FEP 2.01.87 Confocal Laser Endomicroscopy

Effective Date: April 1, 2019

Related Policies:
2.01.84 Chromoendoscopy as an Adjunct to Colonoscopy
6.01.32 Virtual Colonoscopy/Computed Tomography
Colonography

Confocal Laser Endomicroscopy

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.

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 m 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. 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.

OBJECTIVE

The objectives of this evidence review is to determine whether 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.

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 FDA through the 510(k) process.
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 FDA in 2006, can be used with any standard endoscope with a working channel of at least 2.8 mm. According to 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 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 FDA in 2004, is used with a Pentax Video Processor and with a Pentax Confocal Laser System. According to 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).

**RATIONALE**

**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, 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 the technology on health outcomes.

For individuals who have Barrett esophagus who are undergoing surveillance who receive CLE with targeted biopsy, the evidence includes several RCTs and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test validity, and resource utilization. Evidence from RCTs 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 evidence is insufficient to determine the effects of the technology on health outcomes.

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

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. Relevant outcomes are overall survival, 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 the technology on health outcomes.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy
In 2006 (reaffirmed in 2011), the American Society for Gastrointestinal Endoscopy published guidelines on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.[35][36]

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:

- "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."
- "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 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."
- "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 esophagastroduodenoscopy] (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 published a technology status evaluation on confocal laser endomicroscopy (CLE) in 2014.[35]

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:

- "[T]he applicability and practicality of CLE, especially in community settings [because the research has been done] primarily in academic centers."
- The "learning curve of CLE image interpretation … and additional time needed to perform the procedure…."
- The clinical efficacy of the technology … compared to other available advanced imaging technologies…."
- Improvements in CLE imaging and image interpretation….."

American Gastroenterological Association
In 2011, the American Gastroenterological Association published a position statement on the management of Barrett esophagus.[1]
The statement included the following recommendations on endoscopic surveillance of Barrett esophagus (see Table 1).

**Table 1. Recommendations on Endoscopic Surveillance of Barrett Esophagus**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOR</th>
<th>QOE</th>
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<tbody>
<tr>
<td>1 “The guideline developers suggest that endoscopic surveillance be performed in patients with Barrett’s esophagus.”</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>2 “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”</td>
<td>Weak</td>
<td>Low</td>
</tr>
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<td>3 “For patients with Barrett’s esophagus who are undergoing surveillance, 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.”</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>4 The guideline developers suggest against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett’s esophagus at this time.”</td>
<td>Weak</td>
<td>Low</td>
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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. [37]

**Medicare National Coverage**

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

**REFERENCES**

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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>March 2013</td>
<td>New Policy</td>
<td>Policy updated with literature search. No change to policy statement. References 5, 6, 12, 16, 22, &amp; 23 added; others renumbered or removed.</td>
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<tr>
<td>March 2017</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 13 and 29-30 added. Policy statement changed from not medically necessary to investigational due to FDA 510k clearance.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through September 6, 2018; references 35-36 added. Policy statement unchanged.</td>
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