FEP 2.01.87 Confocal Laser Endomicroscopy

Effective Date: April 15, 2018

Related Policies:
2.01.80 Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus
2.01.84 Chromoendoscopy as an Adjunct to Colonoscopy
6.01.32 Virtual Colonoscopy/Computed Tomography Colonography

Confocal Laser Endomicroscopy

Description

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 biopsy/polypectomy and histopathologic analysis during colonoscopy and for targeting areas to undergo biopsy in patients with inflammatory bowel disease or Barrett esophagus.

FDA REGULATORY STATUS

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).

POLICY STATEMENT

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy

In 2006 (reaffirmed in 2011), the American Society for Gastrointestinal Endoscopy published guidelines on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.[35] The guidelines included the following statements on surveillance of patients with Barrett esophagus:

2. “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.”
3. “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."

4. "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 Society published a technology status evaluation on confocal laser endomicroscopy (CLE) in 2014.[36] It concluded that CLE is an emerging technology with the potential to improve patient care. However, before it can be widely accepted, further studies are needed in the following areas:

1. "[T]he applicability and practicality of CLE, especially in community settings [because the research has been done] primarily in academic centers."
2. The "learning curve of CLE image interpretation … and additional time needed to perform the procedure…."
3. The clinical efficacy of the technology … compared to other available advanced imaging technologies…."
4. Improvements in CLE imaging and image interpretation…."

American Gastroenterological Association

In 2011, the American Gastroenterological Association published a position statement on the management of Barrett esophagus.[1] The statement included the following recommendations on endoscopic surveillance of Barrett esophagus (see Table 1).

Table 1. Recommendations on Endoscopic Surveillance of Barrett Esophagus

Recommendation	LOR	QOE
"The guideline developers suggest that endoscopic surveillance be performed in patients with Barrett's esophagus."	Weak	Moderate
"The guideline developers suggest the following surveillance intervals: • No dysplasia: 3-5 years • Low-grade dysplasia: 6-12 months • High-grade dysplasia in the absence of eradication therapy: 3 months"	Weak	Low
"For patients with Barrett's esophagus who are undergoing surveillance, the guideline developers recommend:		
• Endoscopic evaluation be performed using white-light endoscopy.	Strong	Moderate
• 4-quadrant biopsy specimens be taken every 2 cm.	Strong	Moderate
• Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist.	Strong	Moderate
• 4-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia."	Strong	Moderate
The guideline developers suggest against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett's esophagus at this time."	Weak	Low

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.

REFERENCES

1. American Gastroenterological Association, Spechler SJ, Sharma P, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology.* Mar 2011;140(3):1084-1091. PMID 21376940
2. Salvatori F, Siciliano S, Maione F, et al. Confocal laser endomicroscopy in the study of colonic mucosa in IBD patients: a review. *Gastroenterol Res Pract.* Apr 2012;2012:525098. PMID 22474440
3. Neumann H, Vieth M, Atreya R, et al. Prospective evaluation of the learning curve of confocal laser endomicroscopy in patients with IBD. *Histol Histopathol.* Jul 2011;26(7):867-872. PMID 21630216
4. Buchner AM, Gomez V, Heckman MG, et al. The learning curve of in vivo probe-based confocal laser endomicroscopy for prediction of colorectal neoplasia. *Gastrointest Endosc.* Mar 2011;73(3):556-560. PMID 21353852
5. Su P, Liu Y, Lin S, et al. Efficacy of confocal laser endomicroscopy for discriminating colorectal neoplasms from non-neoplasms: a systematic review and meta-analysis. *Colorectal Dis.* Jan 2013;15(1):e1-12. PMID 23006609
6. Dong YY, Li YQ, Yu YB, et al. Meta-analysis of confocal laser endomicroscopy for the detection of colorectal neoplasia. *Colorectal Dis.* Sep 2013;15(9):e488-495. PMID 23810105
7. Wanders LK, East JE, Uitentuis SE, et al. Diagnostic performance of narrowed spectrum endoscopy, autofluorescence imaging, and confocal laser endomicroscopy for optical diagnosis of colonic polyps: a meta-analysis. *Lancet Oncol.* Dec 2013;14(13):1337-1347. PMID 24239209
8. Xie XJ, Li CQ, Zuo XL, et al. Differentiation of colonic polyps by confocal laser endomicroscopy. *Endoscopy.* Feb 2011;43(2):87-93. PMID 21038291
9. Buchner AM, Shahid MW, Heckman MG, et al. Comparison of probe-based confocal laser endomicroscopy with virtual chromoendoscopy for classification of colon polyps. *Gastroenterology.* Mar 2010;138(3):834-842. PMID 19909747
10. Shahid MW, Buchner AM, Raimondo M, et al. Accuracy of real-time vs. blinded offline diagnosis of neoplastic colorectal polyps using probe-based confocal laser endomicroscopy: a pilot study. *Endoscopy.* Apr 2012;44(4):343-348. PMID 22382851
11. Hlavaty T, Huorka M, Koller T, et al. Colorectal cancer screening in patients with ulcerative and Crohn's colitis with use of colonoscopy, chromoendoscopy and confocal endomicroscopy. *Eur J Gastroenterol Hepatol.* Aug 2011;23(8):680-689. PMID 21602687
12. Gupta A, Attar BM, Koduru P, et al. Utility of confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett's esophagus: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* Apr 2014;26(4):369-377. PMID 24535597
13. Xiong YQ, Ma SJ, Zhou JH, et al. A meta-analysis of confocal laser endomicroscopy for the detection of neoplasia in patients with Barrett's esophagus. *J Gastroenterol Hepatol.* Jun 2016;31(6):1102-1110. PMID 26676646
14. Sharma P, Meining AR, Coron E, et al. Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc.* Sep 2011;74(3):465-472. PMID 21741642
15. Dunbar KB, Okolo P, 3rd, Montgomery E, et al. Confocal laser endomicroscopy in Barrett's esophagus and endoscopically inapparent Barrett's neoplasia: a prospective, randomized, double-blind, controlled, crossover trial. *Gastrointest Endosc.* Oct 2009;70(4):645-654. PMID 19559419
16. Canto MI, Anandasabapathy S, Brugge W, et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). *Gastrointest Endosc.* Feb 2014;79(2):211-221. PMID 24219822
17. Ypsilantis E, Pissas D, Papagrigoriadis S, et al. Use of confocal laser endomicroscopy to assess the adequacy of endoscopic treatment of gastrointestinal neoplasia: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech.* Feb 2015;25(1):1-5. PMID 24910941
18. Wallace MB, Crook JE, Saunders M, et al. Multicenter, randomized, controlled trial of confocal laser endomicroscopy assessment of residual metaplasia after mucosal ablation or resection of GI neoplasia in Barrett's esophagus. *Gastrointest Endosc.* Sep 2012;76(3):539-547 e531. PMID 22749368

19. Sorokina A, Danilevskaya O, Averyanov A, et al. Comparative study of ex vivo probe-based confocal laser endomicroscopy and light microscopy in lung cancer diagnostics. *Respirology.* Aug 2014;19(6):907-913. PMID 24909555
20. Wellikoff AS, Holladay RC, Downie GH, et al. Comparison of in vivo probe-based confocal laser endomicroscopy with histopathology in lung cancer: A move toward optical biopsy. *Respirology.* Aug 2015;20(6):967-974. PMID 26094505
21. Fuchs FS, Zirlik S, Hildner K, et al. Confocal laser endomicroscopy for diagnosing lung cancer in vivo. *Eur Respir J.* Sep 20 2012. PMID 22997220
22. Sonn GA, Jones SN, Tarin TV, et al. Optical biopsy of human bladder neoplasia with in vivo confocal laser endomicroscopy. *J Urol.* Oct 2009;182(4):1299-1305. PMID 19683270
23. Liu JJ, Droller MJ, Liao JC. New optical imaging technologies for bladder cancer: considerations and perspectives. *J Urol.* Aug 2012;188(2):361-368. PMID 22698620
24. Nathan CA, Kaskas NM, Ma X, et al. Confocal laser endomicroscopy in the detection of head and neck precancerous lesions. *Otolaryngol Head Neck Surg.* Apr 3 2014;151(1):73-80. PMID 24699456
25. Moore C, Mehta V, Ma X, et al. Interobserver agreement of confocal laser endomicroscopy for detection of head and neck neoplasia. *Laryngoscope.* Mar 2016;126(3):632-637. PMID 26372409
26. Liu J, Li M, Li Z, et al. Learning curve and interobserver agreement of confocal laser endomicroscopy for detecting precancerous or early-stage esophageal squamous cancer. *PLoS One.* Jun 2014;9(6):e99089. PMID 24897112
27. Guo J, Li CQ, Li M, et al. Diagnostic value of probe-based confocal laser endomicroscopy and high-definition virtual chromoendoscopy in early esophageal squamous neoplasia. *Gastrointest Endosc.* Jun 2015;81(6):1346-1354. PMID 25680899
28. Liu T, Zheng H, Gong W, et al. The accuracy of confocal laser endomicroscopy, narrow band imaging, and chromoendoscopy for the detection of atrophic gastritis. *J Clin Gastroenterol.* May-Jun 2015;49(5):379-386. PMID 25485568
29. He XK, Liu D, Sun LM. Diagnostic performance of confocal laser endomicroscopy for optical diagnosis of gastric intestinal metaplasia: a meta-analysis. *BMC Gastroenterol.* Sep 05 2016;16:109. PMID 27596838
30. Qian W, Bai T, Wang H, et al. Meta-analysis of confocal laser endomicroscopy for the diagnosis of gastric neoplasia and adenocarcinoma. *J Dig Dis.* Jun 2016;17(6):366-376. PMID 27129127
31. Karia K, Waxman I, Konda VJ, et al. Needle-based confocal endomicroscopy for pancreatic cysts: the current agreement in interpretation. *Gastrointest Endosc.* May 2016;83(5):924-927. PMID 26382051
32. Napoleon B, Lemaistre AI, Pujol B, et al. In vivo characterization of pancreatic cystic lesions by needle-based confocal laser endomicroscopy (nCLE): proposition of a comprehensive nCLE classification confirmed by an external retrospective evaluation. *Surg Endosc.* Jun 2016;30(6):2603-2612. PMID 26428198
33. De Palma GD, Esposito D, Luglio G, et al. Confocal laser endomicroscopy in breast surgery: a pilot study. *BMC Cancer.* Apr 10 2015;15:252. PMID 25885686
34. Slivka A, Gan I, Jamidar P, et al. Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary strictures: results of a prospective multicenter international study. *Gastrointest Endosc.* Feb 2015;81(2):282-290. PMID 25616752
35. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc.* Apr 2006;63(4):570-580. PMID 16564854
36. ASGE Technology Committee. Confocal laser endomicroscopy. *Gastrointest Endosc.* Dec 2014;80(6):928-938. PMID 25442092

POLICY HISTORY

Date	Action	Description
March 2013	New Policy	
March 2014	Update Policy	Policy updated with literature search. No change to policy statement. References 5, 6, 12, 16, 22, & 23 added; others renumbered or removed.
March 2015	Update Policy	Policy updated with literature review. Policy statement unchanged. References 12, 16-17, 22-23, and 28 added.
June 2016	Update Policy	Policy updated with literature review through October 7, 2015; references 20, 24, 26-27, 33-36, and 38 added. Policy statement unchanged.

March 2017	Update Policy	Policy updated with literature review; references 13 and 29-30 added. Policy statement changed from not medically necessary to investigational.
March 2018	Update Policy	Policy updated with literature review through September 11, 2017; no references added. Policy statement unchanged.