FEP Medical Policy Manual

FEP 2.01.87 Confocal Laser Endomicroscopy

Annual Effective Policy Date: April 1, 2026

Original Policy Date: March 2013

Related Policies:

2.01.84 - Chromoendoscopy as an Adjunct to Colonoscopy
6.01.32 - Virtual Colonoscopy/Computed Tomography Colonography

Confocal Laser Endomicroscopy

Description

Description

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 individuals with inflammatory bowel disease or Barrett esophagus.

OBJECTIVE

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

POLICY STATEMENT

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

FDA 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 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

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

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 College of Gastroenterology

In 2022, the American College of Gastroenterology (ACG) published guidelines on the diagnosis and management of Barrett esophagus (BE).[53,] Recommendations related to this policy include the following:

- "We recommend both white light endoscopy and chromoendoscopy in patients undergoing endoscopic surveillance of BE (quality of evidence: moderate; strength of recommendation: strong)."

Although confocal laser endomicroscopy (CLE) is not explicitly recommended, the guideline does mention it as an advanced imaging tool and states "in centers with a high prevalence of neoplasia or dysplasia, CLE may be helpful in targeting biopsies and guiding therapy, although the value above that of high-definition white light and electronic chromoendoscopy is unclear."

American Gastroenterological Association

In 2011, the American Gastroenterological Association (AGA) published a position statement on the management of BE.[1,] 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: • 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 (for all)	Moderate (for all)
"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.

Recommendations regarding treatment of BE were updated in 2024.[54,] No updates were made to recommendations regarding surveillance. The 2011 guidelines have additional updates in development.

In 2016, the AGA published a clinical practice update expert review on the diagnosis and management of low-grade dysplasia in BE.[55,] 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.[56,] The article makes the following best practice advice statements 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."
- "Advanced imaging technologies such as endomicroscopy may be used as adjunctive techniques to identify dysplasia."

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."

In 2024, the AGA published an expert review on appropriate and tailored polypectomy.[57,] In terms of testing, they state that "a structured visual assessment using high-definition white light and/or electronic chromoendoscopy and with photodocumentation should be conducted for all polyps found during routine colonoscopy." They do not mention CLE within the guideline.

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.[58,] Regarding the use of confocal endoscopy as an adjunct to white-light endoscopy, the guidelines stated that this technique is "still in development." A revision of these guidelines was published in 2015 to include discussion of malignant conditions of the stomach.[59,] Within this guideline, CLE was not mentioned.

In 2019, the ASGE published a guideline on screening and surveillance of BE which recommends against routine use of CLE compared with white-light endoscopy with Seattle protocol biopsy sampling in patients with BE undergoing surveillance.[12,] 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."[60,]

In 2014, the ASGE published a technology status evaluation on CLE.[13,] 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."[61,] 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.[62,]

U.S. Preventive Services Task Force Recommendations

The 2021 **U.S. Preventive Services Task Force** recommendations on colorectal cancer screening do not mention CLE.[63,]

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2013	New policy	
March 2014	Replace 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	Replace policy	Policy updated with literature review. Policy statement unchanged. References 12, 16-17, 22-23, and 28 added.
June 2016	Replace 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	Replace policy	Policy updated with literature review; references 13 and 29-30 added. Policy statement changed from not medically necessary to investigational due to FDA 510(k) clearance.
March 2018	Replace policy	Policy updated with literature review through September 11, 2017; no references added. Policy statement unchanged.
March 2019	Replace policy	Policy updated with literature review through September 6, 2018; references 35-36 added. Policy statement unchanged.
March 2020	Replace policy	Policy updated with literature review through September 9, 2019; references added. Policy statement unchanged.
April 2021	Replace policy	Policy updated with literature review through October 1, 2020; references added. Policy statement unchanged.
December 2022	Replace policy	Policy updated with literature review through September 29, 2021; references added. Policy statement unchanged.
March 2023	Replace policy	Policy updated with literature review through October 17, 2022; references added. Policy statement unchanged.
March 2024	Replace policy	Policy updated with literature review through September 26, 2023; references added. Policy statement unchanged.
March 2025	Replace policy	Policy updated with literature review through October 7, 2024; no references added. Policy statement unchanged.
March 2026	Replace policy	Policy updated with literature review through September 17, 2025; references added. Policy statement unchanged.