Policy Number	**RAD601.042**
Policy Effective Date	**09/15/2024**
Policy End Date	**12/31/2025**

Wireless Capsule Endoscopy for Gastrointestinal (GI) Disorders

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Wireless capsule endoscopy, also known as wireless video endoscopy (WVE) or video capsule endoscopy (VCE), of the small bowel **may be considered medically necessary** for the following indications:

- Initial diagnosis in individuals with suspected Crohn disease without evidence of disease on conventional diagnostic tests such as small bowel follow-through and upper and lower endoscopy.
- In individuals with an established diagnosis of Crohn disease, when there are unexpected change(s) in the course of disease or response to treatment, suggesting the initial diagnosis may be incorrect and reexamination may be indicated.
- In individuals with suspected small bowel bleeding, as evidenced by:
    - Prior inconclusive upper and lower gastrointestinal (GI) endoscopic studies (i.e., colonoscopy and upper gastric endoscopy), performed during the current episode of illness; AND

- Recurrent or persistent iron-deficiency anemia that is not attributable to other etiology (such as malabsorption, dietary insufficiency, etc.), positive fecal occult blood test, or visible bleeding; OR
- For surveillance of the small bowel in individuals with hereditary GI polyposis syndromes, including familial adenomatous polyposis and Peutz-Jeghers syndrome.

Other indications for wireless capsule endoscopy **are considered experimental, investigational and/or unproven,** including but not limited to:

- Evaluation of the extent of involvement of known Crohn disease or ulcerative colitis.
- Evaluation of the esophagus, in individuals with gastroesophageal reflux (GERD) or other esophageal pathologies.
- Evaluation of other GI diseases and conditions not presenting with GI bleeding, including but not limited to, celiac sprue, irritable bowel syndrome, Lynch syndrome (risk for hereditary nonpolyposis colorectal cancer), portal hypertensive enteropathy, small bowel neoplasm, and unexplained chronic abdominal pain.
- Evaluation of the colon, including but not limited to, detection of colonic polyps or colon cancer.
- Initial evaluation of individuals with acute upper GI bleeding.

The patency capsule **is considered experimental, investigational, and/or unproven** for any indication, including use to evaluate patency of the GI tract before wireless capsule endoscopy.

Magnetic capsule endoscopy (i.e., NaviCam™) **is considered experimental, investigational and/or unproven** for the evaluation of individuals with unexplained upper abdominal complaints and all other indications.

Policy Guidelines

None.

Description

The wireless capsule endoscopy (CE), also known as wireless video endoscopy (WVE) or video capsule endoscopy (VCE), uses a noninvasive device to visualize segments of the gastrointestinal (GI) tract. Patients swallow a capsule that records images of the intestinal mucosa as it passes through the GI tract. The capsule is collected after being excreted and images interpreted.

Background

Wireless Capsule Endoscopy

Wireless CE is performed using the PillCam Given Diagnostic Imaging System (previously called M2A), which is a disposable imaging capsule manufactured by Given Imaging. The capsule measures 11 by 30 mm and contains video imaging, self-illumination, and image transmission

modules, as well as a battery supply that lasts up to 8 hours. The indwelling camera takes images at a rate of 2 frames per second as peristalsis carries the capsule through the GI tract. The average transit time from ingestion to evacuation is 24 hours. The device uses wireless radio transmission to send the images to a receiving recorder device that the patient wears around the waist. This receiving device also contains localizing antennae sensors that can roughly gauge where the image was taken over the abdomen. Images are then downloaded onto a workstation for viewing and processing.

CE has been proposed as a method for identifying Crohn disease. There is no single criterion standard diagnostic test for Crohn disease; rather, diagnosis is based on a constellation of findings. (1) Thus, it is difficult to determine the diagnostic characteristics of various tests used to diagnose the condition and difficult to determine a single comparator diagnostic test to CE.

Magnetic Capsule Endoscopy

The United States (U.S.) Food and Drug Administration (FDA) approved a novel magnetically maneuvered CE system (NaviCam™; AnX Robotica, Inc.) in May 2020. (2) This system consists of a single-use ingestible capsule and magnet linked to a physician-operated console. The capsule contains a camera that wirelessly captures images of the desired anatomy. The console allows the operator to control the motion and direction of the capsule, ensuring visualization of the entire stomach. The system is non-invasive, does not require sedation, and has a procedural time of approximately 15 to 20 minutes. The capsule leaves the body in 24 hours on average but may take as long as 2 weeks. The device is contraindicated for use in patients with GI obstruction, stenosis, fistula, or those with dysphagia. Other contraindications include patients with cardiac pacemakers or other implantable electronic medical devices as well as pregnant women, those less than 22 years of age, and those with a body mass index of 38 or greater.

Regulatory Status

Table 1 summarizes various wireless CE devices with clearance by the U.S. FDA.

FDA product code: NEZ

Table 1. Wireless CE Devices Cleared by the U.S. FDA

Device	Manufacturer	Date Cleared	510(k) No.	Indication
Pillcam SB 3 Capsule Endoscopy System, Pillcam Software 9.0e	Given Imaging Ltd.	8/27/2021	K211684	For visualization of the small bowel mucosa. It may be used in the visualization and monitoring of lesions that may indicate Crohn's disease not detected by upper and lower endoscopy; lesions that may be a source of obscure bleeding not detected by upper and lower endoscopy;

				lesions that may be potential causes of iron deficiency anemia not detected by upper and lower endoscopy.
NaviCam Stomach Capsule System	AnX Robotica, Inc.	5/22/2020	K203192	For visualization of the stomach of adults (≥22 years) with a body mass index <38. The system can be used in clinics and hospitals, including emergency room settings.
CapsoCam Plus (SV3)	CapsoVision Inc.	4/19/2019	K183192	For visualization of the small bowel mucosa in adults. It may be used as a tool in the detection of abnormalities of the small bowel.
Olympus Small Intestinal Capsule Endoscope System	Olympus Medical Systems Corp.	3/5/2019	K183053	For visualization of the small intestine mucosa.
MiroCam Capsule Endoscope System	IntroMedic Co. Ltd.	11/8/2018	K180732	May be used as a tool in the detection of abnormalities of the small bowel and this device is indicated for adults and children from 2 years of age.
Olympus Small Intestinal Capsule Endoscope System	Olympus Medical Systems Corp.	03/13/2018	K173459	May be used in the visualization and monitoring of lesions that may indicate Crohn's disease not detected by upper and lower endoscopy. It may be used in the visualization and monitoring of lesions that may be a source of obscure bleeding (either overt or occult) not detected by upper and lower endoscopy. It may be used in the visualization and monitoring of lesions that may be potential causes of iron deficiency anemia (IDA) not detected by upper and lower endoscopy. The Red

				Color Detection Function is intended to mark frames of the video suspected of containing blood or red areas.
PillCam Patency System	Given Imaging Ltd.	3/8/2018	K180171	Intended to verify adequate patency of the GI tract prior to administration of the PillCam video capsule in patients with known or suspected strictures.
MiroCam Capsule Endoscope System	IntroMedic Co. Ltd.	1/30/2018	K170438	For visualization of the small intestine mucosa.
PillCam SBC capsule endoscopy system PillCam Desktop Software 9.0	Given Imaging Ltd.	9/1/2017	K170210	For visualization of the small intestine mucosa.
RAPID Web	Given Imaging Ltd.	5/26/2017	K170839	Intended for visualization of the small bowel mucosa.
AdvanCE capsule endoscope delivery device	United States Endoscopy Group Inc.	3/10/2017	K163495	Intended for visualization of the small bowel mucosa.
OLYMPUS SMALL INTESTINAL CAPSULE ENDOSCOPE SYSTEM	OLYMPUS MEDICAL SYSTEMS CORP.	1/19/2017	K163069	Intended for visualization of the small bowel mucosa.
CapsoCam Plus (SV3) Capsule Endoscope System	CapsoVision Inc.	10/21/2016	K161773	Intended for visualization of the small bowel mucosa.
CapsoCam (SV1)	CapsoVision Inc	2/9/2016	K151635	For use in diagnosing disorders of the small bowel, esophagus, and colon.
PillCam COLON2	Given® Imaging	01/14/2016	K153466	Detection of colon polyps in patients after an incomplete colonoscopy and a complete evaluation of the colon was not technically possible, and for detection of colon polyps in patients with evidence of GI

				bleeding of lower GI origin with major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy or moderate sedation in the event a clinically significant colon abnormality was identified on capsule endoscopy.
MiroCam Capsule Endoscope System	INTROMEDIC CO. LTD	3/17/2015	K143663	Intended for visualization of the small bowel mucosa.
ENDOCAPSULE SOFTWARE 10; ENDOCAPSULE SOFTWARE 10 LIGHT	OLYMPUS MEDICAL SYSTEMS CORP.	2/8/2015	K142680	Intended for visualization of the small bowel mucosa.

GI: gastrointestinal; No: number

Rationale

This medical policy was created in August 2002 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 15, 2024.

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of this policy, and credible information on technical reliability is available from other sources.

Suspected Small Bowel Bleeding

Clinical Context and Test Purpose

The purpose of wireless capsule endoscopy (CE) for individuals who have suspected small bowel bleeding is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

The following PICO was used to select literature to inform this medical policy.

Populations
The relevant population of interest is individuals with suspected small bowel bleeding. Suspected small bowel bleeding, previously referred to as obscure gastrointestinal (GI) tract bleeding, is defined as bleeding from the GI tract that persists or recurs without an obvious etiology after imaging with upper and lower endoscopy and radiologic evaluation of the small bowel. Recurrent or persistent iron deficiency anemia, positive fecal occult blood test (FOBT), or visible bleeding with no bleeding source found at original endoscopy are other indicators of obscure GI tract bleeding. Examples of etiologies for small bowel bleeding include angiodysplasia, tumor, medication-induced infections, Crohn disease (CD), Meckel diverticulum, ZollingerEllison syndrome, vasculitis, radiation enteritis, jejunal diverticula, and chronic mesenteric ischemia.

Interventions
The intervention of interest is wireless CE.

Comparators
The following practice is currently being used to diagnose small bowel bleeding: a standard workup without wireless CE and, with or without direct endoscopic procedures or specialized GI imaging. A "true" reference standard for suspected small bowel bleeding is difficult or impossible to achieve because the bleeding source may resolve and invasive techniques (e.g., surgery) cannot be justifiably used.

Outcomes
The outcomes of interest for diagnostic accuracy include test validity (i.e., sensitivity, specificity). The primary outcomes of interest are symptoms and disease status that would change due to patient management decisions following wireless CE.

Wireless CE would be performed prior to surgical exploration if conventional endoscopy has been inconclusive. Follow-up for further diagnostic evaluation and surveillance for recurrence of symptoms would be immediate to weeks if no etiology is identified. Follow-up of weeks to months would be based on the disease condition identified by CE.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false- positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.

- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Tables 2 and 3 summarize the characteristics and results of selected systematic reviews, which have evaluated a number of case series that compared the diagnostic accuracy of CE with alternative procedures such as intraoperative endoscopy or mesenteric angiography.

Table 2. Characteristics of Systematic Reviews Evaluating CE for IronDeficient Anemia

Study	Dates	Trials	Participants	N (Range)	Design	QUADAS Assessment of Included Trials
Koulaouzidis et al. (2012) (3)	2004-2011	24	Patients with iron deficiency anemia who had SBCE and at last 1 lower and upper GI endoscopy prior to CE	1960 (35652)	Observational	Low to moderate quality

CE: capsule endoscopy; GI: gastrointestinal; SBCE: small bowel capsule endoscopy; QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

Table 3. Results of Systematic Reviews Evaluating CE for Iron-Deficient Anemia

Study	Overall Diagnostic Yield[a]	Diagnostic Yield of Patients with IDA[b]	I^2, %	Diagnostic Yield, n (%)[c]
Koulaouzidis et al. (2012) (3)				
Total N	1960	264		• Angioectasias: 293 (45.9) • Inflammatory lesions: 126 (19.7) • Polyp/mass lesions: 42 (6.6)

				• Not classified: 177 (27.7)
Pooled effect (95% CI), %	47 (42 to 52)	66.6 (61.0 to 72.3)	78.8	
p			<0.001	

CE: capsule endoscopy; CI: confidence interval; IDA: iron-deficient anemia;
[a] Perpatient analysis.
[b] From 4 studies (n=264 patients; 13.47% of total).
[c] Patients with positive SBCE findings.

Randomized Controlled Trials (RCTs)

A small RCT compared CE with mesenteric angiography in patients with acute melena or hematochezia. While CE had a higher diagnostic yield, secondary outcomes such as transfusion, hospitalization, and mortality did not differ significantly between groups. Tables 4 and 5 summarize the characteristics and results of selected RCTs.

Table 4. Characteristics of RCT Evaluating CE for Obscure GI Bleeding

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Leung et al. (2012) (4)	China	1	2005-2007	Consecutive adults with active overt obscure GI bleeding	30 randomized to CE	30 randomized to mesenteric angiography

CE: capsule endoscopy; GI: gastrointestinal; RCT: randomized controlled trial.

Table 5. Results of RCT Evaluating CE for Obscure GI Bleeding

Study	Diagnostic Yield (95% CI), %[a]	Rebleeding Rates (95% CI), %	Hospitalization Rate, n (%)	Transfusion Rate, n (%)	Mean FollowUp (SD), mo.
Leung et al. (2012) (4)					
CE	53.3 (36.1 to 69.8)	16.7 (7.3 to 3.6)	5 (16.7)	3 (10)	48.5 (20.9)
Angiography	20 (9.5 to 37.3)	33.3 (19.2 to 51.2)	5 (16.7)	3 (10)	
Difference	33.3 (8.9 to 52.8)	16.7 (5.3 to 36.8)			
p	0.016	0.23	1.0	1.0	

CI: confidence interval; CE: capsule endoscopy; GI: gastrointestinal; Mo: month; RCT: randomized controlled trial; SD: standard deviation.
[a] Percentage identified with a high probability of bleeding.

The purpose of the limitations tables (see Tables 6 and 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 6. Study Relevance Limitations of RCT Evaluating CE for Obscure GI Bleeding

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FollowUp[e]
Leung et al. (2012) (4)	2. It is possible patients with moderate bleeding would not undergo angiography in clinical setting 4. Patients with overt but non-massive bleeding may not be ideal for CE or angiography		2. A criterion standard is lacking for evaluation of obscure GI bleeding		

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment. CE: capsule endoscopy; GI: gastrointestinal; RCT: randomized controlled trial.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values) ; 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

[e] Follow-up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations of RCT Evaluating CE for Obscure GI Bleeding

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Leung et al. (2012) (4)					3. Study underpowered to detect significant difference in clinical outcome	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
CE: capsule endoscopy; GI: gastrointestinal; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] FollowUp key: 1. High loss to followup or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Case Series

Tables 8 and 9 summarize the characteristics and results of selected case series.

Table 8. Characteristics of Case Series Evaluating CE for Obscure GI Bleeding

Study	Country	Participants	Treatment Delivery	Follow Up (Range), mo
Hartmann et al. (2005) (5)	Germany	47 patients >18 y with obscure GI bleeding	Patients received CE and criterion standard, intraoperative endoscopy	NR
Pennazio et al. (2004) (6)	Italy	100 patients ≥18 y with obscure GI bleeding	51 patients received CE and PE before or after the procedure	Mean: 18 (5 to 25)

CE: capsule endoscopy; GI: gastrointestinal; mo: month; NR: not reported; PE: push enteroscopy; y: year.

Table 9. Results of Case Series Evaluating CE for Obscure GI Bleeding

Study	Treatment	Locating Bleeding With CE, %		Diagnostic Yield for Positive Lesions, %	PPV of CE, %	NPV of CE %
		Sensitivity	Specificity[a]			
Hartmann et al. (2005) (5)	CE and intraoperative endoscopy	95	75	Both procedures: 76.6	95	86

Pennazio et al. (2004) (6)	CE and PE	89	95	67 (95% CI, 54 to 80)	97	82.6

CE: capsule endoscopy; CI: confidence interval; NPV: negative predictive value; PE: push enteroscopy; PPV: positive predictive value.
[a] CE results confirmed by intraoperative endoscopy or other reference standards.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Based on evidence that CE isolates the source of bleeding at least as well as other diagnostic tools and that few diagnostic options are available to patients with suspected small bowel bleeding, a chain of evidence can be constructed to support the clinical utility of CE for this indication.

Section Summary: Suspected Small Bowel Bleeding

A small RCT compared CE with mesenteric angiography in patients with acute melena or hematochezia. While CE had a higher diagnostic yield, secondary outcomes such as transfusion, hospitalization, and mortality did not differ significantly between groups. A large number of uncontrolled studies have evaluated the use of CE in the evaluation of patients with suspected small bowel bleeding. These studies have consistently reported that a substantial proportion of patients receive a definitive diagnosis following this test when there are few other diagnostic options. A meta-analysis of 24 studies estimated that the diagnostic yield in this patient population was approximately half of the included patients and was higher in patients with documented iron deficiency anemia. CE appears to locate the source of bleeding at least as well as other diagnostic methods and direct treatment to the source of bleeding.

Suspected Crohn Disease

Clinical Context and Test Purpose

The purpose of wireless CE for individuals with suspected Crohn disease (CD) is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

The following PICO was used to select literature to inform this medical policy.

Populations
The relevant population of interest is individuals with suspected CD. CD is 1 of the 2 types of inflammatory bowel disease. CD can involve the entire GI tract and is characterized by transmural inflammation.

Interventions
The test being considered is wireless CE.

Comparators
The following tests are currently being used to diagnose CD: Ileocolonoscopy (IC), barium small bowel follow-through, computed tomography enterography (CTE), and magnetic resonance enterography (MRE).

Outcomes
The general outcomes of interest are test validity, other test performance measures, symptoms, and change in disease status.

The diagnosis of CD requires confirmatory imaging when the disease is prominent on the differential diagnosis list. The imaging study would be performed and promptly followed by appropriate treatment. CD is a chronic condition requiring long-term follow-up.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Results from a metaanalysis by Choi et al. (2017) (7), which compared CE with various modalities for diagnosing CD, are summarized in Tables 10 and 11. The reference standards varied for the selected studies, so quantitative data were not synthesized for diagnostic

accuracy. In the pooled analysis, in patients with suspected CD, the sensitivity of CE ranged from 89.6% to 92.0% and the specificity was 100%.

Table 10. Characteristics of Systematic Reviews Assessing the Diagnostic Yield of CE versus Other Modalities[a]

Study	Dates	Trials	Participants	N (Range)	Design
Choi et al. (2017) (7)	20022013	24	Patients with suspected or established CD	NR	RCT, nonrandomized, and diagnostic accuracy studies

CD: Crohn disease; CE: capsule endoscopy; NR: not reported; RCT: randomized controlled trial.
[a] Other modalities include small bowel follow-through, enteroclysis, computed tomography enterography, and magnetic resonance enterography.

Table 11. Results of Systematic Reviews Assessing the Diagnostic Yield of CE Versus Other Modalities

Study	CE vs SBFT[a]	CE vs EC[b]	CE vs CTE[b]	CE vs MRE[b]
Choi et al. (2017) (7)				
N	94			
Diagnostic yield, %	66 vs 21.3	75.7 vs 29.4	72.5 vs 22.5	85.7 vs 100
Weighted incremental yield (95% CI)	0.44 (0.29 to 0.59)	0.50 (0.21 to 0.79)	0.36 (0.18 to 0.90)	0.16 (0.63 to 0.32)
I^2, %	30	52	68	44

CE: capsule endoscopy; CI: confidence interval; CTE: computed tomography enterography; EC: enteroclysis; MRE: magnetic resonance enterography; SBFT: small bowel follow-through; vs: versus
[a] From 4 studies (3 included in metaanalysis).
[b] From 2 studies.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Based on evidence that CE can provide a diagnosis of CD when other tests cannot, a chain of evidence can be constructed to support the clinical utility of CE for this indication.

Section Summary: Suspected CD

For patients with suspected CD who cannot be diagnosed by other modalities, CE can confirm the diagnosis in a substantial number of patients.

Suspected Celiac Disease

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have suspected celiac disease is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with suspected celiac disease. Celiac disease, or glutensensitive enteropathy, is an immunemediated condition of the small intestine. Serologic markers of the disease have good sensitivity and specificity in triaging patients to endoscopy.

Interventions

The test being considered is wireless CE. CE has been evaluated as an alternative method of diagnosing celiac disease, assessing the extent of disease, and in the evaluation of celiac disease unresponsive to treatment.

Comparators

The following test is currently being used to diagnose celiac disease: endoscopy with biopsy. The criterion standard for the diagnosis of celiac disease is obtained through small bowel biopsies obtained during endoscopy.

Outcomes

The general outcomes of interest are test validity, other test performance measures, symptoms, and change in disease status.

The diagnosis of celiac disease requires confirmatory imaging when the disease is prominent on the differential diagnosis list. The imaging study would be performed and promptly followed by appropriate treatment. Celiac disease is a chronic condition requiring long-term follow-up.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

A metaanalysis by ElMatary et al. (2009) compared the diagnostic performance of CE with a reference standard of duodenal biopsy. (8) The pooled analysis of 3 studies showed a sensitivity of 83% and a specificity of 98%. Another metaanalysis by Rokkas and Niv (2012) also compared the diagnostic performance of CE with biopsy, summarizing 6 studies (total n=166 subjects). (9) The overall pooled sensitivity was 89%, and the specificity was 95%.

CE detected involvement of intestines beyond the duodenum; however, the clinical significance of detecting the extent of celiac disease is uncertain. Given the less than 90% sensitivity of CE for celiac disease, it does not appear to be an adequate alternative method of making an initial diagnosis.

Nonrandomized Studies

In a study by Kurien et al. (2013), 62 patients with an equivocal diagnosis of celiac disease and 69 patients with confirmed celiac disease who were unresponsive to standard treatment were evaluated with CE. (10) Results were combined with human leukocyte antigen typing and response to gluten challenge, with the final diagnosis made by 3 expert physicians who received the information from all 3 sources. The main outcome was the increase in diagnostic yield after CE combined with the other tests. The diagnostic yield was greatest in cases with antibody negative villous atrophy where a diagnosis of celiac disease was made in 9 (28%) of 32 patients. In 8 (12%) of the 69 nonresponsive celiac disease patients, CE identified 2 cases of enteropathy associated lymphoma, 4 type 1 refractory disease cases, 1 fibroepithelial polyp, and 1 case of ulcerative jejunitis. This study was limited by the small sample size and use of other tests in conjunction with CE to ascertain a final diagnosis.

One case series by Culliford et al. (2005) evaluated 47 patients with complicated celiac disease and found unexpected additional findings in 60% of patients, most of which were ulcerations. (11) However, the definition of “complicated” celiac disease included other factors such as

evidence of blood loss, itself an indication for CE. The impact on patient management and outcomes is unclear.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for diagnosing celiac disease has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Suspected Celiac Disease

In cases where the diagnosis of celiac disease is equivocal, CE can sometimes reveal morphologic changes in the small bowel consistent with celiac disease. However, it is unlikely that the appearance of small bowel on CE is itself sufficient to make a definitive diagnosis of celiac disease. Small bowel biopsy, celiac serologies, and human leukocyte antigen typing remain the standard tests for confirming celiac disease and have a higher sensitivity and specificity for this purpose. Case series of patients with unresponsive celiac disease undergoing CE have shown some yield of actionable diagnoses that have the potential to improve patient outcomes. Larger studies are needed to better determine the diagnostic yield of CE in these patients.

Unexplained Chronic Abdominal Pain

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have unexplained chronic abdominal pain is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with unexplained chronic abdominal pain.

Interventions
The test being considered is wireless CE.

Comparators
The following practice is currently being used to diagnose chronic abdominal pain: standard workup for abdominal pain without CE.

Outcomes
The general outcomes of interest are test validity, other test performance measures, symptoms, and change in disease status.

The diagnosis of chronic abdominal pain is often one of exclusion after a comprehensive clinical evaluation including empirical treatment. Imaging studies are used during initial and follow-up evaluations. Continued follow-up would be based on a definitive or working diagnosis, which would typically occur over weeks to months.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Xue et al. (2015) reported on a systematic review of 21 studies (total N=1520 patients) evaluating CE for unexplained chronic abdominal pain. (12) The pooled diagnostic yield was 20.9% (95% CI, 15.9% to 25.9%). The most commonly identified findings were inflammatory lesions (78.3%) and tumors (9.0%). Studies in the review were highly heterogeneous. Limitations in interpreting the findings included retrospective study designs, different durations of abdominal pain, and the use of different tests before CE.

Case Series
In a study not included in the systematic review, Yang et al. (2014) reported on a case series evaluating 243 patients with CE for unexplained chronic abdominal pain. (13) The diagnostic

yield of CE was 23.0%. Identified findings included 19 (7.8%) patients with CD, 15 (6.2%) with enteritis, 11 (4.5%) with idiopathic intestinal lymphangiectasia, 5 (2.1%) with uncinariasis, 5 (2.1%) with abnormal transit time and other findings (e.g., small bowel tumor, ascariasis, anaphylactoid purpura).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for diagnosing unexplained chronic abdominal pain has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Unexplained Chronic Abdominal Pain

While CE diagnosed unexplained chronic abdominal pain in a proportion of patients reported in retrospective studies, the sequence and chronology of testing and treatment recommended before CE needs to be defined to determine whether CE had utility to diagnose the condition.

Established Crohn Disease

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have established diagnosis of CD is to inform management decisions based on disease status.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with CD.

Interventions

The intervention of interest is wireless CE.

Comparators

The following tests are currently being used to monitor CD: ileocolonoscopy (IC), barium small bowel follow-through, CTE, and MRE.

Outcomes
The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of endoscopy and unnecessary medications.

Wireless CE would be performed to monitor patients with CD.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Kopylov et al. (2017) published a systematic review of studies evaluating the use of CE for CD. (14) Reviewers included prospective studies comparing CE with MRE and/or small bowel contrast ultrasound in patients who had suspected and/or established CD. In pooled analyses of the 11 studies that included patients with established CD, the diagnostic yield of CE was similar to that of MRE (odds ratio [OR], 1.88; 95% CI, 0.53 to 1.48; I2=48%) and to ultrasound (OR=0.57; 95% CI, 0.27 to 1.20; I2=67%).

Diagnostic Accuracy Studies
Bruining et al. (2020) reported results from the multicenter, prospective BLINK trial comparing the diagnostic accuracy of CE compared to IC and/or MRE in patients with established CD. (15) The per-protocol analysis included 99/158 enrolled subjects with 16 patients tested by all 3 modalities. Major reasons for exclusion from analysis included patency failure or MRE stricture and major protocol violations. The reference standard was defined as the presence or absence of inflammation as designated by the modality-specific scoring system at prospective interpretation by expert central readers. In cases of discrepant findings for any bowel segment, all modalities were reviewed and resolved by a consensus panel consisting of 3 gastroenterologists. Overall sensitivity, specificity, PPV, and negative predictive value (NPV)

were 94% (95% CI, 86% to 98%), 74% (95% CI, 55% to 87%), 91% (95% CI, 82% to 96%), 83% (95% CI, 64% to 94%) for CE compared to 100% (95% CI, 95% to 100%), 22% (95% CI, 10% to 41%), 77% (95% CI, 68% to 85%), and 100% (95% CI, 54% to 100%) for IC and/or MRE. Sensitivity of CE was significantly higher compared to MRE for enteric inflammation in the proximal small bowel (97% vs 71%, P=0.021) and similar in the terminal ileum and colon (P=0.500-0.625). Discrepant reads between the proximal small bowel, terminal ileum, and colon were 57%, 49%, and 81%, respectively. In the proximal small bowel, the majority consensus panel decision was agreement with CE.

Cohort Studies

A study by Elosua et al. (2022) evaluated the therapeutic impact of CE in patients with established CD in this retrospective, single-center study. (16) Therapeutic impact was defined as change in CD-related treatment recommended based on CE results and 305 patients (N=432 procedures) with established CD who underwent a CE procedure between January 2008 and December 2019 were included. Of the included CE procedures, 87.5% were deemed conclusive. Mild inflammation was detected in 41.6% of patients and moderate-to-severe activity was detected in 21.9% of patients. Management changes guided by CE procedures occurred in 51.3% of procedures, with 46.1% of procedures leading to treatment escalation and 5.3% of procedures leading to de-escalation. Disease activity demonstrated by CE results was correlated with therapeutic changes. Mucosal healing assessed via CE was the only independent factor that predicted therapy de-escalation (OR, 6.86; 95% CI, 1.42 to 33). The single-center group of clinicians limited heterogeneity. These results are limited by the retrospective design of the study.

<u>Clinically Useful</u>

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Based on evidence that CE has a similar diagnostic yield as radiography when used to monitor CD and CE can be used when radiography cannot, a chain of evidence can be constructed to support the clinical utility of CE for this indication.

Section Summary: Established Crohn Disease

A 2017 systematic review of 11 studies in patients with established CD found a similar diagnostic yield with CE compared with radiography. A diagnostic accuracy study of CE compared with IC and/or MRE for the detection of active inflammatory CD in patients with established CD found a comparable sensitivity, higher specificity and PPV, and lower NPV compared to IC and/or MRE. Differences may be attributed to high rates of discrepant reads between modalities and high consensus panel agreement with CE results in cases of discrepancy. A retrospective cohort study demonstrated therapeutic management changes based on CE results, but RCTs are still needed to further assess the impact of CE results on therapy management.

Ulcerative Colitis

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have ulcerative colitis is to inform management decisions based on disease status.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with ulcerative colitis.

Interventions

The test being considered is wireless CE.

Comparators

The following test is currently being used to manage ulcerative colitis: optical colonoscopy.

Outcomes

The general outcomes of interest are test validity, other test performance measures, symptoms, and change in disease status.

Wireless CE would be performed to monitor patients after a confirmed diagnosis of ulcerative colitis.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g.,

receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

A number of prospective observational studies have evaluated the diagnostic accuracy of CE in patients with ulcerative colitis. Tables 12 and 13 summarize the characteristics and results of these studies.

Table 12. Characteristics of Observational Comparative Studies Assessing CE for UC

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Shi et al. (2017) (17)	Single center Prospective observational	China	2014 2016	Patients 18-80 y with UC requiring colonoscopy	150 patients underwent CE2 and colonoscopy	NR
San Juan-Acosta et al. (2014) (18)	Single blind prospective comparative	Spain	2010 2012	Patients 18-70 y with UC with flare in disease activity or due for CRC screening	23 underwent CE1, 19 had CE2; all followed by colonoscopy	NR
Oliva et al. (2014) (19)	Prospective observational	Spain	2011 2012	Patients 618 y with a diagnosis at least 3 mo prior to enrollment	30 patients underwent CE2, followed by colonoscopy	NR
Sung et al. (2012) (20)	Prospective cohort	China and Singapore	2000 2008	Patients with suspected or known UC	100 patients underwent CE and same day colonoscopy	NR

CE1: first generation capsule endoscopy; CE2: second-generation capsule endoscopy; CRC: colorectal cancer; Mo: month; NR: not reported; UC: ulcerative colitis; y: year.

Table 13. Results of Observational Comparative Studies Assessing CE for UC

Study	Active Colonic Inflammation, %	PPV, %	NPV, %	Correlation Between Colon CE and Colonoscopy

	Sensitivity[a]	Specificity			Disease Severity	Extent of Inflammation
Shi et al. (2017) (17)						
N	150	150	150		150	150
Mucosal inflammation (MES >0)	97			9495		
MtoS inflammation (MES >1)	94					
Post inflammatory polyps	100	91				
ICC (95% CI)					0.69 (0.46 to 0.81)[a]	0.64 (0.38 to 0.78)[b]
p					<0.001	<0.001
San JuanAcosta et al. (2014) (18)						
N	42	42	42		42	42
CE versus colonoscopy						
Disease activity	77.78	95.83	93.33	85.19		
Disease extent	68.75	96.15	91.67	83.33		
κ (95% CI)					0.79 (0.62 to 0.96)	0.71 (0.52 to 0.90)
Oliva et al. (2014) (19)						
N	30	30	30			
% (95% CI)	96 (79 to 99)	100 (61 to 100)	100 (85 to 100)	85 (49 to 97)		
Sung et al. (2012) (20)						
N	100	100	100			
% (95% CI)	89 (80 to 95)	75 (51 to 90)	93 (84 to 97)	65 (43 to 83)		

CE: capsule endoscopy; CI: confidence interval; ICC: intraclass correlation coefficient; MES: Mayo Endoscopic Subscore; MtoS: moderate to severe; NPV: negative predictive value; PPV: positive predictive value; UC: ulcerative colitis.

[a] MES.

[b] Ulcerative Colitis Endoscopic Index of Severity.

In the study by San JuanAcosta et al. (2014), although the correspondence between the 2 methods was reasonably good, it is uncertain whether management changes based on 1 or the other test would result in similar or different patient outcomes. (18)

Oliva et al. (2014) evaluated 30 patients with known ulcerative colitis with both CE and colonoscopy to assess disease activity. (19) The reference standard for disease activity was a Matts score greater than 6 as judged by colonoscopy. Although the 2 methods had a high concordance at this cutoff level of disease in this study, patient outcomes linked to these assessments of disease activity cannot be determined.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for monitoring ulcerative colitis has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Ulcerative Colitis

Several diagnostic accuracy studies have compared CE with colonoscopy to assess disease activity in patients with ulcerative colitis. Two of 4 studies were small (i.e., <50 patients) and thus data on diagnostic accuracy are limited. Because there are insufficient data on diagnostic accuracy, a chain of evidence on clinical utility cannot be constructed.

Esophageal Disorders

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have esophageal disorders is to inform management decisions based on disease status.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with esophageal disorders. GI reflux disease and chronic sequelae such as Barrett esophagus may require diagnostic and surveillance interventions.

Interventions
The test being considered is wireless CE. In the esophagus, the capsule camera has been proposed as a screening technique for Barrett esophagus associated with gastroesophageal reflux disease. Evaluation of the esophagus requires limited transit time, and it is estimated that the test takes 20 minutes to perform.

CE can visualize several types of esophageal conditions. It could substitute for traditional upper endoscopy for several indications and may have the advantage of comfort and convenience. However, interventional procedures and biopsies cannot be performed with CE. CE could triage patients for endoscopy if either the sensitivity or the specificity is high. Traditional endoscopy could then be performed on the appropriate group to determine false positives or false negatives, having spared the group with a high positive predictive value (PPV) an endoscopy procedure.

Comparators
The following test is currently being used to manage esophageal disorders: upper GI endoscopy.

Outcomes
The general outcomes of interest are test validity, other test performance measures, symptoms, and change in disease status. Wireless CE would be performed to monitor patients after a confirmed diagnosis of an esophageal disorder.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid. The study population represents the population of interest. Eligibility and selection are described.

- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Most studies have shown that CE has inferior diagnostic characteristics compared with traditional upper endoscopy for a variety of esophageal conditions. A metaanalysis by Guturu et al. (2011) evaluated 9 studies comparing CE with traditional endoscopy for detecting esophageal varices and calculated a sensitivity of 83% and specificity of 85%. (21) A meta-analysis by Bhardwaj et al. (2009) assessed 9 studies comparing CE with traditional endoscopy

for detecting Barrett esophagus and reported a sensitivity of 77% and specificity of 86%. (22) Because of the lower sensitivity and specificity of that test, CE cannot substitute for traditional endoscopy, nor can it be used to triage patients to endoscopy.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for monitoring esophageal disorders has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Esophageal Disorders

Other available modalities are superior to CE for monitoring esophageal disorders. The diagnostic characteristics of CE are inadequate to substitute for other modalities or to triage patients to other modalities.

Hereditary GI Polyposis Syndromes

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have hereditary GI polyposis syndromes is to inform management decisions based on disease status.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with hereditary GI polyposis syndromes, including Lynch syndrome and PeutzJeghers syndrome (PJS).

Interventions

The test being considered is wireless CE.

Comparators

The following tests and practices are currently being used to manage hereditary GI polyposis syndromes: IC, barium small bowel follow-through, CTE, and MRE.

Outcomes
The general outcomes of interest are, test validity, other test performance measures, symptoms, and change in disease status.

Wireless CE would be performed to monitor patients after a confirmed diagnosis with hereditary GI polyposis syndromes.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Persons with familial adenomatous polyposis and PJS are genetically at high-risk of small bowel polyps and tumors. Urquhart et al. (2014) compared CE with MRE in 20 patients with PJS. (23) CE identified more polyps 10 mm or larger (47 polyps) than MRE (14 polyps; p=0.02). However, subsequent balloon enteroscopy in 12 patients showed a poor correlation of findings between techniques, with a 100% PPV of finding a polyp on balloon enteroscopy with MRE versus 60% for CE. A study by Brown et al. (2006) in 19 patients showed a greater number of polyps identified with CE than with barium follow-through examinations. (24) Mata et al. (2005) studied the role of CE in 24 patients with hereditary GI polyposis syndromes, including familial adenomatous polyposis (n=20) or PJS (n=4). (25) Compared with barium studies using small bowel enteroclysis, CE identified 4 additional patients with small bowel polyps, which were subsequently removed with endoscopic polypectomy. Although these studies were small, they demonstrated that CE can identify additional lesions compared with other diagnostic methods in persons with disease syndromes at high-risk for such lesions.

The lifetime risk of small bowel cancer in Lynch syndrome has been estimated at 5%. Although not extremely high, this risk is greatly increased compared with the general population. There

are a few case series of the prevalence of neoplastic lesions in asymptomatic patients in patients with Lynch syndrome. Haanstra et al. (2015), evaluated 200 patients with Lynch syndrome that underwent CE. (26) Small bowel neoplasia was detected in the duodenum in 2 patients (1 adenocarcinoma, 1 adenoma). These lesions would have been in the reach of a gastroduodenoscope. In a smaller study by Saurin et al. (2010), 35 asymptomatic patients with Lynch syndrome underwent colon CE. (27) Small bowel neoplasms were diagnosed in three (8.6%) patients (one adenocarcinoma, two adenomas with lowgrade dysplasia).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for monitoring hereditary GI polyposis syndromes has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Hereditary GI Polyposis Syndromes

Although studies have shown at least a low prevalence of small bowel neoplasms, these data are insufficient to determine whether evaluation with CE would improve patient outcomes. Additional data on the prevalence and natural history of small bowel polyps in Lynch syndrome patients are necessary. At this time, surveillance of the small bowel is not generally recommended as a routine intervention for patients with Lynch syndrome.

Portal Hypertensive Enteropathy

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have portal hypertensive enteropathy is to inform management decisions based on disease status.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with portal hypertensive enteropathy.

Interventions
The test being considered is wireless CE.

Comparators
The following test is currently being used to manage portal hypertensive enteropathy: upper and lower endoscopy.

Outcomes
The general outcomes of interest are test validity, other test performance measures, symptoms, and change in disease status.

Wireless CE would be performed to monitor patients after a confirmed diagnosis with portal hypertensive enteropathy.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Several systematic reviews, including a Cochrane review, have been published. Tables 14 and 15 summarize the characteristics and results of select systematic reviews.

Table 14. Characteristics of Systematic Reviews Assessing CE for Portal Hypertensive Enteropathy

Study	Dates	Trials	Participants	N (Range)	Design
McCarty et al. (2017) (28)	20052015	17	Patients with portal hypertension	1328 (8330)	NR

Colli et al. (2014) (29)	20052014	16	Adults with cirrhosis	936 (NR)	Cohort

NR: not reported.

Table 15. Results of Systematic Reviews Assessing CE for Portal Hypertensive Enteropathy

Study	CE, %		Likelihood Ratios		Diagnostic Accuracy	
	Sensitivity	Specificity	Positive	Negative	CE	Medium to Large Varices
McCarty et al. (2017) (28)						
N	1328	1328	1328			
PE (95% CI), %	83 (76 to 89)	85 (75 to 91)	5.4 (3.3 to 9.0)	0.20 (0.14 to 0.28)	90 (88 to 93)	92 (90 to 94)
Studies with low risk of bias, n						
PE (95% CI), %	80 (81 to 88)	86 (68 to 94)			85 (81 to 88)	92 (89 to 94)
Colli et al. (2014) (29)						
N	936	936	936			
PE (95% CI), %	84.8 (77.3 to 90.2)	84.3 (73.1 to 91.4)	5.4 (3.1 to 9.5)	0.18 (0.12 to 0.27)		
Studies with low risk of bias, n	396	396	396			
PE (95% CI), %	79.7 (73.1 to 85.0)	86.1 (64.5 to 95.5)	5.8 (2.1 to 16.1)	0.24 (0.18 to 0.31)		

CE: capsule endoscopy; CI: confidence interval; PE: pooled effect.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for monitoring portal hypertensive enteropathy has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Portal Hypertensive Enteropathy

CE has been used to diagnose portal hypertensive enteropathy. Systematic reviews of studies of its diagnostic performance have reported limited sensitivity and specificity. Because neither the sensitivity nor the specificity was high for identifying esophageal varices, CE should not be used instead of esophagogastroduodenoscopy nor should it be used to triage patients to esophagogastroduodenoscopy. Based on these diagnostic characteristics, the test does not appear to have clinical utility.

Acute Upper GI Tract Bleeding

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who have acute upper GI tract bleeding is to inform management decisions based on disease status.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with acute upper GI tract bleeding.

Interventions

The intervention of interest is wireless CE.

Comparators

The following practices are currently being used to manage acute upper GI tract bleeding: standard workup of acute bleeding without wireless CE and, with or without direct endoscopic procedures or specialized GI imaging.

Outcomes

The primary outcomes of interest for clinical utility are symptoms and disease status that would change due to patient management decisions following wireless CE. Other outcomes of interest are the avoidance of hospitalizations and reductions in resource utilization (e.g., need for additional testing or procedures).

Wireless CE would be performed as soon as possible after acute bleeding is identified. Wireless CE would be performed to monitor patients after a confirmed diagnosis with acute GI tract bleeding.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Randomized Controlled Trials (RCTs)

Sung et al. (2016) reported on a prospective RCT to evaluate the use of CE in the emergency department for patients with suspected upper GI bleeding. (30) CE was used to determine whether patients would be admitted to the hospital or sent home, versus an alternative strategy of admitting all patients. Eligible patients presented with signs and/or symptoms of acute upper GI bleeding but were without hemodynamic shock or conditions likely to preclude the use of the capsule endoscope. Seventy-one patients were randomized to CE in the emergency department (n=37), followed by monitoring for upper GI bleeding, or standard care (n=34), which included mandatory hospital admission. Seven CE patients with active bleeding or endoscopic findings were admitted, with the remainder discharged home. There were no deaths or morbid outcomes in either group, indicating that CE could result in equivalent patient outcomes with many patients safely avoiding emergency hospitalization.

Tables 16 and 17 summarize the characteristics and results of select

Table 16. Characteristics of RCTs Assessing CE for Acute GI Tract Bleeding

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Sung et al. (2016) (30)	China	NR	20132014	Patients presenting to ED with symptoms suggestive of UGIB	37 randomized to CE; admission determined by CE	34 randomized to SOC; admission determined by GBS
Gutkin et al. (2013) (31)	U.S.	3	NR	Patients ≥18 y with history suggestive of	12 randomized to VCE prior to	12 randomized to endoscopy

				acute UGIB ≤48 h prior to endoscopy ED presentation		

CE: capsule endoscopy; ED: emergency department; GBS: Glasgow Blatchford score; GI: gastrointestinal; NR: not reported; RCT: randomized controlled trial; SOC: standard of care; UGIB: upper gastrointestinal bleeding; U.S.: United States; VCE: video capsule endoscopy.

Table 17. Results of RCTs Assessing CE for Acute GI Tract Bleeding

Study	Active Bleeding or Endoscopic Findings, n	Hospital-ization, n	Mortality, n	GBS Score	Agreement Between CE and EGD
Sung et al. (2016) (30)					
N	68	68	68	68	68
CE	• "Coffee ground" material: 2 • Peptic ulcer with Forrest Ib stigmata: 2 • Forrest IIa: 2 • Esophageal varix: 1	7	0	• 6 patients: 0 • 3 patients: 1 • 25 patients: ≥2	
SOC	• Peptic ulcer: 14 • Duodenal ulcer: 12 • Gastritis/duodenitis: 10 • Gastric or duodenal erosions: 5 • Mallory Weiss tear: 1	34	0	• No patients scored 0 • 7 patients: 1 • 27 patients: ≥2	
Gutkin et al. (2013) (31)					
N	24				24
VCE	8 (67.7%) had positive findings confirmed by endoscopy; for these patients, average Rockall score was 3; average Blatchford score was 13				VCE data identical to EGD results (p=1.0)

CE: capsule endoscopy; EGD: esophagogastroduodenoscopy; GBS: Glasgow Blatchford score; GI: gastrointestinal; N: number; RCT: randomized controlled trial; RR: relative risk; SOC: standard of care; VCE: video capsule endoscopy.

The purpose of the limitations tables (see Tables 18 and 19) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 18. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FollowUp[e]
Sung et al. (2016) (30)					
Gutkin et al. (2013) (31)					

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

[e] FollowUp key: 1. Followup duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 19. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Sung et al. (2016) (30)						3. As a feasibility study, confidence intervals and p values were not reported
Gutkin et al.					2. Small sample size based on pilot/	

(2013) (31)					feasibility study	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Cohort Studies
Two 2013 studies with small cohorts of patients (range, 49 to 83 patients) have reported on the use of CE before upper endoscopy for acute GI bleeding, to triage and/or riskstratify patients in the emergency department or hospital. (32, 33) These studies reported that CE provides useful information, such as identifying gross bleeding and inflammatory lesions in a substantial proportion of patients and in stratifying patients into high or lowrisk categories. However, the yield of CE in localizing the bleeding source was lower than for esophagogastroduodenoscopy, which is the standard initial evaluation for acute upper GI bleeding.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for diagnosing acute upper GI tract bleeding has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Acute Upper GI Tract Bleeding

Use of CE in the emergency department setting for suspected upper GI bleeding is based on efficiency (avoiding hospitalization, avoiding immediate endoscopy). Controlled studies are needed to assess further the impact of CE on health outcomes compared with standard management. Patients should be followed to their ultimate diagnosis to determine whether the use of CE versus other triage strategies or immediate endoscopy results in lower health care resource utilization.

Colon Cancer Screening

Clinical Context and Test Purpose

The purpose of wireless CE for individuals who are being screened for colon cancer is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals who are undergoing colon cancer screening.

Interventions

The intervention of interest is wireless CE.

Comparators

The following test is currently being used to diagnose colon cancer: standard workup using optical colonoscopy.

Outcomes

The outcomes of interest for diagnostic accuracy include test validity (i.e., sensitivity, specificity). The primary outcomes of interest for clinical utility are overall mortality and disease-specific mortality from colon cancer.

Wireless CE would be performed after an initial clinical examination. Though not completely standardized, follow-up screening for colon cancer would be based on guidelines for asymptomatic screening or for follow-up of significant screening findings.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.

- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Several studies have assessed the accuracy of CE for detecting colonic lesions. Spada et al. (2016) reported on a systematic review and meta-analysis of the diagnostic accuracy of CE for detecting colorectal polyps with stratified results for first- and second-generation capsules. (34) Across the 14 eligible studies, the indications for endoscopy included colorectal cancer screening (n=1261 [47%]), postpolypectomy surveillance or family history of colorectal cancer (n=636 [24%]), symptoms suggestive of cancer and/or fecal occult blood test (FOBT) positivity (n=619 [23%]), positive imaging tests (n=136 [5%]), or other indication (24 [1%]). There were no missed cancers (n=11) in the series using second-generation CE (per-patient sensitivity, 100%). In series using the first-generation CE, 6 of 26 proven cancers were missed on CE (per-patient sensitivity, 100%). In series using the first-generation CE, 6 of 26 proven cancers were missed on CE (per-patient sensitivity, 77%).

Kjolhede et al. (2020) reported on a systematic review and meta-analysis of the diagnostic accuracy of CE compared to colonoscopy with stratified results for polyps of any size, polyps ≥ 6mm, and polyps ≥ 10 mm. (35) Across analyzed patients in the 12 eligible studies, the indications for endoscopy included colorectal cancer screening or history of polyps or colorectal cancer (n=1200 [63.2%]), positive fecal immunochemical test (n=493 [26%]), first-degree relatives of patients with colorectal cancer (n=177 [9.3%]), or unspecified (n=28 [1.5%]). The rate of patients with an adequate bowel preparation ranged from 40% to 100%. The rates of complete CE transits ranged from 57% to 100%. The authors note that the relatively high rate of incomplete CE investigations limits the utility of CE in the colorectal cancer setting. All but 1 study was assessed to have a high risk of bias and applicability concerns for the reference standard.

Characteristics of the systematic reviews and their main findings are summarized in Tables 20 and 21, respectively.

Table 20. Characteristics of Systematic Review Assessing CE for Colon Cancer Screening

Study	Dates	Trials	N (Range)	Design	Outcome
Spada et al. (2016) (34)	20062015	14	2681 (40884)	Diagnostic accuracy studies	Per patient sensitivity of CCE for different categories of polyp size and for cancer
Kjolhede et al.	2009-2020	12	2199 (20-884)	Diagnostic accuracy studies	Per patient sensitivity of CCE for various polyp size thresholds

(2020) (35)					

CCE: colon capsule endoscopy.

Table 21. Results of Systematic Review Assessing CE for Colon Cancer Screening

RandomEffects Model	Trials	N	Outcomes	Effect Size	95% CI	I^2, %
Spada et al. (2016) (34)						
For ≥10 mm polyps	10	NR	Diagnostic accuracy for ≥10 mm polyps	Sens=80.0% Spec=96.2% PLR=18.6 NLR=0.22 DOR=90.4	66% to 90.3% 94.0% to 97.6% 12.0 to 28.2 0.13 to 0.34 44 to 163	53.4 31.3
For ≥6 mm polyps	7	NR	Diagnostic accuracy for ≥6 mm polyps using 1st-generation CCE	Sens=58% Spec=85.7% PLR=3.7 NLR=0.51 DOR=7.4	44% to 70% 80.2% to 90.0%	65
For ≥6 mm polyps	6	NR	Diagnostic accuracy for ≥6 mm polyps using 2nd-generation CCE	Sens=86% Spec=88.1% PLR=7.9 NLR=0.16 DOR=50.5	82% to 89% 74.2% to 95.0% 3.7 to 16.1 0.12 to 0.21 20.3 to 107.0	0
For ≥10 mm polyps	3	NR	Diagnostic accuracy for ≥6 mm polyps using 1st-generation CCE	Sens=54% Spec=97.4% PLR=NR NLR=NR DOR=NR	29% to 77% 96.0% to 98.3%	76.2 0
For ≥10 mm polyps	6	NR	Diagnostic accuracy for ≥6 mm polyps using 2nd-generation CCE	Sens=88% Spec=95.3% PLR=NR NLR=NR DOR=NR	81% to 91% 91.5% to 97.5%	0 67
Kjolhede et al. (2020) (35)						
For polyps of any size	4	338	Diagnostic accuracy for polyps of any size	Sens=85% Spec=85% PLR=NR NLR=NR DOR=30.5	73% to 92% 70% to 93% 16.2 to 57.2	NR

For polyps ≥ 6 mm	6	1324	Diagnostic accuracy for polyps ≥ 6 mm	Sens=87% Spec=88% PLR=NR NLR=NR DOR=51.1	83% to 90% 75% to 95% 19.8 to 131.8	NR
For polyps ≥ 10 mm	7	1577	Diagnostic accuracy for polyps ≥ 10 mm	Sens=87% Spec=95% PLR=NR NLR=NR DOR=136.0	82% to 90% 92% to 97% 70.6 to 262.1	NR

CCE: colon capsule endoscopy; CI: confidence interval; DOR: diagnostic odds ratio; mm: millimeter; NLR: negative likelihood ratio; NR: not reported; PLR: positive likelihood ratio; Sens: sensitivity; Spec: specificity.

Prospective Studies

Other recent studies by Saito et al. (2015), Morgan et al. (2016), Parodi (2018), and Cash et al. (2021) have evaluated the diagnostic characteristics of CE, using subsequently performed colonoscopy as the reference standard. (36-39) Of note, the Cash et al. (2021) study randomized patients to colon CE or CT colonography followed by optical colonoscopy. (39) In the Saito et al. (2015) study, of 66 evaluable patients, per-patient sensitivity for the detection of polyps was 94% (95% CI, 88.2% to 99.7%). In the Morgan et al. (2016) study, for lesions 10 mm or larger, sensitivity of CE was 100% (95% CI, 56.1% to 100%), with a specificity of 93.0% (95% CI, 79.9% to 98.2%). For lesions 6 mm or larger, sensitivity was 93.3% (95% CI, 66.0% to 99.7%) and the specificity was 80.0% (95% CI, 62.5% to 90.9%). The Parodi (2018) study included 177 first-degree relatives of individuals with colorectal cancer and found, for lesions 6 mm or larger, a sensitivity of 91% (95% CI, 81% to 96%) and a specificity of 88% (95% CI, 81% to 93%). (38) In the Cash et al. (2021) study, data from 286 patients revealed that the proportion of enrollees with any polyp 6 mm or larger confirmed by subsequent blinded optical colonoscopy was 31.6% for colon CE versus 8.6% for CT colonography. (39) The sensitivity and specificity of colon CE for polyps 6 mm or larger was 79.2% and 96.3%, respectively, while that of CT colonography was 26.8% and 98.9%. For polyps 10 mm or larger, the sensitivity and specificity of colon CE was 85.7% and 98.2% compared with 50% and 99.1% for CT colonography. The authors concluded that colon CE should be considered comparable or superior to CT colonography as a screening test; however, neither test was as effective as optical colonoscopy.

<u>Clinically Useful</u>

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for diagnosing colon cancer has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Colon Cancer Screening
Studies of diagnostic characteristics alone are insufficient evidence to determine the efficacy of CE for colon cancer screening. Because diagnostic performance is worse than standard colonoscopy, CE would need to be performed more frequently than standard colonoscopy to have comparable efficacy. Without direct evidence of efficacy in a clinical trial of colon cancer screening using CE, modeling studies using established mathematical models of colon precursor incidence and progression to cancer could provide estimates of efficacy in preventing colon cancer mortality. Studies of CE in screening populations are necessary to determine the diagnostic characteristics of the test in this setting.

Lower GI Tract Bleeding and Major Risks for Colonoscopy or Moderate Sedation
Clinical Context and Test Purpose
The purpose of wireless CE for individuals with evidence of GI bleeding of lower GI origin and major risks for colonoscopy or moderate sedation is to visualize the colon for the detection of polyps or other sources of lower GI bleeding and inform a decision to proceed to further treatment and testing.

The following PICO was used to select literature to inform this medical policy.

Populations
The relevant population of interest is individuals with evidence of GI bleeding of lower GI origin and major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy and moderate sedation in the event a clinically significant colon abnormality was identified with wireless CE.

Interventions
The intervention of interest is wireless CE for the visualization of the colon and detection of polyps or other sources of lower GI bleeding.

Comparators

The following reference standard is currently being used to detect colon polyps: standard workup using optical colonoscopy.

Outcomes
The outcomes of interest for diagnostic accuracy include test validity. The primary outcomes of interest are symptoms, disease status, and resource utilization that would change due to patient management decisions following wireless CE.

Beneficial outcomes resulting from a true-negative test result are avoiding unnecessary subsequent testing. Harmful outcomes resulting from a false-positive test result are unnecessary testing or therapeutic intervention. Harmful outcomes resulting from a false-negative test result are increased risk of further disease progression and missed colorectal disease.

Therefore, in the evaluation of wireless CE as a triage test, the test would need to identify precisely a group of patients that could safely forgo additional testing; therefore, the sensitivity, specificity, NPV and negative likelihood ratio are key test validity characteristics.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false- positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Diagnostic Accuracy Studies
Several studies have evaluated the diagnostic characteristics of CE for the detection of colon polyps in patients with evidence of lower GI bleeding (e.g., hematochezia, positive fecal occult blood test [FOBT]). Study characteristics and results are described in Table 22 and 23.

Table 22. Study Characteristics of Clinical Validity

Study	Study Population	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comments
Kobaek-Larsen et al. (2017) (40)	FOBT-positive individuals participating in a CRC screening program in Denmark (N=253; median age, 64 y)	OC adjusted by any findings from all follow-up procedures; repeat colonoscopy was offered for suspected missed polyps	Polyps >9 mm within ±50% of CE measure	OC performed 1 day after CE	Investigators were blinded to both CE and OC; in the case of a second endoscopy, investigator was unblinded to CE findings	RS adjusted in 75 patients due to follow-up procedures; only 50% (126) had complete OC and CE
Rondonotti et al. (2014) (41)	FOBT-positive individuals participating in a CRC screening program in Italy (N=54; age range, 50-69)	OC followed by colon segment re-inspection if double unblinding to CTC and CE results revealed a disparity	Polyps ≥6 mm	CTC and OC performed 15 days after CE	Initial blinding to CE and CTC results followed by double-unblinding and opportunity for re-inspection and adjustment of RS	4 patients excluded from analysis (consent withdrawal [2], endoscopist not blinded [2])
Eliakim et al. (2009) (42)	Individuals with known or suspected colonic disease in Israel; 21% of patients had hematochezia or positive FOBT (N=104; mean age, 49.8)	OC	Polyps ≥6 mm and ≥10 mm within +50% of CE measure	OC performed within 10 hours of CE	Investigators blinded to both OC and CE.	6 patients excluded from analysis (did not complete bowel prep [2], withdrawal [1], could not ingest capsule [1],

						capsule retention [1], technical failure [1])

CE: capsule endoscopy; CRC: colorectal cancer; CTC: computed tomography colonography; FOBT: fecal occult blood test; OC: optical colonoscopy; RS: reference standard; y:year.

Table 23. Study Results of Clinical Validity

Study	N	CE Completion Rate, % (95% CI)	Sensitivity, % (95% CI)[1]	Specificity, % (95% CI)[1]	PLR; NLR	Adverse Events
Kobaek-Larsen et al. (2017) (40)						None related to OC or CE
All patients; CE >9mm	253	54 (48 to 60)	87 (83 to 91)	92 (89 to 95)	NR	
Complete CE and OC; CE >9 mm	126	---	97 (94 to 100)	90 (85 to 95)	NR	
All patients; OC > 9 mm	253	90 (86 to 94)	88 (84 to 92)	100 (100)	NR	
Complete CE and OC; OC > 9 mm	126	---	89 (84 to 94)	100 (100)	NR	
Rondonotti et al. (2014) (41)						None related to OC or CE. 10 cases of mild abdominal pain and 2 cases of significant pain during CTC

CE ≥6 mm	50	100	88.2 (62.2 to 97.9)	87.8 (70.8 to 96.0)	3.75; 0.06	
CTC ≥6 mm	50	100	88.2 (62.2 to 97.9)	84.8 (67.3 to 94.3)	3.0; 0.07	
Eliakim et al. (2009) (42)						1 capsule retention; 7 cases of mild-moderate headache, nausea, or vomiting related to CE bowel preparation
CE ≥6 mm	98	NR	89 (70 to 97)	76 (72 to 78)	NR	
CE ≥10 mm	98	NR	88 (56 to 98)	89 (86 to 90)	NR	

CE: capsule endoscopy; CI: confidence interval; CTC: computed tomography colonography; mm: millimeter; NLR: negative likelihood ratio; NR: not reported; OC: optical colonoscopy; PLR: positive likelihood ratio.
[1] Per-patient analysis.

Kobaek-Larsen et al. (2017) reported on FOBT-positive individuals participating in a colorectal cancer screening program in Denmark. (40) The reference standard consisted of OC adjusted by any findings from all additional follow-up procedures, including repeat endoscopy due to suspected missed polyps unblinded to CE results in 53 patients, repeated OC due to inadequate bowel preparation in 8 patients, and follow-up CT colonography in 14 patients. CE completion rate was significantly lower than OC ($P < 0.001$), with only 50% of patients (n = 126) having complete OC and CE investigations.

Rondonotti et al. (2014) reported on FOBT-positive individuals participating in a colorectal cancer screening program in Italy. (41) Unblinded colonoscopy, integrating OC, CTC, and CE results, was used as the reference standard. Investigations were completed in all patients with a PLR and NLR of 3.75 and 0.06 for CE, respectively.

Eliakim et al. (2009) conducted a prospective, multicenter study evaluating CE compared to colonoscopy in individuals with known or suspected colonic disease. (42) Twenty-one percent of patients had hematochezia or positive FOBT. The majority of patients were referred for OC due to personal or family history of colorectal cancer or for colorectal cancer screening. Polyps of any size were detected in 44% of patients, with 53% identified as having adenomas. Overall colon cleanliness for CE was considered adequate in 78% of patients (95% CI, 68 to 86%).

Study relevance, design, and conduct limitations are described in Table 24 and 25.

Table 24. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kobaek-Larsen et al. (2017) (40)	4. Study did not specifically evaluate individuals with major risks for colonoscopy or moderate sedation.		2. Adjusted and/or unblinded reference standard not uniformly applied to all patients.	1, 3. Impact of findings on health outcomes not assessed. Predictive values not reported.	
Rondonotti et al. (2014) (41)	4. Study did not specifically evaluate individuals with major risks for colonoscopy or moderate sedation.			1. Impact of findings on health outcomes not assessed.	
Eliakim et al. (2009) (42)	4. Study did not specifically evaluate individuals with major risks for colonoscopy or moderate sedation; only 21% of subjects had evidence of lower gastrointestinal bleeding.			1, 3. Impact of findings on health outcomes not assessed. Predictive values not reported.	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 25. Study Design and Conduct Limitation

Study	Selection [a]	Blinding[b]	Delivery of Test[c]	Selective Reporting [d]	Data Completeness [e]	Statistical [f]
Kobaek-Larsen et al. (2017) (40)	1. Selection not described	1. In case of second endoscopy for suspected missed polyps, endoscopist not blinded to results of CE			1, 3. Unclear how many complete investigations included patients with comparison to adjusted and/or unblinded reference standard. High loss due to low CE completion rate	
Rondonotti et al. (2014) (41)	1. Selection not described	1. Endoscopist was unblinded to results of CE and CTC in event polyps were missed prior to segment	2. CTC and OC performed 15 days later			

		reinspection.				
Eliakim et al. (2009) (42)	1. Selection not described			1. Not registered		

CE: capsule endoscopy; CTC: computed tomography colonography; OC: optical colonoscopy. The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for detecting colon polyps in this population has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Lower GI Tract Bleeding and Major Risks for Colonoscopy or Moderate Sedation

Studies evaluating the diagnostic characteristics of CE as a triage test have primarily involved colorectal cancer screening populations that have not specifically enrolled patients with major risks for optical colonoscopy (OC) or moderate sedation. The 3 studies identified have been heterogeneous in the timing of delivery of the reference standard, in the definition and blinding of the reference standard, and in the significant polyp size threshold determining a positive test result. Only 1 small study reported positive and negative likelihood ratios. Per-patient sensitivity and specificity ranged from 88 to 97% and 76 to 92%, respectively, and was generally reported with wide confidence intervals. While 1 study reported a higher sensitivity and specificity compared to OC versus the defined reference standard, a consistent reference standard was not applied to all patients and carried a low combined rate of complete OC and CE investigations (50%). No studies assessed the impact of study findings on specific health outcomes. Adherence to recommended follow-up diagnostic or therapeutic interventions in patients with major risks for colonoscopy or moderate sedation is unknown. Studies of CE in the intended use population are necessary to determine the diagnostic characteristics of the test in the triage setting.

Incomplete Colonoscopy

Clinical Context and Test Purpose

The purpose of wireless CE for individuals with an incomplete colonoscopy after adequate preparation where a complete evaluation of the colon was not technically possible is to visualize the colon for the detection of polyps and inform a decision to proceed to further treatment and testing.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals undergoing screening for colon polyps who experience an incomplete colonoscopy after adequate bowel preparation where a complete visualization of the colon was not technically possible. Factors that may contribute to incomplete colonoscopies include patient pain and discomfort, diverticulosis, tortuosity, adhesions due to prior surgeries, angulation or fixation of bowel loops, ineffective sedation, and endoscopist and technician expertise. (43)

Interventions

The intervention of interest is wireless CE for the detection of colon polyps.

Comparators

The comparator of interest is repeat optical colonoscopy. Repeat colonoscopy following a prior incomplete procedure may be modified with adjusted endoscopic techniques, pediatric instruments, abdominal pressure and position changes, water exchange and water immersion techniques, carbon dioxide insufflation, magnetic endoscope imaging, alternate sedation methods, anesthesia assistance, and management with more experienced physicians. (43)

Outcomes

The outcomes of interest for diagnostic accuracy include test validity. The primary outcomes of interest are symptoms, disease status, and resource utilization that would change due to patient management decisions following wireless CE.

Beneficial outcomes resulting from a true-negative test result are avoiding unnecessary repeat colonoscopy. Harmful outcomes resulting from a false-positive test result are unnecessary testing or therapeutic intervention. Harmful outcomes resulting from a false-negative test result are increased risk of missed colorectal disease.

Therefore, in the evaluation of wireless CE as a triage test, the test would need to identify precisely a group of patients that could safely forgo additional testing; therefore, the sensitivity, specificity, NPV and negative likelihood ratio are key test validity characteristics.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-negative results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Case Series

Studies evaluating the diagnostic characteristics of CE compared to a reference standard for the detection of colon polyps in patients with an incomplete colonoscopy following adequate bowel preparation were not identified. Several prospective case series describing the diagnostic yield of CE following incomplete colonoscopy for various indications are summarized in Table 26a and 26b. Study relevance, design, and conduct limitations are described in Table 27 and 28.

Table 26a. Study Characteristics and Results

Study	Study Population		Indications for OC	Threshold for Significant Polyps
Hussey et al. (2018) (44)	Patients aged ≥18 y who had an incomplete OC for reasons other		NR	> 6mm or ≥ 3 polyps

	than poor bowel preparation or suspected obstruction of the colonic lumen (N=50)			
Baltes et al. (2018) (45)	Patients aged ≥18 y who had an incomplete OC due to failure to reach the cecum or ileo-cecal anastomosis due to looping, bowel angulation, adhesions, and intolerance of sedation or inflammation (N=81)		CRC screening (22%), anemia (15%), hematochezia (15%), irregular stool (12%), abdominal pain (12%), B symptoms (7%), colitis (5%), other reasons (12%)	≥ 6mm or ≥ 3 polyps
Nogales et al. (2017) (48)	Patients aged ≥18 y who had an incomplete OC when cecal intubation was not achieved despite adequate bowel preparation (N=96)		NR	>6mm or > 3 polyps
Negreanu et al. (2013) (46)	Patients who are risk for CRC who 1) refused (n=37) or failed prior OC (n=30), or 2) were unable to undergo OC because of anesthetic risk and co-morbidities (n=3) (N=70)		Abnormal transit (8), abdominal pain (4), anemia or overt bleeding (22), weight loss (1), average and high-risk CRC screening (29), abnormal imaging or tumor markers (6)	>6 mm or ≥ 3 polyps
Pioche et al. (2012) (47)	Patients with an indication for OC per the recommendations of the French National Authority for Health, including symptoms or screening who had 1) colonoscopy failure due to difficult sigmoid loop or adhesions not related to stenosis or inadequate bowel cleansing (n=77) or 2) contraindication to OC with anesthesia due to cardiovascular		Abnormal transit (14), abdominal pain (22), anemia or overt bleeding (30), weight loss (2), CRC screening (39)	>5 mm or ≥ 3 polyps

	or respiratory disease (n=30) (N=107)			

CE: capsule endoscopy; CI: confidence interval; CRC: colorectal cancer; IC: incomplete colonoscopy; NR: not reported; OC: optical colonoscopy.

Table 26b. Study Characteristics and Results

Study	Timing of CE	Incremental CE Diagnostic Yield, n/N (%)	Complete Visualization of the Colon, n/N (%)	*Comments*
Hussey et al. (2018) (44)	Administered 90 min after IC	CE (any polyps): 19/50 (38) CE (significant polyps): 7/50 (14) CE + IC (any diagnosis): 37/50 (74)	CE: 38/50 (76) CE + IC: 42/50 (84)	CCE Findings (n): normal (13), polyps (19; 7/19 significant), inflammation (1), diverticular disease (1), angiodysplasia (1), cancer (1). 7 patients with significant polyps were referred for polypectomy which detected 14 adenomas and hyperplastic polyps.
Baltes et al. (2018) (45)	Protocol A: next day CE (n=38) Protocol B: CE within 30 d (n=36)	CE (significant polyps): NR (24) CE + IC (significant polyps): 21/74 (28)	Protocol A: CE: 24/38 (63.3) CE + IC: 34/38 (89.5) Protocol B: CE: 24/36 (66.7) CE + IC: 35/36 (97.2)	Per protocol analysis: 74/81 due to 7 exclusions for technical failure Adverse events: 1 capsule retention; 1 case of nausea and vomiting due to prep
Nogales et al. (2017) (48)	Within 72 hours in 8 cases of suspected CRC. During the following week for all other patients.	CE (any diagnosis): 58/96 (60.4) CE (significant polyps): 25/96 (26)	CE: 69/96 (71.9) CE + IC: 89/96 (92.7)	CCE Findings (n): polyps (41; 25/41 significant), diverticula (11), colon cancer (2), angioectasia (2), solitary colonic ulcers (2). In 43/58 patients (44.8%) the new findings modified the therapeutic approach.
Negreanu et al. (2013) (46)	NR	CE (relevant lesions): 23/67 (34) [95% CI, 21.6 to 44.1] CE (significant polyps): 15/67 (22)	CE: 51/67 (76.1)	Exclusions: technical failures (3) CCE Findings (n): polyps > 6mm (5), ≥ 3 polyps (10), multiple colonic angiomas (2), newly discovered CD (1), radiation enteritis (1), diverticulosis (17), ulcerative colitis and inflammatory pseudopolyps (1), <6 mm polyp (1).

				17/23 patients with relevant lesions agreed to therapeutic interventions. 1 clinical failure (ulcerated rectal tumor) who refused OC following incomplete CE was reported. Adverse events: capsule impaction and retention (5)
Pioche et al. (2012) (47)	NR	CE (significant polyps, screening): 12/39 (30.8) [95% CI, 22.1 to 39.5] CE (any lesions explaining symptoms): 16/68 (23.5) CE (significant polyps not explaining symptoms): 8/68 (11.8) CE (any significant diagnosis): 36/107 (33.6) [95% CI, 24.7 to 42.5]	CE: 89/107 (83.2) [95% CI, 76.1 to 90.3]	CCE Findings (n): significant polyps (20), insignificant polyps (2), diverticulosis (6), telangiectasia (1), lesions explaining symptoms (16) Adverse events: capsule retention (6) Management: Screening group (12) (endoscopic treatments [6], follow-up [5], refusal [1]); Negative findings (9/64) (OC - normal findings or nonsignificant lesions [5], adenomas [1]; CTC - normal findings [3]); Symptomatic group (24) (medical treatments [8], colectomy [1], endoscopic APC [1], follow-up [6], endoscopic treatments [7], refusal [1])

APC: Argon plasma coagulation; CCE: colon capsule endoscopy; CD: Crohn disease; CE: capsule endoscopy; CI: confidence interval; CRC: colorectal cancer; CTC: computed tomography colonography; IC: incomplete colonoscopy; NR: not reported; OC: optical colonoscopy.

Table 27. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Hussey et al. (2018) (44)	2,3. Original indications for OC not reported.		2. Not compared to a reference standard.	1, 3. Impact of findings on health outcomes not assessed. Clinical validity	1. No follow-up with reference standard.

				outcomes cannot be assessed.	
Baltes et al. (2018) (45)	1. It is not clear whether detection of polyps was the primary goal of CE for symptomatic patients.		2. Not compared to a reference standard.	1, 3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.
Nogales et al. (2017) (48)	2,3. Original indications for OC not reported.		2. Not compared to a reference standard.	1, 3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.
Negreanu et al. (2013) (46)	1,4. It is not clear whether detection of polyps was the primary goal of CE for symptomatic patients. Only a small subset of study patients reported IC.		2. Not compared to a reference standard.	1, 3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.
Pioche et al. (2012) (47)	1,4. It is not clear whether detection of		2. Not compared to a reference standard.	1, 3. Impact of findings on health outcomes	1. No follow-up with

	polyps was the primary goal of CE for symptomatic patients. Only a subset of study patients reported IC.			not assessed. Clinical validity outcomes cannot be assessed.	reference standard.

CE: capsule endoscopy; IC: incomplete colonoscopy; OC: optical colonoscopy.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 28. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Complete-ness[e]	Statistical[f]
Hussey et al. (2018) (44)	1. Selection not described.	1. No comparison to reference standard.		1. Not registered.		2. Comparison to other tests not reported.
Baltes et al. (2018) (45)	1. Selection not described.	1. No comparison to reference standard.		1. Not registered.		2. Comparison to other tests not reported.
Nogales et al. (2017) (48)		1. No comparison to		1. Not registered.		2. Comparison to other

		reference standard.				tests not reported.
Negreanu et al. (2013) (46)	1. Selection not described.	1. No comparison to reference standard.	1. Timing of CE not described.	1. Not registered.		2. Comparison to other tests not reported.
Pioche et al. (2012) (47)	1. Selection not described.	1. No comparison to reference standard.	1. Timing of CE not described.	1. Not registered.		2. Comparison to other tests not reported.

CE: capsule endoscopy.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of wireless CE for detecting colon polyps in this population has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Incomplete Colonoscopy

No studies evaluating the diagnostic characteristics of CE compared to a reference standard for the detection of colon polyps in patients with an incomplete colonoscopy following adequate bowel preparation were identified. Case series describing the incremental diagnostic yield of CE varied in their reporting of original indications for OC and inclusion of symptomatic and/or screening patients. It is unclear whether the primary goal of CE was the detection of colon polyps in symptomatic patients, as these lesions were reported as not explaining symptoms in 1 study. Successful CE completion rates were low (range, 63.3 to 83.2%) with 3/5 studies reporting full visualization of the colon for combined CE and IC in 84 to 97.2% of patients. Given the variable prevalence of significant and actionable findings for patients with mixed indications for colonoscopy, the diagnostic yield is insufficient to determine the clinical validity of the test. No studies assessed the impact of study findings on specific health outcomes. Information on adherence to recommended follow-up diagnostic or therapeutic interventions in patients with incomplete colonoscopies are limited, with several refusals and clinical failures reported. Studies of CE compared to standard management with repeat colonoscopy in the intended use population are necessary to determine the diagnostic characteristics of the test in the triage setting.

Known or Suspected Small Bowel Stricture

Clinical Context and Test Purpose

The purpose of the patency capsule for individuals scheduled to undergo CE for known or suspected small bowel stricture is to confirm a diagnosis and inform a decision to proceed to CE.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals scheduled to undergo CE for known or suspected small bowel stricture. Contraindications to the use of CE include known or suspected obstruction or stricture, Zenker diverticulum, intestinal pseudoobstruction, and motility disorders. Certain patients with known or suspected strictures of the small bowel may be at risk of retaining the capsule. Surgical removal may be necessary.

Interventions

The test being considered is a patency capsule as a technique to evaluate patients with known or suspected strictures before using wireless CE. The capsule could be to select patients for CE instead of assessing clinical risk factors.

The use of the patency capsule has some risk itself. Published studies are small and do not provide comparative data on the incremental value of this capsule over standard clinical evaluation. In some series, the administration of the patency capsule has produced symptoms requiring hospitalization and even surgery. In a European study, Spada et al. (2007) reported findings for 27 patients, 24 with CD. (49) In this study, 25 (92.6%) patients retrieved the patency

capsule in their stools. Six patients complained of abdominal pain, 4 of whom excreted a nonintact capsule, and hospitalization was required in 1 patient due to the occlusive syndrome.

Comparators
The following practices are currently being used to diagnose known or suspected small bowel stricture: CE without patency capsule and alternative workup without CE.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, and treatment related morbidity.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Case Series
In a series from Europe, Delvaux et al. (2005) reported on findings in 22 patients with suspected intestinal stricture, 15 of whom had CD. (50) In this study, at 30 hours after ingestion, the patency capsule was detected in 17 (72.3%) patients. In all patients in whom the capsule was blocked in the small intestine, the stenosis had been suspected on CT scan or small bowel follow-through. In 3 patients, the delay in the progression of the patency capsule led to the cancellation of CE. In 3 patients, the patency capsule induced a symptomatic intestinal occlusion, which resolved spontaneously in 1 and required emergency surgery in 2. The authors commented that the current technical development of the patency capsule limits its use in clinical practice, because it did not detect stenosis undiagnosed by CT or small bowel follow-through, and the start of dissolution at 40 hours after ingestion is too slow to prevent episodes of intestinal occlusion. They also commented that a careful interview eliciting the patient's history and symptoms remains the most useful indicator for suspicion of an intestinal stenosis.

Several studies have shown that patients who had an uncomplicated passage of the patency capsule subsequently underwent uncomplicated CE. (51-53) These patients often had

significant findings on CE. (51, 52) However, it is difficult to determine whether CE findings in these patients improved their outcomes beyond any alternative testing regimen available. In 1 of these studies, 3 of 106 patients had severe adverse events, including 1 patient who required surgery. (51)

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of wireless CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of the patency capsule for diagnosing known or suspected strictures has not been established, a chain of evidence supporting the test's clinical utility for this indication cannot be constructed.

Section Summary: Known of Suspected Small Bowel Stricture

The overall balance of harm and benefit of using the patency capsule cannot be determined from the existing studies.

Unexplained Upper Abdominal Complaints

Clinical Context and Test Purpose

The purpose of magnetic CE for individuals who have unexplained upper abdominal complaints is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with unexplained upper abdominal complaints such as upper abdominal pain and/or anemia.

Interventions

The intervention of interest is magnetic CE. Magnetic CE is indicated for visualization of the stomach of adults (≥22 years) with a body mass index <38. The device is contraindicated for use in patients with GI obstruction, stenosis, fistula, or those with dysphagia. Other

contraindications include patients with cardiac pacemakers or other implantable electronic medical devices as well as pregnant women, those <22 years of age, and those with a body mass index ≥38.

Comparators
The following practice is currently being used to evaluate upper abdominal complaints: standard workup for abdominal pain without magnetic CE.

Outcomes
The outcomes of interest for diagnostic accuracy include test validity (i.e., sensitivity, specificity). The primary outcomes of interest are symptoms and disease status that would change due to patient management decisions following magnetic CE.

Follow-up for further diagnostic evaluation and surveillance for recurrence of symptoms would be immediate to weeks if no etiology is identified. Follow-up of weeks to months would be based on the disease condition identified by magnetic CE.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false- positive results are ideal. Studies reporting other measures (e.g., receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Diagnostic Accuracy Studies
Denzer et al. (2015) prospectively evaluated a magnetically guided gastric capsule as compared to conventional gastroscopy in 189 patients with upper abdominal complaints (e.g., upper abdominal pain and/or anemia) from 2 French centers. (54) In this study, capsule gastroscopy was performed initially followed by conventional gastroscopy, with a maximum delay of 1 day but a minimum delay of 4 hours. For conventional gastroscopy, the examination was performed blinded initially. If results of the magnetic capsule and blinded gastroscopy differed, then a subsequent unblinded gastroscopy was performed. Biopsies were taken whenever appropriate. The combined endoscopic assessment (blinded and unblinded gastroscopy) including biopsy was used as the final gold standard. The primary outcome parameters were the accuracy and

the sensitivity, specificity, and predictive values of magnetically guided capsule gastroscopy compared with the final gold standard with regard to major lesions on a per-patient and per-lesion basis. Overall, 23 major lesions were discovered in 21 patients. Capsule accuracy on a per-patient basis was 90.5% (95% CI, 85.4% to 94.3%) with a specificity of 94.1% (95% CI, 89.3% to 97.1%) and a sensitivity of 61.9% (95% CI, 38% to 82%). The PPV and NPV were 56.5% (95% CI, 34.5% to 76.8%) and 95.2% (95% CI, 90.7% to 97.9%), respectively. Similar results for these values were seen on a per-lesion basis. Of the other 168 patients, 94% had minor and mostly multiple lesions; the capsule made a correct diagnosis in 88.1% (95% CI, 82.2% to 92.6%). No complications of capsule or conventional gastroscopy were noted. Patient preference for capsule use for a future gastroscopy, if indicated, was 100%. In this first large study to evaluate magnetically guided capsule gastroscopy in patients with upper abdominal symptoms, the authors concluded that this technique was feasible in practice and clearly preferred by patients; however, further studies are needed to define its role in the clinical setting (e.g., as a filter test to stratify patients to undergo conventional gastroscopy or some other role). Of note, this non-US study reported a low sensitivity with a wide CI and provided an extremely limited discussion of the types of upper abdominal complaints experienced by enrolled patients. No discussion in terms of the severity and duration of the complaints, as well as prior testing and treatment was undertaken, which makes determination of the appropriate place in therapy for magnetic CE in patients with unexplained upper abdominal complaints difficult.

Liao et al. (2016) evaluated the accuracy of magnetically controlled CE as compared with conventional gastroscopy in 350 patients with upper abdominal complaints in a prospective, multicenter, blinded comparison study conducted in China. (55) All patients underwent magnetic CE followed by conventional gastroscopy 2 hours later, without sedation. The primary outcome of the study was an evaluation of gastric focal lesions. Overall, with conventional gastroscopy as the gold standard, magnetic CE detected gastric focal lesions in the entire stomach with 90.4% sensitivity (95% CI, 84.7% to 96.1%), 94.7% specificity (95% CI, 91.9% to 97.5%), and 93.4% accuracy (95% CI, 90.83% to 96.02%). The PPV and NPV were 87.9% (95% CI, 81.7% to 94%) and 95.9% (95% CI, 93.4% to 98.4%). Similar sensitivity and specificity results were observed with magnetic CE as compared to conventional gastroscopy when detecting focal lesions in the upper or lower stomach specifically. No lesions of significance were missed by magnetic CE. Additionally, 335 (95.7%) patients preferred magnetic CE over conventional gastroscopy and only 5 patients reported an adverse event; the majority of these events were considered to be related to gastric preparation. The authors concluded that magnetic CE detects upper abdominal focal lesions with comparable accuracy to conventional gastroscopy and is a promising alternative for screening for gastric diseases; however, similar to the prior study, this non-U.S. study provided no discussion of the types of upper abdominal complaints experienced by patients or prior tests or treatments undertaken.

The purpose of the limitations tables (Tables 29 and 30) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 29. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Denzer et al. (2015) (54)	4. Study population non-U.S. (conducted in France).			1. Sensitivity is low with a wide confidence interval.	
Liao et al. (2016) (55)	4. Study population non-U.S. (conducted in China).		2. Conventional gastroscopy performed without sedation.		

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 30. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Denzer et al. (2015) (54)	1. Selection of patients not clearly described.	1. Final gold standard of conventional gastroscopy with biopsy was unblinded.				
Liao et al. (2016) (55)	1. Selection of patients					

	not clearly described.					

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of magnetic CE for this indication were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Although magnetic CE has a similar diagnostic yield as conventional gastroscopy when evaluating patients with unexplained upper abdominal complaints, the sequence and chronology of testing and treatment recommended before magnetic CE needs to be defined to determine whether magnetic CE has utility to diagnose the condition.

Section Summary: Unexplained Upper Abdominal Complaints

Studies evaluating the diagnostic characteristics of magnetic CE as compared to conventional gastroscopy in the target population have generally demonstrated similar accuracy, sensitivity, and specificity, with increases in patient preference and an acceptable safety profile with the magnetic CE approach. However, the sequence and chronology of testing and treatment recommended before magnetic CE needs to be defined to determine whether magnetic CE has utility to diagnose the condition. No RCTs assessing the clinical utility of magnetic CE for this indication were identified.

Summary of Evidence

Patients with Suspected Gastrointestinal (GI) Disorders

For individuals who have suspected small bowel bleeding (previously referred to as obscure gastrointestinal (GI) bleeding who receive wireless capsule endoscopy (CE), the evidence includes numerous case series evaluating patients with a nondiagnostic standard workup and a randomized control trial (RCT). Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. The evidence has demonstrated that CE can identify a bleeding source in a substantial number of patients who cannot be diagnosed by other methods, with a low incidence of adverse events. Because there are few other options for diagnosing obscure small bowel bleeding in patients with negative upper and lower endoscopy, this technique will likely improve health outcomes by directing specific treatment when a bleeding source is identified. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected small bowel Crohn Disease (CD) who receive wireless CE, the evidence includes case series. Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. Although the test performance characteristics and diagnostic yields of the capsule for this indication are uncertain, the diagnostic yields are as good as or better than other diagnostic options, and these data are likely to improve health outcomes by identifying some cases of CD and directing specific treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected celiac disease who receive wireless CE, the evidence includes case series and diagnostic accuracy studies. Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. The diagnostic characteristics of CE are inadequate to substitute for other modalities or to triage patients to other modalities. For other conditions (e.g., determining the extent of CD), (e.g., determining the extent of CD), direct evidence of improved outcomes or a strong indirect chain of evidence to improved outcomes is lacking. The evidence is insufficient to determine that the effects of technology results in an improvement in the net health outcome.

For individuals who have unexplained chronic abdominal pain who receive wireless CE, the evidence includes case series and diagnostic accuracy studies. Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. The diagnostic characteristics of CE are inadequate to substitute for other modalities or to triage patients to other modalities. For other conditions (e.g., determining the extent of CD), direct evidence of improved outcomes or a strong chain of evidence to improved outcomes is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Patients with Confirmed GI Disorders

For individuals who have an established diagnosis of CD who receive wireless CE, the evidence includes diagnostic accuracy studies, a systematic review, and a retrospective cohort study. Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. A 2017 systematic review of 11 studies in patients with established CD found a similar diagnostic yield with CE and with radiography. Because there is evidence that the diagnostic yields are as good as or better than other diagnostic options, there is indirect evidence that CE is likely to improve health outcomes by identifying some cases of CD and directing specific treatment. A retrospective cohort study demonstrated therapeutic management changes based on CE results. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have ulcerative colitis who receive wireless CE, the evidence includes case series and diagnostic accuracy studies. Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. Several diagnostic accuracy studies have compared CE with colonoscopy to assess disease activity in patients with ulcerative colitis. Two of 3 studies were small (i.e., <50 patients) and thus data on diagnostic accuracy are limited. Direct evidence of improved outcomes and a strong chain of evidence to improved outcomes are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have esophageal disorders who receive wireless CE, the evidence includes case series and diagnostic accuracy studies. The relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. Other available modalities are superior to CE. The diagnostic characteristics of CE are inadequate to substitute for other modalities or to triage patients to other modalities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have hereditary GI polyposis syndromes who receive wireless CE, the evidence includes case series and diagnostic accuracy studies. Relevant outcomes are test validity, other test performance measures, symptoms, and change in disease status. The data are insufficient to determine whether evaluation with CE would improve patient outcomes. Further information on the prevalence and natural history of small bowel polyps in Lynch syndrome patients is necessary. At present, surveillance of the small bowel is not generally recommended as a routine intervention for patients with Lynch syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have portal hypertensive enteropathy who receive wireless CE, the evidence includes case series and diagnostic accuracy studies. Relevant outcomes are test validity, and other test performance measures, symptoms, and change in disease status. Systematic reviews of studies of CE's diagnostic performance for this indication have reported limited sensitivity and specificity. Due to insufficient data on diagnostic accuracy, a chain of evidence on clinical utility cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Acute Upper GI Bleeding

For individuals who have acute upper GI tract bleeding who receive wireless CE, the evidence includes RCTs and several cohort studies. Relevant outcomes are test validity, and other test performance measures, symptoms, hospitalizations, and resource utilization. The use of CE in the emergency department setting for suspected upper GI bleeding is intended to avoid unnecessary hospitalization or immediate endoscopy. Controlled studies are needed to assess further the impact of CE on health outcomes compared with standard management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Colon Cancer Screening

For individuals who are screened for colon cancer who receive wireless CE, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test validity, and other test performance measures. Studies of CE in screening populations are necessary to determine the diagnostic characteristics of the test in this setting. Studies of diagnostic characteristics alone are insufficient evidence to determine the efficacy of CE for colon cancer screening. Because diagnostic performance is worse than standard colonoscopy, CE would need to be performed more frequently than standard colonoscopy to have comparable efficacy. Without direct evidence of efficacy in a clinical trial of colon cancer screening using CE, modeling studies using established mathematical models of colon precursor incidence and progression to cancer could provide estimates of efficacy in preventing colon cancer mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Lower GI Tract Bleeding and Major Risks for Colonoscopy or Moderate Sedation

For individuals who are screened for colon polyps with evidence of lower GI tract bleeding and major risks for colonoscopy or moderate sedation who receive wireless CE, the evidence includes diagnostic accuracy studies. Relevant outcomes are test accuracy, test validity, other test performance measures, symptoms, change in disease status, and resource utilization. Studies of CE in the intended use population are necessary to determine the diagnostic characteristics of the test in the triage setting. Studies of diagnostic characteristics alone are insufficient evidence to determine the clinical utility of CE in this population, and no studies adequately assess the impact of findings on specific health outcomes or patient adherence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Incomplete Colonoscopy

For individuals who are screened for colon polyps following an incomplete colonoscopy with adequate preparation who receive wireless CE, the evidence includes case series. Relevant outcomes are test accuracy, test validity, other test performance measures, symptoms, change in disease status, and resource utilization. Studies of CE compared to standard management with repeat colonoscopy in the intended use population are necessary to determine the diagnostic characteristics of the test in the triage setting. Studies of diagnostic characteristics

alone are insufficient evidence to determine the clinical utility of CE in this population, and no studies adequately assess the impact of findings on specific health outcomes or patient adherence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Patency Capsule for Patients with Bowel Stricture

For individuals who are scheduled to undergo CE for known or suspected small bowel stricture who receive a patency capsule, the evidence includes case series. Relevant outcomes are test validity, symptoms, change in disease status, and treatmentrelated morbidity. The available studies have reported that CE following a successful patency capsule test results in high rates of success with low rates of adverse events. The capsule is also associated with adverse events. Because of the lack of comparative data to other diagnostic strategies, it is not possible to determine whether the use of the patency capsule improves the net health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Magnetic Capsule Endoscopy for Patients with Suspected GI Disorders

For individuals who have unexplained upper abdominal complaints who receive magnetic CE, the evidence includes diagnostic accuracy studies. Relevant outcomes are test validity, symptoms, change in disease status, and treatment- related morbidity. Studies evaluating the diagnostic characteristics of magnetic CE as compared to conventional gastroscopy in the target population have generally demonstrated similar accuracy, sensitivity, and specificity, with increases in patient preference and an acceptable safety profile with the magnetic CE approach. However, the diagnostic characteristics of magnetic CE are inadequate to substitute for other modalities or to triage patients to other modalities based on the current literature. Direct evidence of improved outcomes or a strong chain of evidence to improved outcomes is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Gastroenterology (ACG)

In 2013, the ACG issued guidelines on the diagnosis and management of celiac disease. (56) The guidelines recommended that CE not be used for initial diagnosis, except for patients with positive celiac specific serology who are unwilling or unable to undergo upper endoscopy with biopsy (strong recommendation, moderate level of evidence). These guidelines were updated in 2023, with no mention of Capsule endoscopy (CE). (57)

In 2018, the ACG updated its guidelines on the management of Crohn Disease (CD) in adults. (58) It makes 2 recommendations specific to video capsule endoscopy:

- “Video capsule endoscopy (VCE) is a useful adjunct in the diagnosis of patients with small bowel Crohn’s disease in patients in whom there is a high index of suspicion of disease.”
- “Patients with obstructive symptoms should have small bowel imaging and/or patency capsule evaluation before VCE to decrease risk of capsule retention.”

These recommendations are based on multiple studies. Capsule endoscopy (CE) was found to be "superior to small bowel barium studies, computed tomography enterography (CTE) and ileocolonoscopy (IC) in patients with suspected CD, with incremental yield of diagnosis of 32%, 47%, and 22%, respectively….Capsule endoscopy has a high NPV of 96%."

In 2015, the ACG issued guidelines on the diagnosis and management of small bowel bleeding (including using "small bowel bleeding" to replace "obscure GI [gastrointestinal] bleeding," which should be reserved for patients in whom a source of bleeding cannot be identified anywhere in the GI tract). (59) As of July 2024, a guideline update is in progress. (60) The 2015 guidelines made the following statements related to video CE (see Table 31).

Table 31. Recommendations on Diagnosis and Management of Small Bowel Bleeding

Recommendation	SOR	LOE
"… VCE should be considered as a firstline procedure for SB evaluation after upper and lower GI sources have been excluded, including secondlook endoscopy when indicated"	Strong	Moderate
"VCE should be performed before deep enteroscopy to increase diagnostic yield. Initial deep enteroscopy can be considered in cases of massive hemorrhage or when VCE is contraindicated"	Strong	High

GI: gastrointestinal; LOE: level of evidence; SB: small bowel; SOR: strength of recommendation; VCE: video capsule endoscopy.

In 2021, the ACG issued guidelines on colorectal cancer screening. (61) They "suggest consideration of the following screening tests for individuals unable or unwilling to undergo a colonoscopy or FIT [fecal immunochemical testing]: flexible sigmoidoscopy, multitarget stool DNA test, CT [computed tomography] colongraphy, or colon capsule [capsule endoscopy]" (conditional recommendation, very low quality of evidence).

American Gastroenterological Association Institute

In 2017, the American Gastrointestinal Association Institute issued guidelines on the use of CE. (62) Table 32 summarizes the most relevant recommendations (not all recommendations are included).

Table 32. AGA 2017 CE Recommendations

Statement Number	Recommendation	Grade	QOE
Recommendations Supporting the Use of CE			
1	For suspected Crohn's disease (CD), with negative ileocolonoscopy and imaging studies (CE of small bowel)	Strong	Very low
2	For CD and clinical features unexplained by ileocolonoscopy or imaging studies	Strong	Very low

3	For CD, when assessment of small bowel mucosal healing (beyond reach of ileocolonoscopy) is needed	Conditional	Very low
4	For suspected small bowel recurrence of CD after colectomy, undiagnosed by ileocolonoscopy or imaging studies	Strong	Very low
7	For celiac disease with unexplained symptoms despite treatment and appropriate investigations	Strong	Very low (efficacy) Low (safety)
8	For documented overt GI bleeding (excluding hemoatemesis) and negative findings on high-quality EGD and colonoscopy	Strong	Very low
9	For overt, obscure bleeding episode, as soon as possible	Strong	Very low
10	With prior negative CE with repeated obscure bleeding, repeated studies (endoscopy, colonoscopy and/or CE)	Strong	Very low
11	For suspected obscure bleeding and unexplained mild chronic iron deficiency anemia, in selected cases	Strong	Very low
12	For polyposis syndromes, which require small bowel studies, for ongoing surveillance	Conditional (efficacy)	Very low (efficacy) Low (safety)
Recommendations Against the Use of CE			
5	For diagnosing CD when chronic abdominal pain or diarrhea are only symptoms, and with no evidence of biomarkers associated with CD	Conditional	Low
6	For diagnosing celiac disease	Strong	Very low (efficacy) Low (safety)
13	For routine substitution of colonoscopy	Strong	Very low
14	For inflammatory bowel disease (IBD), as substitute for	Strong	Very low (efficacy) Low (safety)

	colonoscopy to assess extent and severity of disease		

AGA: American Gastroenterological Association; CD: Crohn disease; CE: capsule endoscopy; EGD: esophagogastroduodenoscopy; GI: gastrointestinal; IBD: inflammatory bowel disease; QOE: quality of evidence.

American Society of Gastrointestinal Endoscopy

In 2017, the American Society of Gastrointestinal Endoscopy released guidelines for the use of endoscopy in the management of suspected small bowel bleeding. (63) These guidelines made the following recommendations on CE (see Table 33).

Table 33. Recommendations on Use of Endoscopy to Manage Suspected Small Bowel Bleeding

Recommendation	QOE
"We suggest VCE as the initial test for patients with overt or occult small bowel bleeding. Positive VCE results should be followed with push enteroscopy if within reach or DAE."	Moderate
"We suggest DAE or push enteroscopy if VCE is unavailable or nondiagnostic in patients with overt small bowel bleeding."	Moderate

DAE: deviceassisted enteroscopy; QOE: quality of evidence; VCE: video capsule endoscopy.

U.S. Multi-Society Task Force

The U.S. Multi-Society Task Force (2017) issued recommendations for colorectal cancer screening with representation from the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for GI Endoscopy. (64) CE every 5 years received a tier 3 ranking with the following recommendation:

- "We suggest that capsule colonoscopy (if available) is an appropriate screening test when patients decline colonoscopy, FIT, FIT-fecal DNA, CT colonography, and flexible sigmoidoscopy (weak recommendation, low-quality evidence)."

In tandem with the U.S. Preventative Services Task Force (USPSTF) 2021 recommendations, the Multi-Society Task Force released a focused update to these guidelines in 2021, however, no changes were made regarding CE. (65)

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USFSTF) published its most recent recommendations for colorectal cancer screening in 2021. (66) Colorectal cancer screening was recommended starting at age 50 years and continuing until age 75 years (A recommendation) and in adults aged 45 to 49 years (B recommendation). The USPSTF recommendation for screening for colorectal cancer does not include serum tests, urine tests, or CE for colorectal cancer screening because of the limited available evidence on these tests and because other effective tests are available.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 34.

Table 34. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04472364	Impact of Blood Detection Capsule "HemoPill Acute" on the Time to Emergency Endoscopy in Case of Suspected Nonvariceal Upper Gastrointestinal Bleeding	72	Dec 2024
NCT02738359	Efficacy of Colonoscopy, Colon Capsule and Fecal Immunological Test for Colorectal Cancer Screening (FAMCAP)	3250	Nov 2023 (recruiting)
NCT04307901	Safety of Colorectal Assessment and Tumor Evaluation by Colon Capsule Endoscopy (SOCRATEC)	600	Dec 2030
NCT05108844	A Randomized Controlled Trial Evaluating the Efficacy of Early Videocapsule Endoscopy Following Negative Gastroscopy in Patients Presenting With Suspected Upper Gastrointestinal Bleeding	70	Oct 2024
NCT03616041	Video Capsule Endoscopy for lesion localization and Diagnosis in Patients With Severe Hematochezia	50	Jul 2023 (unknown status)
Unpublished			
NCT03458000[a]	Capsule Endoscopy for Hemorrhage in the ER	24	Sept 2020

No.: number; NCT: national clinical trial.

[a] Denotes industrysponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	91110, 91111, 91113, 91299, 0651T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/15/2024	Document updated with literature review. Coverage unchanged. Added references 16, 57, 60, 61, and 65; others updated.
09/15/2023	Reviewed. No changes.
11/01/2022	Document updated with literature review. The following changes were made to Coverage: Added magnetic capsule endoscopy (i.e., NaviCam™) is considered experimental, investigational and/or unproven for the evaluation of patients with unexplained upper abdominal complaints and all other indications. Added references 2, 39, 54, 55, 62; some removed. Title changed from "Wireless Capsule Endoscopy to Diagnose Disorders of The Small Bowel, Esophagus, and Colon".
08/01/2021	Document updated with literature review. Coverage unchanged. Added references 15, 34, 38-46, 57, 59; others updated.
10/15/2020	Document updated with literature review. The following changes were made in Coverage: 1) Expanded language to clarify "upper and lower" endoscopy 2) updated criteria for small bowel to state "In patients with suspected small bowel bleeding, as evidenced by prior inconclusive upper and lower gastrointestinal (GI) endoscopic studies performed during the current episode of illness 3) Added "celiac sprue" and "risk for hereditary nonpolyposis colorectal cancer" to the experimental, investigational, and/or unproven statement. Added reference 15. Title changed from Wireless Capsule Endoscopy (WCE)
04/15/2018	Document updated with literature review. Coverage unchanged.
04/15/2017	Reviewed. No changes.
04/15/2016	Document updated with literature review. Coverage unchanged.
02/01/2016	Reviewed. No changes.
12/15/2014	Document updated with literature review. The following changed in Coverage: 1) Wireless capsule endoscopy (WCE) of the small bowel may be considered medically necessary in patients with an established diagnosis of Crohn disease, when there are unexpected change(s) in the course of disease or response to treatment, suggesting the initial diagnosis may be incorrect and re-examination may be indicated; 2) Portal hypertensive enteropathy and unexplained chronic abdominal pain were added as examples to the experimental, investigational and/or unproven list.
12/15/2013	Document updated with literature review. The following was added to Coverage as experimental, investigation and/or unproven: 1) Evaluation of the extent of involvement of ulcerative colitis; 2) Lynch syndrome; 3) Initial evaluation of patients with acute upper GI bleeding.
09/15/2011	Document updated with literature review. Coverage unchanged; however, the following was added to the list of examples of indications that are considered experimental, investigational and unproven: Evaluation of the colon including, but not limited to, detection of colonic polyps or colon cancer. Rationale was extensively revised.

08/15/2009	Policy updated with literature review. Policy revised to allow small bowel capsule endoscopy when criteria are met for initial diagnosis of Crohn's disease and for surveillance of patients with hereditary GI polyposis. The list of indications that are experimental, investigational and unproven has been revised. The patency capsule is considered experimental, investigational and unproven.
08/15/2007	Revised/Updated Entire Document
06/01/2007	Coverage Revised
08/15/2003	Position Statement Converted to Medical Policy
08/01/2002	New Medical Document