TECHNOLOGY STATUS EVALUATION REPORT

Video capsule endoscopy

Prepared by: ASGE TRAINING COMMITTEE


The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the “related articles” feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through September 2019 using terms such as “wireless capsule endoscopy,” “capsule endoscopy,” “video capsule endoscopy,” “colon capsule,” and “colon capsule endoscopy,” among others. Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

Video capsule endoscopy (VCE) enables visualization of the mucosal surface throughout the GI tract in a minimally invasive manner. Since initial U.S. Food and Drug Administration (FDA) approval in 2001, this technology has been refined to provide superior resolution, increased battery life, and capabilities to view different parts of the GI tract. VCE has an established, essential role in the evaluation of small-bowel lesions and bleeding. Potential clinical applications for VCE have expanded to include the evaluation of inflammatory bowel disease and screening for colorectal neoplasia in selected patients. This document is an update of a 2013 ASGE Technology Committee article entitled “Wireless Capsule Endoscopy” and reviews currently available VCE systems and their applications.

TECHNOLOGY UNDER REVIEW

Commercially available VCE systems intended for imaging of the upper GI (UGI) tract, small bowel, and colon are detailed in Table 1. VCE systems marketed in the United States typically consist of a capsule endoscope, a sensing system attached to the patient that includes either sensing arrays or a sensing belt, a data recorder and battery pack, and software for image review and interpretation. Many systems include external viewers or viewers integrated with the data recorder that allow real-time review of images during VCE examinations (RAPID Real-Time [Given Imaging/Medtronic, Minneapolis, Minn, USA], Real Time Viewer [Olympus America, Center Valley, Penn, USA], and MiroView Express [IntroMedic, Seoul, South Korea]).

Capsule endoscopes may be swallowed or placed endoscopically after activation and subsequently progress through the GI tract by peristalsis until excreted naturally. Typical device setup includes placement of a lead sensor array onto the patient’s abdomen; the sensors are connected to the recorder, which is worn or carried by the patient. The CapsoCam Plus (CapsoVision, Saratoga, Calif, USA) is the only VCE system that does not include a sensing system. Instead, its capsule endoscope stores images in onboard memory for subsequent download after the capsule is retrieved by the patient after excretion. For most VCE systems, a simplified belt that includes
internal sensors can be used instead of affixing sensor
arrays directly to the patient’s skin. Traditional sensor
arrays are generally suggested for use in obese patients.
After ingestion of the capsule, patients are instructed to
avoid intense exercise or activities that may cause the
sensors to detach.

Capsule endoscopes measure 24 to 32 mm in length
and 11 to 15 mm in diameter, depending on the manufac-
turer and product line. All capsule endoscopes have similar
components: a disposable plastic-coated capsule, a metal
oxide semiconductor or high-resolution charge-coupled
device image capture system, a compact lens, light-
emitting diode illumination sources, and an internal bat-
tery source. The mode of data transmission from the
capsule is either via ultra-high frequency band radio telem-
etry (PillCam [Medtronic, Minneapolis, Minn, USA], Endo-
Capsule [Olympus, Center Valley, Penn, USA]) or human
body communications (Mirocam, Intromedic Seoul, Seoul,
South Korea). The latter technology uses the capsule itself
to generate an electrical field that uses human tissue as the
conductor for data transmission. Capsule endoscopes with
extended battery life may be beneficial in patients with de-
layed gastric and small-bowel transit (Table 1).

Proprietary software is used to process and display the
images in single or multiple views at user selectable rates
of 3 to 40 frames per second (fps). Representative images
and video clips can be annotated and saved. All available
software can identify red pixels to facilitate detection of
bleeding lesions. Additional software features available on
all systems include localization data and progress of
capsule transit within the GI tract, quick reference image
atlases, and report generation capabilities (Table 2).

Upper GI VCE

The PillCam UGI capsule (Medtronic, Minneapolis,
Minn, USA) is the only VCE system currently marketed
for gastric and esophageal applications. The capsule di-
ensions, transmission wavelength, field of view, resolu-
tion, and interpretation software are identical to the
PillCam SB3. However, the capsule battery life is only 90
minutes (vs 8-12 hours for small-bowel capsules), cameras
are located on both ends of the capsule, and the capsule
captures images at a higher frame rate (18-35 fps). Variable
frame rate technology operates at 35 fps for the first 10 mi-
utes of the procedure and 18 fps for the last 80 minutes.

According to the manufacturer, the patient should be
fasting for at least 2 hours before ingestion of the UGI-
VCE. Three thoracic sensors should then be affixed to
the patient in a designated pattern that are connected to the
data recorder. Finally, a specific ingestion protocol is rec-
mended by the manufacturer to maximize time for the
capsule to capture images as it traverses the esophagus.

Small-bowel VCE

Small-bowel (SB)-VCE systems are detailed in Table 1.
Before SB-VCE, fasting or consumption of clear liquids
for 10 to 12 hours is commonly recommended; some cen-
ters instruct a clear liquid diet for 24 hours before the
study. A full or partial bowel preparation the night before
the study has been advocated to improve visualization of
the small intestine, although data are conflicting.4-5 A diet
of clear liquids is allowed after 2 hours from capsule
ingestion and a light meal after 4 hours. An exception
to these dietary recommendations is with the Mirocam
system, where the manufacture stipulates that patients
may drink water immediately after the capsule is
swallowed and may continue to drink water throughout
the entire procedure. The reusable data recording
system can be disconnected from the patient after the
lifespan of the battery has expired or after the capsule is
excreted, whichever comes first. Most capsules are
designed to be excreted without a need for collection.
The CapsoCam Plus capsule does require that the
capsule be retrieved for data to be uploaded by use of a
magnetic wand that retrieves the capsule once excreted.
After data upload from the capsule, the images are
available for review and interpretation via the proprie-
tary software. As an alternative, CapsoVision also
markets a service in which patients mail in their
retrieved capsules to a central download center, which
then uploads the examination data into a secure, cloud-
based portal, allowing remote access and review by the
clinician.

Colon VCE

Two video colon capsule endoscopy (CCE) systems
(PillCam COLON 2 and PillCam Crohn’s, Medtronic, Sunny-
vale, Calif, USA) have been cleared by the FDA for colon
visualization. PillCam COLON 2 is designed for visualiza-
tion of the colon, whereas PillCam Crohn’s is designed
for the visualization of both the small bowel and the colon
and has been specifically marketed for the assessment of
Crohn’s disease (CD) activity. Specifications on these sys-
tems are summarized in Tables 1 and 2, and additional
information is provided in the next sections.

CCE is intended to completely image the colorectal mu-
cosa. CCE has been used when colonoscopy is incomplete,
for colorectal cancer (CRC) screening in patients at
increased risk for procedural adverse events, and for
assessment of inflammatory bowel disease activity. CCE
was first introduced in 2008 and does not require sedation.
PillCam COLON 2 (CCE-2) has replaced the original Pill-
Cam COLON capsule endoscopy system (Medtronic, Min-
neapolis, Minn, USA) and features a wider field of view
(up to 172 degrees), improved camera optics, and a higher
frame rate (up to 35 fps).6

To ensure adequate colon imaging while maintaining
battery life (≥10 hours), the CCE-2 captures images at
14 frames per minute after duodenal recognition. After
a built-in time delay, the capsule uses adaptive frame
rate technology to allow image capture at a variable
rate: 4 fps when the capsule is moving slowly and 35 fps

www.giejournal.org
when moving quickly through the colon. The CCE-2 software includes a polyp size estimation tool. Lesion location is estimated using landmarks visible in the video (particularly the cecum and anus) and a software program that displays the approximate position of the capsule in the abdominal–pelvic cavity. Mucosal visualization is inherently dependent on and frequently limited by the quality of the bowel preparation. Studies have used various polyethylene glycol–based preparations followed by "boosters" (eg, sodium phosphate or sodium picosulfate), and optimal preparation for CCE remains an area of investigation.8,9 Current technology does not allow tissue extraction, inflation of air, suction of debris, or movement control. Thus, adequate bowel cleansing and expansion to ensure a "submarine view" are the most important factors for CCE success. Bowel preparations for CCE-2 are more intensive than those used for colonoscopy. A clear liquid diet is recommended on the day before the procedure, and a split-dose 4-L polyethylene glycol preparation is used. After CCE-2 ingestion, an alert from the recorder (Alert 0) occurs if the capsule has not passed from the stomach in 1 hour, prompting those patients to take metoclopramide 10 mg on an as-needed basis. After the capsule enters the small bowel, an alert (Alert 1) prompts all patients to ingest a "booster" of 6 ounces of sodium sulfate/potassium sulfate/magnesium sulfate diluted in water to 8 ounces followed by 1 L of water). If the capsule is not excreted by 2 hours after the second booster, Alert 3 prompts the administration of two 10-mg bisacodyl suppositories.10

### SB-VCE and CCE

PillCam Crohn’s was cleared by the FDA in 2017 and permits visualization of the small bowel and colon in a single procedure. The PillCam Crohn’s system includes the same data recorder, sensors, and capsule endoscope as the CCE-2 system as well as the 4- to 35-fps adaptive frame rate technology. In contrast, however, the PillCam Crohn’s capsule begins adaptive frame rate mode immediately on duodenal recognition. The software program includes additional tools to enable quantitative assessment and reporting of CD over time and an ulcer size estimation tool.

### Capsule deployment assistance device

The AdvanCE (US Endoscopy, Mentor, Ohio, USA) device allows endoscopic delivery of the capsule endoscope in those patients who cannot ingest the capsule or have an anatomic or motility abnormality. The system includes a disposable 180-cm catheter with a sheath diameter of 2.5 mm that is preloaded through the endoscope device channel. A specialized capsule cup is screwed onto the distal end of the catheter, and the activated video capsule is loaded into the cup. The upper endoscope and device are then advanced to the desired anatomic area, and the capsule is released via actuation of a thumb ring in the handle at the proximal aspect of the catheter.

<table>
<thead>
<tr>
<th>Company</th>
<th>Size (mm)</th>
<th>Weight (g)</th>
<th>Field of view (degree)</th>
<th>Images/s</th>
<th>Battery life (battery life depends on storage conditions; the warmer the shorter)</th>
<th>Resolution (pixels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PillCam SB 3 capsule, Medtronic</td>
<td>11 x 26</td>
<td>3</td>
<td>156°</td>
<td>2-6</td>
<td>8 hours</td>
<td>320 x 320</td>
</tr>
<tr>
<td>PillCam SB 3 EX capsule, Medtronic</td>
<td>11 x 26</td>
<td>3</td>
<td>156°</td>
<td>2-6</td>
<td>Minimum of 12 hours</td>
<td>320 x 320</td>
</tr>
<tr>
<td>PillCam COLON 2 capsule, Medtronic</td>
<td>11 x 32</td>
<td>2.9</td>
<td>172</td>
<td>4-35</td>
<td>Minimum of 10 h</td>
<td>256 × 256</td>
</tr>
<tr>
<td>PillCam Crohn’s capsule, Medtronic</td>
<td>11 x 32</td>
<td>2.9</td>
<td>168</td>
<td>4-35</td>
<td>Minimum of 10 h</td>
<td>256 × 256</td>
</tr>
<tr>
<td>PillCam UGI, Capsule, Medtronic</td>
<td>11 x 32</td>
<td>2.9</td>
<td>172</td>
<td>18-35</td>
<td>90 min</td>
<td>256 × 256</td>
</tr>
<tr>
<td>EndoCapsule, Olympus</td>
<td>11 x 26</td>
<td>3.3</td>
<td>160</td>
<td>2</td>
<td>12 h</td>
<td>Pixels, 221, 884</td>
</tr>
<tr>
<td>CapsoCam Plus, CapsoVision, Inc</td>
<td>11 x 31</td>
<td>4</td>
<td>360</td>
<td>5 fps per camera (max. fps)</td>
<td>15 h (approximate)</td>
<td>320 x 320</td>
</tr>
<tr>
<td>Mirocam single-lens capsule</td>
<td>10.8 x 24.5</td>
<td>3.2</td>
<td>170</td>
<td>3 fps</td>
<td>12 h minimum</td>
<td>320 x 320</td>
</tr>
<tr>
<td>Mirocam dual-lens capsule</td>
<td>10.8 x 230.1</td>
<td>3.5</td>
<td>340</td>
<td>3 fps per camera</td>
<td>12 h minimum</td>
<td>320 x 320</td>
</tr>
</tbody>
</table>

UGI, Upper GI.
AdvanCE system is compatible with capsules ranging from 10.5 mm to 11.5 mm in diameter and 23.5 mm to 26.5 mm in length.

**Luminal patency assessment devices**

Capsule retention proximal to an intestinal stenosis is a well-recognized adverse event of VCE and may necessitate removal either endoscopically or surgically. A radiopaque nonvideo capsule, the PillCam Patency capsule, consists of a small radiofrequency identification tag surrounded by an absorbable material with a small amount of barium. The PillCam Patency capsule has similar dimensions (11.4 mm × 26.4 mm) and the same shape as a standard capsule. At 30 hours, time-controlled plugs at the ends of a retained capsule erode, which allows intestinal fluids to dissolve the capsule body. The radiofrequency identification tag is 3 mm × 13 mm and is activated and detected by a handheld, battery-operated scanner, or, alternatively, a kidneys, ureters, bladder (KUB) x-ray could be performed to detect a retained capsule. Nondegraded parts are small enough that they can ultimately pass through tight strictures.

## INDICATIONS AND CONTRAINDICATIONS

The PillCam UGI capsule has been cleared by the FDA for visualization of the esophagus and stomach. The most common applications include evaluation for suspected Barrett’s esophagus (BE), reflux esophagitis, or esophageal varices, typically in patients who either refuse or are otherwise unable to undergo upper endoscopy. The most common clinical applications of SB-VCE include evaluation of both overt and occult small-bowel bleeding, suspected CD activity assessment, surveillance in patients with polyposis syndromes, suspected small intestine tumors, and suspected or refractory malabsorptive syndromes (eg, celiac disease).

The CCE-2 has been cleared by the FDA for detection of colon polyps in patients after an incomplete colonoscopy with adequate preparation and in patients for whom complete evaluation of the colon was not technically feasible. The CCE-2 has also been approved by the FDA for colonic evaluation in patients with major risks for colonoscopy or moderate sedation but who could tolerate colonoscopy and moderate sedation in the event a clinically significant colon abnormality is identified. The CCE-2 can be used for detection of colon polyps in patients with evidence of GI bleeding of lower GI origin. PillCam Crohn’s has been cleared by the FDA for visualization of the small bowel and colonic mucosa. It is marketed for the visualization and monitoring of lesions in the colon and small bowel that may indicate CD. PillCam Crohn’s may also be used for the same clinical applications as routine SB-VCE.

VCE is contraindicated in patients with known or suspected intestinal obstruction, strictures, or fistulas and in patients with cardiac or other implanted electrical devices. Theoretical and clinical evidence shows that patients with implanted cardiac devices (eg, pacemakers, defibrillators, or left ventricular assist devices) can safely undergo VCE; however, compromise of VCE videos has been reported. Although capsule manufacturers still cite these cardiac devices as a contraindication, the most recent guidelines from the American Gastroenterological Association and

---

**TABLE 2. Additional software features**

<table>
<thead>
<tr>
<th></th>
<th>Bleeding mode</th>
<th>Image compression</th>
<th>Camera position</th>
<th>Rapid reader/express play</th>
<th>Image viewing single image</th>
<th>Image viewing 2 images</th>
<th>Image viewing quad images</th>
<th>Image viewing range view 19 consecutive images</th>
<th>Panoramic viewing</th>
<th>Cloud reading access</th>
<th>Server and networking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirocam single lens</td>
<td>X</td>
<td>Full Images with 3 reading modes</td>
<td>Forward</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mirocam dual lines</td>
<td>X</td>
<td>Full Images with 3 reading modes</td>
<td>Forward X2 Ends</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pill cam SB3</td>
<td>X</td>
<td>Software Calculates</td>
<td>Forward</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pill cam EX</td>
<td>X</td>
<td>Software Calculates</td>
<td>Forward</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Capsovision</td>
<td>X</td>
<td>Software Calculates</td>
<td>Side Viewing Only</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Endocapsule</td>
<td>X</td>
<td>Software Determines</td>
<td>Forward</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
the European Society of Gastrointestinal Endoscopy advocate that VCE can be performed in patients with pacemakers without special precautions. Concerns relevant to implantable electrical devices do not apply to the CapsoCam Plus VCE, because it does not transmit an external signal. If cardiac monitoring is necessary during VCE, wired systems should be used.

Manufacturers also discourage use of VCE in patients in whom magnetic resonance imaging is anticipated within 1 week of capsule ingestion. The theoretical concern in this setting is migration of the capsule and potential for bowel injury because of heat or high forces. Nevertheless, to date case reports of patients with retained VCEs undergoing magnetic resonance imaging have not described any adverse events. Endoscopic placement of the capsule should be considered in patients with swallowing disorders to avoid aspiration. Safety data regarding VCE during pregnancy are limited to single case reports.

EASE OF USE

VCE is a relatively straightforward test for patients who can swallow the capsule. Once the capsule is ingested, the patient may continue most daily activities as the capsule traverses the alimentary tract. Oral intake can occur within minutes to hours of swallowing the capsule, depending on the system used. A protocol should be in place to identify cases of capsule retention. Commonly, patients are asked to have an abdominal radiograph if capsule passage into the colon is not observed during review of the examination. During SB-VCE the entire small bowel can usually be visualized within the lifespan of the battery. However, factors such as luminal debris and gastric or small-bowel dysmotility can preclude a complete examination. Factors such as luminal debris and gastric or small-bowel dysmotility can preclude a complete examination. During SB-VCE the entire small bowel can usually be visualized within the lifespan of the battery. However, factors such as luminal debris and gastric or small-bowel dysmotility can preclude a complete examination. During SB-VCE the entire small bowel can usually be visualized within the lifespan of the battery. However, factors such as luminal debris and gastric or small-bowel dysmotility can preclude a complete examination. During SB-VCE the entire small bowel can usually be visualized within the lifespan of the battery. However, factors such as luminal debris and gastric or small-bowel dysmotility can preclude a complete examination.

ASGE guidelines state that readers of VCE should have either undergone formal VCE training during fellowship or have completed a formal GI- or surgical society–endorsed training course with proctoring of the first 10 capsule readings. UGI-VCE administration may be performed in an office or endoscopy lab setting and captures images for 90 minutes. CCE requires a more intensive bowel preparation than is used for colonoscopy, which may be potentially challenging for patients.

ASGE guidelines state that readers of VCE should have either undergone formal VCE training during fellowship or have completed a formal GI- or surgical society–endorsed training course with proctoring of the first 10 capsule readings. In a prospective single-center study, 39 trainees completed structured didactic VCE training, interpreted a variable number of VCE studies in a proctored manner, and then took a standardized examination that included multiple video clips and a complete VCE study for interpretation and labeling. The authors concluded that at least 20 proctored VCE studies should be interpreted before attempting to assess competency. Competency in VCE reading appears more dependent on VCE experience than prior endoscopy experience or type of specialty medical training. Typical reading times vary between 30 and 120 minutes and may be influenced by small-bowel transit time and the experience of the reader. For capsule examinations of the UGI tract the average reading time varies between 5 and 15 minutes.

OUTCOMES AND COMPARATIVE EFfICACY DATA

Upper GI VCE

A meta-analysis of 9 studies involving 618 patients that used upper endoscopy as a reference standard showed a pooled sensitivity and specificity of VCE for the diagnosis of BE of 77% and 86%, respectively. For the subgroup of 4 studies (n = 304) that reported results using histologic confirmation of intestinal metaplasia as a reference standard, the pooled sensitivity and specificity of VCE for the diagnosis of BE was 78% and 73%, respectively. A randomized controlled trial comparing transnasal endoscopy and UGI-VCE for outpatient BE screening in 184 veterans with or without GERD symptoms showed that both modalities are acceptable but UGI-VCE was better tolerated by patients. The rate of detection of BE was similar between the 2 modalities (3.2% for transnasal endoscopy vs 5.4% for UGI-VCE, P = .47). A sedated EGD with biopsy sampling was performed when abnormalities were detected and served as the reference standard. In a Markov model that compared UGI-VCE with EGD for BE screening in 50-year-old white men with reflux symptoms, EGD was more cost-effective than UGI-VCE.

How VCE compares with alternative minimally invasive modalities to detect BE devices such as Cytosponge (Medtronic, Fridley, Minn, USA) has not been compared directly.

UGI-VCE has also been evaluated for the detection of esophageal varices. A meta-analysis of 17 studies (n = 1328) reported a pooled sensitivity of 83% (95% confidence interval [CI], 76-89) and a pooled specificity of 85% (95% CI, 75-91), with EGD used as a reference standard. The diagnostic accuracy of UGI-VCE for the grading of esophageal varices (medium/large vs small) was 92% (95% CI, 90-94). In a French multicenter prospective study that evaluated 300 cirrhotic patients with sequential UGI-VCE and sedated EGD for variceal screening, UGI-VCE demonstrated suboptimal sensitivity for both variceal diagnosis (76%) and correct classification (64%) but was associated with higher patient satisfaction using a visual analog scale. In relation to both screening for BE and esophageal variceal assessment, VCE could have an individualized role in patients who refuse or have contraindications to EGD such as those who have high risk for sedation. Currently, VCE is not considered a current viable competitor to EGD based on the limited test characteristics as reported above.

UGI-VCE has also been studied as an initial triage tool to evaluate the location and severity of UGI bleeding before conventional endoscopic evaluation.
randomized controlled trial of 71 patients who presented with symptoms or signs suggestive of UGI bleeding, subjects were randomized to receive either standard treatment or an upfront UGI-VCE with real-time interpretation before any endoscopic evaluation. Of the 37 patients enrolled into the UGI-VCE arm, only 7 patients (18.9%) had active bleeding or significant endoscopic findings necessitating hospital admission for endoscopy, whereas all 34 in the control group were admitted. There was no difference in recurrent bleeding or 30-day mortality between the 2 groups. Currently, UGI-VCE cannot be considered an alternative to EGD in the setting of GI bleeding; further work is needed on how to safely use UGI-VCE in low-risk patients as a tool to delay or forego EGD.

Small-bowel VCE

SB-VCE has been used in the evaluation of diverse diseases of the small bowel, and multiple studies have compared SB-VCE with other imaging and endoscopic modalities. Studies frequently report detection in terms of “diagnostic yield” or the ability to detect a finding deemed clinically significant. However, because the reference standard of pathologic tissue acquisition is not always possible during SB-VCE studies, diagnostic yield might not necessarily correlate with true diagnostic accuracy. For evaluation of possible inflammatory lesions, bleeding, or CD it is recommended that nonsteroidal anti-inflammatory drugs (NSAIDs) be stopped before the VCE for at least 1 month if possible because erosions and ulcerations from NSAID use can be challenging to differentiate from inflammatory bowel disease. A meta-analysis of 11 studies compared the diagnostic yield of SB-VCE with double-balloon enteroscopy (DBE) in overall diagnostic yield for small-bowel pathology. The pooled overall yield was not significantly different between SB-VCE (60%, n = 397) and DBE (57%, n = 360). In subanalyses, the ability to diagnose inflammatory conditions, vascular lesions, and tumors also did not differ between the modalities. Given the similar diagnostic yield across varied pathologies, SB-VCE is frequently the preferred modality for small-bowel evaluations including iron deficiency anemia after EGD and colonoscopy given the minimally invasive nature of VCE.

There may be instances when alternative small-bowel imaging approaches may be preferential to SB-VCE. CT enterography (CTE) or magnetic resonance enteroscopy (MRE) can be complementary to SB-VCE, with superior detection of some specific lesions. In a study of 52 patients with potential small-bowel bleeding, all subjects underwent both VCE and CTE. The diagnostic yield was higher with VCE (59.6%) compared with CTE (30.8%, P = .004). VCE was better for detecting ulcers, enteritis, and angiodysplasia, whereas CTE was more sensitive in detecting tumors and Meckel diverticula. MRE and CTE provide additional extraluminal information and permit contrast enhancement and can be considered first-line studies when small-bowel tumors are suspected. Finally, patency capsule or multiphase CTE or MRE should be performed before SB-VCE if the patient has risk factors for capsule retention.

Small-bowel bleeding. Approximately 5% to 10% of GI bleeding originates from the small intestine, and small-bowel bleeding is the most common indication for SB-VCE. Multiple GI society guidelines recommend SB-VCE as the first-line procedure for evaluation of small-bowel bleeding after nondiagnostic EGD and colonoscopy. Exceptions to this may include consideration of push enteroscopy in the setting of overt bleeding or urgent angiography in patients with hemodynamically unstable bleeding. Overt bleeding in comparison with occult bleeding has been associated with a higher diagnostic yield of SB-VCE. Most studies do not differentiate between occult and overt small-bowel bleeding, and thus the reported diagnostic yield for SB-VCE often encompasses both. In a meta-analysis of 10 studies (n = 757) comparing SB-VCE and DBE for suspected small-bowel bleeding, the pooled yield for SB-VCE and DBE was 24% for both modalities. In a meta-analysis of 26 studies (n = 3657) that evaluated SB-VCE in both overt and occult small-bowel bleeding, the pooled rate of rebleeding after negative SB-VCE was 19% (95% CI, 14%–25%; P < .0001) and not different for occult versus overt bleeding. These data suggest that a negative SB-VCE may be reassuring and obviate the need for further testing unless rebleeding occurs.

Small-bowel tumors. SB-VCE is safe and feasible in patients with known or suspected polyposis syndromes such as familial adenomatous polyposis or Peutz-Jeghers syndrome, even after prior intestinal surgery. Jejunal and ileal polyps occur in 40% to 70% of familial adenomatous polyposis patients, and an association between the severity of duodenal polyposis and presence of more distal small-bowel polyposis has been established. Although VCE may be useful in identifying adenomas distal to the proximal jejunum, the clinical impact of these findings is uncertain. An American College of Gastroenterology guideline on management of familial adenomatous polyposis does not recommend SB-VCE or surveillance imaging distal to the ligament of Treitz unless clinically indicated. The ASGE has recommended that an optimal strategy would be to screen patients who have stage IV or advanced duodenal polyposis because they are at highest risk for jejunal and ileal adenomas either by CE or MRE. VCE and MRE have both been used for small-bowel screening in patients with Peutz-Jeghers syndrome. In studies evaluating their performance, VCE is more sensitive for the detection of small polyps (<5 mm), and VCE and MRE have similar detection rates for polyps >10 mm, but MRE appears to be more sensitive for polyps >15 mm. In addition, MRE more accurately characterizes the size.
and location of polyps and provides information on extraintestinal structures. In a multicenter study evaluating 25 Peutz-Jeghers syndrome patients who underwent VCE followed by DBE, there was strong agreement for polyp location and size between DBE and VCE, although DBE detected more polyps. In summary, the role of SB-VCE is uncertain and not routinely needed in familial adenomatous polyposis patients but is indicated for routine surveillance in patients with Peutz-Jeghers syndrome.

**Crohn’s disease. Diagnosis.** Nearly two-thirds of patients with CD have small-bowel involvement, and 90% of small-bowel CD involves the terminal ileum. However, disease activity in the terminal ileum may be patchy, resulting in false-negative results at ileocolonoscopy. In a meta-analysis comparing SB-VCE with other modalities in patients with suspected CD, there was a significantly greater incremental diagnostic yield with SB-VCE compared with ileoscopy (4 studies, n = 59) and CTE (3 studies, n = 59) but not in comparison with MRE (3 studies, n = 31). Disease activity assessment. Mucosal healing, defined as the resolution of active inflammatory Crohn’s lesions, correlates with fewer hospitalizations, and perianal fistulae. In CD, VCE allows pan-intestinal assessment of mucosal disease activity with a single minimally invasive procedure; this information may have both prognostic and therapeutic implications. Although CTE or MRE may be sufficient for the investigation of most CD patients, VCE detected more lesions in the proximal small bowel when compared with CTE/MRE, and these additional findings influenced disease management and clinical outcomes. In a meta-analysis of 12 prospective studies (n = 428) comparing VCE with other modalities in patients with established CD, there was a significantly greater incremental diagnostic yield for disease activity with VCE compared with small-bowel follow through (SBFT) and CTE (3 studies, n = 66) but not for ileoscopy (7 studies, n = 158) or MRE (4 studies, n = 63). Standardized quantitative scoring systems such as the Capsule Endoscopy Crohn’s Disease Activity Index score and Lewis score that describe the type, location, and severity of small-bowel lesions have been described and validated. Both scores are strongly correlated and perform similarly for the quantitative assessment of mucosal inflammation in established CD. In a study that prospectively followed patients with active small-bowel CD on baseline VCE, clinical remission after 12 weeks of treatment was observed in 20 of 37 patients (54%), including decreases in C-reactive protein and fecal calprotectin levels. However, mucosal response (Capsule Endoscopy Crohn’s Disease Activity Index normalization) on follow-up VCE was observed in just 10 of 37 patients (27%), suggesting that VCE may be a more sensitive marker of persistent inflammation. Similarly, a prospective, longitudinal study showed that VCE and ileocolonoscopy activity scores may have limited correlation with clinical symptom scores over time. VCE can be a particularly useful option in patients with aggressive proximal or mid–small-bowel CD that is beyond the reach of ileocolonoscopy.

Endoscopic recurrence of CD in the neoterminal ileum after surgical resection is common within the first year after surgery. Prospective multicenter studies have shown a high correlation between ileocolonoscopy and VCE of active disease in the terminal ileum or neoterminal ileum. The sensitivity of VCE for a diagnosis of recurrent CD across multiple observers ranged from 62% to 76% and the specificity ranged from 90% to 100%. Although VCE has limitations in its sensitivity, leading to potentially missed activity, it is a viable alternative to assess CD status in the postsurgical patient not suitable for endoscopic assessment.

**Celiac disease.** The mucosal changes of celiac disease may be patchy and at times distal to the second portion of the duodenum, where diagnostic biopsy samplings are usually performed. A meta-analysis of 6 studies involving 166 patients with celiac disease reported a pooled sensitivity of 89% (95% CI, 82-94) and pooled specificity of 95% (95% CI, 89-98) for celiac disease detection by VCE using a pathology reference standard. Severe disease was detected more readily than milder disease. The specificity and positive predictive value was 100% in patients with a high pretest probability of celiac disease, such as those with symptoms and elevated serum tissue transglutaminase IgA antibody levels. No studies have established a correlation between disease extent on VCE and clinical severity. VCE is generally not recommended as a diagnostic modality in the evaluation of suspected CD, except in patients who are unwilling or unable to undergo endoscopy with a high pretest probability with positive celiac serologies.

VCE may be useful in the evaluation of celiac pathology more commonly seen in the distal small bowel, such as ulcerative jejunitis and enteropathy-associated T-cell lymphoma. In a single-center study, 42 consecutive patients with refractory celiac disease (persistent or recurrent symptoms despite 6 months of a gluten-free diet) who underwent VCE were compared with 84 matched control subjects and 30 asymptomatic celiac patients who also underwent VCE. The frequency of villous atrophy was not different between the refractory and asymptomatic patients, and mucosal erosions were seen in all 3 groups with similar frequency. In a meta-analysis involving 10 studies and 439 patients with refractory celiac disease, the diagnostic yield of VCE for either ulcerative jejunitis or neoplasia was 13% (95% CI, 5.6-22.5). In a retrospective multicenter study involving 189 patients with either refractory celiac disease or alarm features, VCE detected ulcerative jejunitis or neoplasia in 29 patients (15.3%). Additionally, the authors reported that VCE findings changed the treatment plan in 112 patients (59.3%). The reported proportion of complete (ie, capsule reaching the cecum) VCE examinations in celiac...
patients has ranged broadly, from 62% to 100%, and some studies have suggested a lower VCE completion rate in patients with refractory celiac disease.74

Colon capsule endoscopy

Ulcerative colitis. CCE is used to assess the severity and extent of inflammation in patients with ulcerative colitis. The inherent nature of CCE precludes tissue sampling, and the ability of CCE to detect dysplasia or early cancer is unknown. In a tandem study of 30 consecutive pediatric ulcerative colitis patients undergoing CCE followed by colonoscopy on the same day, CCE had an overall sensitivity of 96% for the detection of active mucosal inflammation using a validated scoring system, with a lower sensitivity for those patients with only proctitis. The interobserver agreement for disease activity (κ = .90) and extent (κ = .86) between 4 reviewers was excellent. CCE had a higher overall tolerability than colonoscopy.76 In a prospective study of 42 adult patients with indeterminate colitis, CCE contributed to a change of diagnosis to CD in 3 patients based on the presence of small-bowel lesions.79

Colorectal neoplasia. Performance characteristics in neoplasia detection. Most CCE trials for neoplasia detection have been designed as blinded tandem studies with standard colonoscopy and assume colonoscopy to be the reference standard.6,10,80 In a meta-analysis of 7 studies (n = 1292) that used the CCE-2 system, the sensitivity for polyps ≥6 mm was 86.0% and specificity was 88.1%.81 For detection of ≥10-mm polyps, the sensitivity and specificity of CCE-2 were 87.0% and 95.3%, respectively. The largest single trial evaluating CCE-2 in an average-risk screening population was a prospective 16-center trial of 884 patients enrolled in the United States and Israel.10 All patients underwent a colonoscopy after CCE-2 with the colonoscopist blinded to the results of the capsule study. If a polyp ≥6 mm was observed on CCE-2 but not on colonoscopy, a repeat colonoscopy was immediately performed with the colonoscopist unblinded to the CCE-2 results. Seventy-seven patients (9%) were excluded for inadequate cleansing or whole-colon capsule transit time <40 minutes. Capsule colonoscopy identified subjects with 1 or more polyps ≥6 mm with 81% sensitivity (95% CI, 77-84) and 93% specificity (95% CI, 91-95). Sessile serrated polyps were responsible for 26% of false-negative CCE-2 examinations. In assessment of accuracy of CCE-2 it should be noted that colonoscopy is an imperfect reference standard, and suboptimal lesion detection at colonoscopy may lead to improper categorization of CCE-2 findings as false positives.

Patient acceptance. The uptake of CCE as a screening modality in comparison with other modalities is not well defined. In a Spanish single-center prospective study, 329 asymptomatic first-degree relatives of CRC patients were randomly assigned to CCE-2 versus colonoscopy. Patients were given an opportunity to cross over if they declined their initially assigned screening method. The rate of crossover was higher from CCE to colonoscopy (57.4%) versus crossover from colonoscopy to CCE (30.2%). Unwillingness to repeat bowel preparation in the case of a positive result was the primary reason that subjects initially assigned to CCE crossed over.80 It is possible that a single bowel preparation may be able to serve for both CCE and (if needed) subsequent colonoscopy, but this poses logistical challenges and remains investigational.

CCE after incomplete colonoscopy. Incomplete colonoscopy, defined as failure to achieve cecal intubation, has been reported in up to 9.7% of patients.82 In an analysis of 34 consecutive patients with an incomplete colonoscopy who underwent subsequent CCE, the capsule imaged the colon beyond the most proximal point reached during incomplete colonoscopy in 85% of cases. However, in 14 of 34 cases the CCE was deemed inconclusive because of poor preparation of the bowel (n = 12) or excessively slow (n = 1) or rapid (n = 1) capsule transit.83 In a single-center prospective study of 100 patients referred to a tertiary center after incomplete colonoscopy, participants underwent both CCE-2 and CT colonography examinations on the same day.84 Colonoscopy was repeated if there were significant findings on either CCE-2 or CT colonography. The relative sensitivity of CCE compared with CT colonography for polyps ≥6 mm was 2.0 (95% CI, 1.34-2.98). Positive predictive values for polyps ≥6 mm were 96% and 85.7% for CCE and CT colonography, respectively. No missed cancer occurred at clinical follow-up of a mean of 20 months. Lesions missed by CT colonography tended to be sessile or flat and in the proximal colon.

Limitations. Despite the extensive preparation, a significant proportion (up to 19%) of CCE studies are not interpretable or are suboptimally interpreted because of limited mucosal visualization. Because there is no ability to wash or suction, CCE is even more dependent on bowel preparation quality than colonoscopy. Bowel preparation for CCE also impacts the antegrade movement of the capsule. With use of the regimen recommended by the manufacturer (including boosters), rates of successful excretion within battery time ranging from 90.5% to 92.8% have been reported.85 However, studies eliminating preparation boosters have shown significantly slower colonic transit times, resulting in a lower proportion of completed studies within the battery life of the capsule.6

Most advanced neoplasia occurs in polyps ≥10 mm, and the specificity of CCE-2 is significantly higher for lesions ≥10 mm in comparison with ≥6 mm.6 Using a lower size threshold will expose an increased number of patients to more colonoscopies, sometimes unnecessarily because of false-positive CCE-2 examinations. Serrated lesion detection is limited with CCE10; strategies to improve identification of serrated lesions are needed. The entirety of the GI tract proximal to the colon is
visualized during CCE, although with limited views. This may be of potential benefit in some situations (eg, GI bleeding); however, extracolonic findings may prompt further testing, thus increasing costs.

**Current status of CCE-2 as an alternative for CRC screening.** The U.S. Multi-Society Task Force has described a tiered system for various modalities for CRC screening based on available evidence. Tier 1 tests include colonoscopy every 10 years and annual fecal immunochemical testing; these tests represent the cornerstone of CRC screening. The use of 1 of these 2 screening modalities is usually a viable option in nearly every clinical scenario. The U.S. Multi-Society Task Force designated CCE as a lower tiered (tier 3) alternative screening method for CRC. The performance characteristics of CCE in isolation compare favorably with tier 2 screening modalities such as fecal DNA testing and CT colonography. Future data that define test accuracy for cancer and advanced neoplasia detection of CCE in relation to alternative modalities such as capsule colonography will aid in defining prioritization of CCE in relation to other alternatives to colonoscopy. However, concerns regarding availability, reimbursement, onerous bowel preparation, and logistics of accomplishing same-day colonoscopy led the U.S. Multi-Society Task Force authors to stratify CCE as a tier 3 screening alternative.

**SAFETY**

VCE is a safe procedure, with a low overall rate of adverse events. The most common adverse event is capsule retention, defined as a capsule remaining in the digestive tract for ≥2 weeks or requiring intervention to aid its passage. The potential consequences of capsule retention include total or subtotal bowel obstruction and GI perforation. VCE retention is more common in the setting of NSAID strictures, CD, small-bowel tumors, radiation enteritis, and surgical anastomotic strictures. Occasional cases of retention can occur with other anatomic abnormalities (eg, diverticuli). An abdominal radiograph is recommended after 2 weeks if there is concern for VCE retention.

In a systematic review of 22,840 VCE procedures, the overall retention rate was 1.4% (95% CI, 1.2-1.6). Stratified by indication, retention rates in obscure GI bleeding were 1.2% (95% CI, 0.9-1.6), in CD (definite or suspected) 2.6% (95% CI, 1.6-3.9), and in the neoplastic lesions subgroup 2.1% (95% CI, 0.7-4.3). Of 104 patients with capsule retention, 88 (85%) were asymptomatic. Of the retained capsules, 58.7% were removed surgically, 12.5% were removed endoscopically, and the remainder passed without intervention. Risk factors in cases of capsule retention included CD (53.3%), neoplastic lesions (22.1%), NSAID-induced enteropathy (18.4%), and postsurgical stenosis (7.4%).

Intestinal perforation complicating VCE is an exceedingly rare event but has been described after impaction of the CE in patients with CD. Capsule aspiration is a rarely reported event (1%), typically necessitating bronchoscopy for retrieval.

**AREAS FOR FUTURE RESEARCH**

Video capsule endoscopes currently serve diagnostic purposes but in the future may be able to provide therapeutic interventions. Locomotion systems may permit antiperistaltic capsule movement; alternatively, the application of external magnetic fields can be used to influence capsule movement. Magnets have been used to guide the capsule and therefore improve visualization of the UGI tract. Magnets have shown in preliminary studies to assist in transgastric passage of the capsule, reducing pyloric transit times in preliminary studies. The ability to reliably control the capsule by magnets to obtain visualization is still a field in development. Proof of principle using magnetic-assisted capsule endoscopy studies have reported accuracy higher than previously reported for conventional VCE for esophageal varices (EV) and BE detection. Magnetic-assisted capsule endoscopy can achieve longer times for visualization of the distal esophageal mucosa, and the extent to which this makes it a viable alternative to assess for BE and presence of varices deserves further study.

VCE studies are time-consuming to read and interpret. Artificial intelligence–assisted VCE with a deep learning convolutional neural network algorithm enabled the identification of small-bowel mucosal abnormalities and bleeding with higher sensitivity and shorter reading times than conventional analysis by gastroenterologists. Automated VCE interpretation using convolutional neural network platforms have been investigated for other nonbleeding indications including colonic and small-bowel neoplasia, erosions, ulcerations, and motility disorders. Application of artificial intelligence to VCE could automate lesion identification and characterization with improved sensitivity and reduced time demands by highlighting pathologic images for physician review. However, artificial intelligence–assisted VCE interpretation remains investigational because further development is necessary before their incorporation into commercial platforms.

**SUMMARY**

- VCE allows a minimally invasive approach to visualize the mucosal surface throughout the GI tract. VCE is a first-line approach in the evaluation of small-bowel bleeding.
• VCE has a potential role in evaluating other UGI tract pathology (eg, varices or BE) but has not yet found a role in routine practice. Magnet-assisted and automated detection capsule endoscopy are new developments that may make VCE a more viable alternative for UGI tract screening.

• VCE also has an evolving role in the assessment of disease activity in some patients with inflammatory bowel disease. It is an emerging modality in the evaluation of disease severity of CD.

• VCE could be considered as a diagnostic modality in the evaluation of suspected celiac disease in patients who are unable to undergo endoscopy with a high pretest probability including positive celiac serologies.

• CCE for the detection of colorectal neoplasia has acceptable performance characteristics and is an emerging screening modality for those unable or unwilling to consider colonoscopy for screening. CCE is limited by a challenging approach to bowel preparation and a significant proportion of procedures that are suboptimal for interpretation because of capsule transit times. Further studies are required for the consideration of VCE in additional diagnostic and potentially even therapeutic endoscopic clinical indications.

**DISCLOSURE**

The following authors disclosed financial relationships relevant to this publication: J. Melson received an investigator-initiated grant from Boston Scientific and has stock options with Virgo Imaging. G. Trikudanathan is on the advisory board for AbbVie. B. Abu Dayyeh is a consultant for Metamodix, BFKW, DyaMx, Medtronic, Hemostasis, and Boston Scientific; has received research support from Apollo Endosurgery, USGI, Spatz Medical, GI Dynamics, Cairn Diagnostics, Aspire Bariatrics, and Medtronic; and is a speaker for Johnson and Johnson, Endogastric Solutions, and Olympus. M. Bhutani has received research grants from Silenseed Inc., Galera Inc., Oncosil Inc., and Augmenix Inc.; has received food and beverage from Boston Scientific Corporation, Augmenix Inc., and Conmed Corporation. V. Chandrasekhar is on the advisory board for Interpace Diagnostics, and is a shareholder in Nevakar Inc. P. Jirapinyo has received research support from Apollo Endosurgery; is a consultant for Endogastric Solutions, and Olympus. M. Krishnan is a consultant for Medtronic and Olympus Medical. N. Kumta is a consultant for Boston Scientific, Olympus Corporation of the Americas, Gyrus ACMII, Inc., and Apollo Endosurgery US Inc. R. Pannala is a consultant for HCL Technologies; has received travel compensation and food and beverage from Boston Scientific Corporation, has received food and beverage from Apollo Endosurgery US Inc., and owns stock in AbbVie. M. Parsi disclosed no financial relationships. A. Setbi is a consultant for Olympus America Inc., Boston Scientific, Fujifilm, Medtronic, Micro-tech; has received food and beverage and travel compensation from ERBE, Coredien, Cook Medical, Endogastric solutions, and ER Squibb. A. Trindade is a consultant for Olympus Corporation of the Americas, and PENTAX of America, Inc., and has a research grant from NinePoint Medical, Inc. R. Watson is a consultant and speaker for Apollo Endosurgery and Boston Scientific Corporation; and a consultant for Medtronic and Neptune Medical Inc. J. Maple disclosed no financial relationships. D. Lichtenstein is a consultant and has received travel compensation and food and beverage from Olympus America, Inc., is a consultant for AUGMENIX, Inc., and has received food and beverage from Boston Scientific Corporation.

**ACKNOWLEDGMENTS**

We thank Jennifer Lightdale, MD, Priya Jamidar, MD, Amitabh Chak, MD, Glenn Littenberg, MD, and John Vargo, MD, for their review of the document.

**REFERENCES**


Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett’s esophagus; CCE, colon capsule endoscopy; CD, Crohn’s disease; CRC, colorectal cancer; CTE, CT enterography; DBE, double-balloon enteroscopy; FDA, U.S. Food and Drug Administration; MRE, magnetic resonance enteroscopy; NSAID, nonsteroidal anti-inflammatory drug; SB-VCE, small-bowel video capsule endoscopy; UGI, upper GI; VCE, video capsule endoscopy.

Copyright © 2021 by the American Society for Gastrointestinal Endoscopy 0016-5107/$36.00 https://doi.org/10.1016/j.gie.2020.12.001
Received November 30, 2020. Accepted December 1, 2020.

Current affiliations: Division of Digestive Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, USA (1), Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, Minnesota, USA (2), Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA (3), Department of Gastroenterology Hepatology and Nutrition, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (4), Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA (5), Department of Gastroenterology, Hepatology and Endoscopy, Brigham and Women’s Hospital, Boston, Massachusetts, USA (6), Division of Gastroenterology, Department of Internal Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA (7), Division of Gastroenterology, Mount Sinai Hospital, New York, New York, USA (8), Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA (9), Section for Gastroenterology and Hepatology, Tulane University Health Sciences Center, New Orleans, Louisiana, USA (10), Department of Digestive and Liver Diseases, Columbia University Medical Center/New York-Presbyterian, New York, New York, USA (11), Department of Gastroenterology, Zucker School of Medicine at Hofstra/Northwell, Long Island Jewish Medical Center, New Hyde Park, New York, USA (12), Department of Gastroenterology, Interventional Endoscopy Services, California Pacific Medical Center, San Francisco, California, USA (13), Division of Digestive Diseases and Nutrition, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA (14), Division of Gastroenterology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA (15).