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Medical Benefit		Effective Date: 07/01/13	Next Review Date: 03/19
Preauthorization	No	Review Dates: 03/13, 03/14, 03/15, 03/16, 03/17, 03/18	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With suspected or known colorectal lesions 	Interventions of interest are: <ul style="list-style-type: none"> Confocal laser endomicroscopy as an adjunct to colonoscopy 	Comparators of interest are: <ul style="list-style-type: none"> White-light colonoscopy alone Colonoscopy used with alternative adjunctive diagnostic aids 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Resource utilization
Individuals: <ul style="list-style-type: none"> With Barrett esophagus who are undergoing surveillance 	Interventions of interest are: <ul style="list-style-type: none"> Confocal laser endomicroscopy with targeted biopsy 	Comparators of interest are: <ul style="list-style-type: none"> Standard endoscopy with random biopsy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Resource utilization
Individuals: <ul style="list-style-type: none"> With gastrointestinal lesions and have had endoscopic treatment 	Interventions of interest are: <ul style="list-style-type: none"> Confocal laser endomicroscopy to assess the adequacy of endoscopic treatment 	Comparators of interest are: <ul style="list-style-type: none"> Standard endoscopy (i.e., white-light endoscopy) 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Resource utilization
Individuals: <ul style="list-style-type: none"> With suspicion of a condition diagnosed by identification and biopsy of lesions (e.g., lung, bladder, or gastric cancer) 	Interventions of interest are: <ul style="list-style-type: none"> Confocal laser endomicroscopy 	Comparators of interest are: <ul style="list-style-type: none"> Standard diagnostic procedures 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Resource utilization

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.

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 accuracy and 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 (e.g., 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 accuracy and 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 four-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 accuracy and 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 (e.g., 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 accuracy and 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.

Policy

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

Background

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 is 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 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

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. 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.¹ The American Gastroenterological Association has further recommended that random four-quadrant biopsies every two 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 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.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 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.^{3,4}

Regulatory Status

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

Cellvizio® (Mauna Kea Technologies, Paris, France) is a confocal microscopy 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 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 confocal laser 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. FDA product code: GCJ.

Confocal Video Colonoscope (Pentax Medical, Montvale, NJ) 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).

Related Protocol

Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus

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

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