Confocal Laser Endomicroscopy

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus is addressed separately in medical policy 00261.

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, 2 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. Confocal laser endomicroscopy 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. CLE would be proposed as an alternative to the current standard approach, recommended by the American Gastroenterological Association, which is that patients with Barrett esophagus who do not have dysplasia undergo endoscopic surveillance every 3 to 5 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, 2 systems have been used in a number of studies conducted in different countries. These include 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 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.

Cellvizio®‡ (Mauna Kea Technologies) is a confocal microscopy device 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 (F400-v2) 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, 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. FDA product codes: GCJ, GWG, OWN.

Confocal Video Colonoscope (Pentax Medical) is an endoscopy-based CLE system. The EC-38 70 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 device is intended to provide optical and

microscopic visualization of and therapeutic access to the lower gastrointestinal tract. FDA product code: GCJ/FDF (endoscope and accessories). This device is no longer commercially available from the manufacturer.

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows in vivo microscopic imaging of cells during endoscopy. Confocal laser endomicroscopy 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 confocal laser endomicroscopy (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. In 3 published systematic reviews, pooled estimates of the overall

sensitivity of CLE ranged from 81% to 94%, and pooled estimates of the specificity ranged from 88% to 95%. 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 that the technology results in an improvement in the net health outcome.

For individuals who have Barrett esophagus (BE) who are undergoing surveillance and receive CLE with targeted biopsy, the evidence includes several randomized-controlled trials (RCTs) and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. Evidence from RCTs has suggested 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 (NPV) of available studies were not sufficiently high to replace the standard surveillance protocol. In a 2022 meta-analysis, the absolute increase in neoplasia detection using CLE compared with the Seattle protocol randomized biopsies was 5%. Additionally, dysplasia prevalence was 4% with Seattle protocol randomized biopsies and 9% with CLE. National guidelines continue to recommend 4-quadrant random biopsies for patients with BE 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.

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 that includes a single RCT and 2 prospective, nonrandomized studies. Relevant outcomes are OS, disease-specific survival, test validity, and resource utilization. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 mainly consists of 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Gastrointestinal Endoscopy
The American Society for Gastrointestinal Endoscopy (ASGE, 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."

In 2019, the ASGE published a guideline on screening and surveillance of Barrett esophagus (BE) which recommends against routine use of confocal laser endomicroscopy (CLE) compared with white-light endoscopy with Seattle protocol biopsy sampling in patients with BE undergoing surveillance. An older guideline from the Society (2012) on the role of endoscopy in BE and other premalignant conditions of the esophagus stated the following: "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."

In 2014, the ASGE published a technology status evaluation on 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...Although current studies of CLE seem promising, these have primarily been in academic centers, and their generalizability in nonacademic practices is unknown."
2. The "learning curve of CLE image interpretation, use of CLE devices, and additional time needed to perform the procedure...."

3. "The clinical efficacy of the technology … compared with other available advanced imaging technologies...."
4. "Improvements in CLE imaging and image interpretation...."

The ASGE published guidelines on the role of endoscopy in benign pancreatic disease in 2015 and stated that "confocal endomicroscopy is an emerging technology that may prove useful for the evaluation of indeterminate pancreatic strictures." Similarly, in the ASGE's 2016 guidelines on the role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms, they acknowledged that CLE was an emerging technique for pancreatic lesion evaluation, but made no formal recommendations regarding its use.

American Gastroenterological Association

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

Table 2. Recommendations on Endoscopic Surveillance of Barrett Esophagus

Recommendation	LOR	QOE
"We [the guideline developers] suggest that endoscopic surveillance be performed in patients with Barrett's esophagus."	Weak	Moderate
"We [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, we [the guideline developers] recommend:	Strong (for all)	Moderate (for all)

• 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."		
"We [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.

In 2016, the AGA published a clinical practice update expert review on the diagnosis and management of low-grade dysplasia in BE. Regarding the use of other advanced endoscopic imaging techniques, the guideline stated that the use of confocal laser endomicroscopy "cannot be recommended in the routine clinical management" of patients undergoing surveillance.

In 2022, the AGA published a clinical practice update on new technology for surveillance and screening in BE. The article makes the following best practice advice statement relevant to screening and surveillance for BE:

- "Screening and surveillance endoscopic examination should be performed using high-definition white light endoscopy and virtual chromoendoscopy, with endoscopists spending adequate time inspecting the Barrett's segment."

None of the best practice advice statements mentioned CLE. While the article did summarize data in support of innovative screening technologies such as CLE, the panelists noted that: "the use of these techniques was not required for a high-quality exam and the data to date did not support its

routine use." However, the panelists also noted that "these technologies were promising and carried potential benefits in select cases and currently might be best utilized in expert centers."

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
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04154683	Diagnostic Performance of Optical Biopsy by Cellvizio®‡ in Gynecological Surgery (GYNECOPTIC)	100	Jun 2025
NCT03492151	Confocal Laser Endomicroscopy as an Imaging Biomarker for the Diagnosis of Pancreatic Cystic Lesions (CLIMB)	500	Dec 2024
NCT01034670	Advanced Gastrointestinal Endoscopic Imaging	500	Dec 2025
NCT04535414	Phase II Randomized Trial of Bethesda Protocol Compared to Cambridge Method for Detection of Early Stage Gastric Cancer in CDH1 Mutation Carriers	350	Dec 2027

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05556525	Needle-Based Confocal Laser Endomicroscopy With Fluorescein and Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Lung Cancer in Patients With Peripheral Pulmonary Nodules	118	May 2024

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

Confocal Laser Endomicroscopy

Policy # 00416
Original Effective Date: 09/17/2014
Current Effective Date: 10/14/2024

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.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/07/2023	Medical Policy Committee review
09/13/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/05/2024	Medical Policy Committee review
09/11/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2025

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 2023 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units,

conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.