Corporate Medical Policy

Confocal Laser Endomicroscopy

File Name: confocal_laser_endomicroscopy
Origination: 1/2013
Last Review: 11/2023

Description of Procedure or Service

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 biopsy in patients with inflammatory bowel disease and Barrett's esophagus.

Background

CLE allows *in vivo* microscopic imaging of the mucosal epithelium during endoscopy. According to the American Society for Gastrointestinal Endoscopy (ASGE), 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 resolution of CLE images.

To date, 2 types of CLE systems have been cleared by the Food and Drug Administration (FDA). One is an endoscope-based system in which 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 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 (see policy Chromoendoscopy as an Adjunct to Colonoscopy) 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 Barrett's esophagus undergoing surveillance endoscopy. This is an alternative to the current standard approach recommended by the American Gastroenterological Association which is that individuals with Barrett's Esophagus who do not have dysplasia undergo endoscopic surveillance every 3 to 5 years. 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 currently no internationally accepted classification system for colorectal lesions, 2 systems 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 (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.

Regulatory Status
Two confocal laser endomicroscopy devices have been cleared for marketing by the FDA through the 510(k) process. These include:

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 2.8mm. According to FDA, 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. The 100 series version of the system (F400-v2) was cleared by FDA in 2015 for imaging of the internal microstructure of tissues and for visualization of body cavities, organs and canals during endoscopic and laparoscopic surgery, and has been approved for use with several miniprobes for specific indications. Confocal Miniprobes™ approved for use with the Cellvizio 100 series that are particularly relevant to this review include the GastroFlex™ and ColoFlex™ (for imaging of anatomical tracts, ie, gastrointestinal systems, accessed by an endoscope or endoscopic accessories), and the CranioFlex™ (for visualization within the central nervous system during cranial diagnostic and therapeutic procedures such as tumor biopsy and resection). In 2020, the Cellvizio 100 series system received extended FDA approval to allow for use of fluorescein sodium as a contrast agent for visualization of blood flow for all of its approved indications. Later in 2020, the Cellvizio I.V.E. system with Confocal Miniprobes was approved by the FDA as a newer version of the previously approved 100 series system, designed to reduce the system footprint and improve device usability. The 2 devices are otherwise equivalent and are approved for the same indications. In 2022, the Cellvizio 100 series system F800 model received extended FDA approval to allow for use of indocyanine green (ICG) and pafolacianine as contrast agents. Intravenous administration of ICG is used to perform fluorescence angiography and interstitial administration of ICG is used to perform fluorescence imaging and visualization of the lymphatic system. Intravenous administration of pafolacianine is used to perform fluorescence imaging of tissues.

Confocal Video Colonoscope (Pentax Medical) is an endoscopy-based CLE system. The EC-3870 CILK 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 intended use of the device is to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract. This device is no longer commercially available from the manufacturer.

Related Policy
Chromoendoscopy as an Adjunct to Colonoscopy

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Use of confocal laser endomicroscopy is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Confocal Laser Endomicroscopy

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When it is covered

Not applicable.

When it is not covered

Use of confocal laser endomicroscopy is considered investigational.

Policy Guidelines

The evidence for confocal laser endomicroscopy (CLE) as an adjunct to colonoscopy in patients who have suspected or known colorectal lesions, includes multiple diagnostic accuracy studies. Relevant outcomes are overall survival, 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 about the use of this technology in clinical practice (eg, the learning curve, interpretation of lesions). The evidence is insufficient to determine that the technology results in an improvement in health outcome.

The evidence for CLE with targeted biopsy in patients who have Barrett's esophagus and are undergoing surveillance includes several randomized controlled trials (RCTs) and 2 meta-analyses. Relevant outcomes are overall survival, disease-specific survival, test validity, and resource utilization. Evidence from RCTs suggests that CLE has similar or higher sensitivity 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 are not sufficiently high to replace the standard surveillance protocol. National guidelines continue to recommend 4-quadrant random biopsies for patients with Barrett's esophagus undergoing surveillance. One 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 that the technology results in an improvement in the net health outcome.

The evidence for patients who have gastrointestinal lesions and have had endoscopic treatment and received CLE, includes a systematic review with a single RCT and 2 prospective, nonrandomized studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and resource utilization. The evidence is insufficient to determine that the technology results in an improvement in net health outcome.

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 validity, and resource utilization. There is limited evidence on diagnostic accuracy of CLE for these other indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *43206, 43252, 88375, 0397T*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 1/10/13

Specialty Matched Consultant Advisory Panel 10/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 1/9/14

Specialty Matched Consultant Advisory Panel 11/2014

Senior Medical Director review 12/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 1/15/15

Specialty Matched Consultant Advisory Panel 11/2015

Medical Director review 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 11/12/15

Specialty Matched Consultant Advisory Panel 11/2016

Medical Director review 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 11/2016

Specialty Matched Consultant Advisory Panel 11/2017

Medical Director review 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 11/2017

Specialty Matched Consultant Advisory Panel 11/2018

Medical Director review 11/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 11/2018

Specialty Matched Consultant Advisory Panel 11/2019

Medical Director review 11/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 11/2019

Specialty Matched Consultant Advisory Panel 11/2020

Medical Director review 11/2020

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.87, 12/2020

Specialty Matched Consultant Advisory Panel 11/2021

Medical Director review 11/2021

Specialty Matched Consultant Advisory Panel 11/2022

Medical Director review 11/2022

Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. Mar 2011; 140(3): 1084-91. PMID 21376940

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. 2012; 2012: 525098. PMID 22474440

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): 867-72. PMID 21630216

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): 556-60. PMID 21353852

Specialty Matched Consultant Advisory Panel 11/2023

Medical Director review 11/2023

Policy Implementation/Update Information

2/26/13 New policy issued. Use of confocal laser endomicroscopy is considered investigational. Medical Director review 1/2013. Notification given 2/26/13. Policy effective 5/28/13. (sk)

11/12/13 Specialty Matched Consultant Advisory Panel review 10/16/13. No change to Policy statement. (sk)

4/1/14 Reference added. No change to Policy statement. (sk)

1/13/15 References updated. Specialty Matched Consultant Advisory Panel review 11/2014. Senior Medical Director review 12/2014. No change to policy intent. (td)

2/24/15 References updated. Policy Guidelines section updated. Policy Statement unchanged. (td)

5/26/15 Description section updated to remove archived Evidence Based Guideline. Policy Statements unchanged. (td)

12/30/15 Billing/Coding section updated to add code 0397T effective 1/1/16. References updated. Specialty Matched Consultant Advisory Panel review 11/18/2015. Medical Director review 11/2015. (td)

1/26/16 Policy Guidelines section revised. References updated. (td)

12/30/16 Regulatory Status and Policy Guidelines updated with minor revisions. Specialty Matched Consultant Advisory Panel review 11/2016. Medical Director review 11/2016. (jd)

12/15/17 References updated. Specialty Matched Consultant Advisory Panel 11/2017. Medical Director review 11/2017. (jd)

12/14/18 Minor revisions. References updated. Specialty Matched Consultant Advisory Panel 11/2018. Medical Director review 11/2018. (jd)

12/31/19 References updated. Specialty Matched Consultant Advisory Panel 11/2019. Medical Director review 11/2019. (jd)

12/8/20 References updated. Specialty Matched Consultant Advisory Panel 11/2020. Medical Director review 11/2020. (jd)

11/30/21 Specialty Matched Consultant Advisory Panel 11/2021. Medical Director review 11/2021. (jd)

11/29/22 Minor edits to the Description section for clarity, no change to policy statement. References updated. Specialty Matched Consultant Advisory Panel 11/2022. Medical Director review 11/2022. (tm)

12/29/23 Description, Policy Guidelines and References updated. Specialty Matched Consultant Advisory Panel 11/2023. Medical Director review 11/2023. (tm)