Protocol

Confocal Laser Endomicroscopy

(20187)

Medical Benefit		**Effective Date**: 07/01/13	**Next Review Date**: 03/21
Preauthorization	No	**Review Dates**: 03/13, 03/14, 03/15, 03/16, 03/17, 03/18, 03/19, 03/20	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected or known colorectal lesions	Interventions of interest are: • Confocal laser endomicroscopy as an adjunct to colonoscopy	Comparators of interest are: • White-light colonoscopy alone • Colonoscopy used with alternative adjunctive diagnostic aids	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Resource utilization
Individuals: • With Barrett esophagus who are undergoing surveillance	Interventions of interest are: • Confocal laser endomicroscopy with targeted biopsy	Comparators of interest are: • Standard endoscopy with random biopsy	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Resource utilization
Individuals: • With gastrointestinal lesions and have had endoscopic treatment	Interventions of interest are: • Confocal laser endomicroscopy to assess the adequacy of endoscopic treatment	Comparators of interest are: • Standard endoscopy (i.e., white-light endoscopy)	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Resource utilization
Individuals: • With suspicion of a condition diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer)	Interventions of interest are: • Confocal laser endomicroscopy	Comparators of interest are: • Standard diagnostic procedures	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Resource utilization

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.

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 (OS), disease-specific survival, test 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 (e.g., the learning curve, interpretation of lesions). The evidence is insufficient to determine the effects of technology on net health outcomes.

For individuals who have Barrett esophagus who are undergoing surveillance who receive CLE with targeted biopsy, the evidence includes several randomized controlled trials and a meta-analysis. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. Evidence from randomized controlled trials 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 single randomized controlled trial, 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 technology on net health outcomes.

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

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

For individuals who have suspected or known colorectal lesions who receive CLE as an adjunct to colonoscopy, the evidence includes multiple diagnostic accuracy studies. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. While the reported sensitivity and specificity in these studies.

The objective of this evidence review is to determine whether the use of CLE improves the net health outcome compared with standard diagnostic or disease monitoring procedures.

POLICY

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

BACKGROUND

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows in vivo microscopic imaging of the mucosal epithelium during endoscopy. The process uses light from a low-power laser to illuminate tissue and, subsequently, the same lens detects light reflected from the tissue through a pinhole. The term confocal refers to having both illumination and collection systems in the same focal plane. Light reflected and scattered at other geometric angles that are not reflected through the pinhole is excluded from detection, which dramatically increases the resolution of CLE images.

To date, two CLE systems have been cleared by the U.S. Food and Drug Administration (FDA). One is an endoscope-based system with a confocal probe 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 mm with the probe-based system. A limited area can be examined - no more than 700 µm in the endoscopic-based system and less with the probe-based system. As pointed out in systematic reviews, the limited viewing area emphasizes the need for careful conventional endoscopy to target 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 characterize the cellular structure of lesions immediately. 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 overlooked rather than removed and sent for histologic evaluation. Using CLE would reduce risks associated with biopsy and reduce the number of biopsies and histologic evaluations.

Another potential application of CLE technology is targeting areas for biopsy in patients with Barrett esophagus undergoing surveillance endoscopy. This alternative to the current standard approach, recommended by the American Gastroenterological Association, is that patients with Barrett esophagus who do not have dysplasia undergo endoscopic surveillance every three to five years.[1] The American Gastroenterological Association has further recommended that random 4-quadrant biopsies every 2 cm be taken with white-light endoscopy in patients without known dysplasia.

Other potential uses of CLE under investigation include better diagnosis and differentiation of conditions such as gastric metaplasia, lung cancer, and bladder cancer.

As noted, limitations of CLE systems include a limited viewing area and depth of view. Another issue is the standardization of systems for classifying lesions viewed with CLE devices. Although there is currently no internationally accepted classification system for colorectal lesions, two systems have been used in a number of studies conducted in different countries. They are the Mainz criteria for endoscopy-based CLE devices and the Miami classification system for probe-based CLE devices.[2] Lesion classification systems are less developed for non-gastrointestinal lesions viewed by CLE devices (e.g., those in the lung or bladder). Another challenge is the learning curve for obtaining high-quality images and classifying lesions. Several recent studies, however, have found that the ability to acquire high-quality images and interpret them accurately can be learned relatively quickly; these studies were specific to colorectal applications of CLE.[3,4]

REGULATORY STATUS

Two CLE devices have been cleared for marketing by the FDA through the 510(k) process.

Cellvizio® (Mauna Kea Technologies) 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 the FDA, the device is intended for 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 the FDA in 2015 for imaging the internal microstructure of tissues and for visualization of body cavities organs and canals during endoscopic and laparoscopic surgery. In 2018, the CranioFlex™ Confocal Miniprobe (Mauna Kea Technologies) was cleared to "provide visualization within central nervous system during cranial diagnostic and therapeutic procedures such as tumor biopsy and resection." FDA product codes: GCJ, GWG, OWN.

Confocal Video Colonoscope (Pentax Medical) is an endoscopy-based CLE system. The EC-3S7OCILK system, cleared by the FDA in 2004, is used with a Pentax Video Processor and with a Pentax Confocal Laser System. According to the FDA, 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).

FDA product code: GCJ/OWN (endoscope and accessories).

Table 1. Endomicroscopy Devices Cleared by the U.S. Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	Indication
Cellvizio 100 Series Confocal Laser Imaging Systems And Their Confocal Miniprobes	Mauna Kea Technologies	02/22/2019	K183640	For use in endomicroscopy
Ec-3870cilk, Confocal Video Colonoscope	Pentax Medical Company	10/19/2004	K042741	For use in endomicroscopy

RELATED PROTOCOL

Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus

---

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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. ASGE Technology Committee. Confocal laser endomicroscopy. Gastrointest Endosc. Dec 2014;80(6):928-938. PMID 25442092.
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. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.

25. Nathan CA, Kaskas NM, Ma X, et al. Confocal laser endomicroscopy in the detection of head and neck pre-cancerous lesions. Otolaryngol Head Neck Surg. Apr 3 2014;151(1):73-80. PMID 24699456.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. Park CH, Kim H, Jo JH et al. Role of probe-based confocal laser endomicroscopy-targeted biopsy in the molecular and histopathological study of gastric cancer. J. Gastroenterol. Hepatol., 2018 Sep 18;34(1). PMID 30221400.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. Evans JA, Early DS, Fukami N et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest. Endosc., 2012 Nov 21;76(6). PMID 23164510.
39. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. Jun 21 2016;315(23):2576-2594. PMID 27305422.