<tr>
<td></td>
<td>Admin update 1/1/17: Product variation section reformatted</td>
</tr>
</tbody>
</table>