Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

RELATED PROTOCOL
Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With suspected or known colorectal lesions</td>
<td>• Confocal laser endomicroscopy as an adjunct to colonoscopy</td>
<td>• White-light colonoscopy alone</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Colonoscopy used with alternative adjunctive diagnostic aids</td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With Barrett esophagus who are undergoing surveillance</td>
<td>• Confocal laser endomicroscopy with targeted biopsy</td>
<td>• Standard endoscopy with random biopsy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With gastrointestinal lesions and have had endoscopic treatment</td>
<td>• Confocal laser endomicroscopy to assess the adequacy of endoscopic treatment</td>
<td>• Standard endoscopy (i.e., white-light endoscopy)</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With suspicion of a condition diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer)</td>
<td>• Confocal laser endomicroscopy</td>
<td>• Standard diagnostic procedures</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resource utilization</td>
</tr>
</tbody>
</table>

DESCRIPTION
Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy,
Confocal Laser Endomicroscopy, allows in vivo microscopic imaging of the mucosal epithelium 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 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 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 (e.g., 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 who are undergoing surveillance who receive CLE with targeted biopsy, the evidence includes several randomized controlled trials (RCTs) and 2 meta-analyses. Relevant outcomes are OS, 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 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 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 (e.g., 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.

POLICY
Use of confocal laser endomicroscopy is considered investigational.

BACKGROUND
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 pin-
hole 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 μm 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 conven-
tional 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 colon-
oscropy, 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 associa-
tion with screening or surveillance colonoscopy, which could allow for small hyperplastic lesions to be over-
looked 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.2 The American Gastroenterologi-
cal 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 inter-
nationally 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.2 Lesion classification systems are less developed for
non-gastrointestinal lesions viewed by CLE devices (e.g., 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.3,4.

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 (i.e., a probe-based
CLE system). The device consists of a laser scanning unit, proprietary software, a flat-panel display, and miniatur-
ized 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 endo-
scope. 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 laparo-
scopic 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, i.e., 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. 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).

### Table 1. Endomicroscopy Devices Cleared by the U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Date Cleared</th>
<th>510(k) No.</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellvizio 100 Series Confocal Laser Imaging Systems and Their Confocal Miniprobes</td>
<td>Mauna Kea Technologies</td>
<td>02/22/2019</td>
<td>K183640</td>
<td>For use in endomicroscopy</td>
</tr>
<tr>
<td>Ec-3870cilk, Confocal Video Colonoscope</td>
<td>Pentax Medical Company</td>
<td>10/19/2004</td>
<td>K042741</td>
<td>For use in endomicroscopy</td>
</tr>
</tbody>
</table>

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

### REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


