



Louisiana

Confocal Laser Endomicroscopy

Policy # 00416

Original Effective Date: 09/17/2014

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of confocal laser endomicroscopy (CLE) to be **investigational**.*

Background/Overview

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 120mm with the probe-based system. A limited area can be examined $\frac{3}{4}$ 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.

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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. 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. Lesion classification systems are less developed for non-gastrointestinal lesions viewed by CLE devices (eg, 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

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Cellvizio^{®‡} (Mauna Kea Technologies) 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 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 US 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

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Rationale/Source

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.

For individuals who have suspected or known colorectal lesions who receive CLE as an adjunct to colonoscopy, the evidence includes multiple diagnostic accuracy studies. The 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 (eg, 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. The 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. The 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.

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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. The 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. The 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.

Supplemental Information

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy

The American Society for Gastrointestinal Endoscopy (2006; reaffirmed in 2011) published guidelines on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract. Regarding the use of confocal endoscopy as an adjunct to white-light endoscopy, the guidelines stated that this technique is “still in development.” The guidelines also included the following statements on surveillance of patients with Barrett esophagus (BE):

1. "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."
2. "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

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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."

3. "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 (2012) stated the following in their guideline on the role of endoscopy in BE and other premalignant conditions of the esophagus: "Adjuncts to white-light endoscopy used to improve the sensitivity for the detection of BE and dysplastic BE include chromoendoscopy, electrical enhanced imaging, magnification, and confocal endoscopy."

The Society (2014) published a technology status evaluation on confocal laser endomicroscopy (CLE). 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

The American Gastroenterological Association (2011) published a position statement on the management of BE. The statement included the following recommendations on endoscopic surveillance of BE (see Table 2).

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Table 2. 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Endoscopic evaluation be performed using white-light endoscopy. • 4-quadrant biopsy specimens be taken every 2 cm. • Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist. • 4-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia."	Strong Strong Strong Strong	Moderate Moderate Moderate 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

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

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Currently, ongoing and unpublished trials that might influence this review are listed in Table 3.



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Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02922049	Probe-based Confocal Laser Endomicroscopy in Accurate Histopathologic Diagnosis of Neoplastic Gastrointestinal Lesion	80	Apr 2020
<i>Unpublished</i>			
NCT03013894	Feasibility of Confocal Laser Microendoscopy in Bladder Cancer Diagnosis	60	Oct 2017 (recruitment completed)
NCT02672774	Study of Minimally Invasive Endoscopic Imaging Methods for the Evaluation of Neoangiogenesis in Gastrointestinal Cancers	50	Sep 2017 (unknown; last updated Feb 2016)
NCT02799420	Role of Probe-based Confocal Laser Endomicroscopy Targeted Biopsy in the Molecular Study of Undifferentiated Gastric Cancer	74	Sep 2017 (recruitment completed; last updated Oct 2017)
NCT02930616	A Comparison of pCLE Based Targeted Biopsy and WLE Based Standard Biopsy in Staging the Operative Link on Gastric Intestinal Metaplasia (OLGIM): A Randomized Cross-over Study	40	Jun 2017 (unknown; last updated Oct 2016)
NCT01887509	Evaluation of Rectal Tumor Margin Using Confocal Endomicroscopy and Comparison to Histopathology	21	Oct 2016 (terminated due to patient recruitment,)

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02632682	Real-Time Diagnosis of Barrett’s Esophagus: Comparing Confocal Laser Endomicroscopy with Conventional Histology for the Identification of Specialized Intestinal Metaplasia	172	Sep 2016 (completed; last updated Dec 2016)
NCT01931579	Assessment of Probe Based Confocal Laser Endo-microscopy for In-vivo Diagnosis of Peripheral Lung Nodules and Masses (NODIVEM Study)	120	Jun 2016 (completed; last updated Aug 2016)
NCT02515721			

NCT: national clinical trial.

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- 09/04/2014 Medical Policy Committee review
- 09/17/2014 Medical Policy Implementation Committee approval. New policy.
- 09/03/2015 Medical Policy Committee review
- 09/23/2015 Medical Policy Implementation Committee approval. No change to coverage.
- 09/08/2016 Medical Policy Committee review
- 09/21/2016 Medical Policy Implementation Committee approval. No change to coverage.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 10/01/2017 Coding update: Removing ICD-9 Diagnosis codes
- 09/07/2017 Medical Policy Committee review
- 09/20/2017 Medical Policy Implementation Committee approval. No change to coverage.
- 09/06/2018 Medical Policy Committee review
- 09/19/2018 Medical Policy Implementation Committee approval. No change to coverage.
- 09/05/2019 Medical Policy Committee review
- 09/11/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/03/2020 Medical Policy Committee review
- 09/09/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Policy # 00416

Original Effective Date: 09/17/2014

Current Effective Date: 10/12/2020

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0397T, 43206, 43252, 88375
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

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diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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