Indications for Imaging the Small Bowel

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Background

In recent years, science and technology have come a long way in imaging the small bowel. These new modalities have reinvigorated our interest and understanding of small bowel diseases. The small bowel has traditionally been difficult to evaluate because of the fact that it is approximately 600 cm in length and extremely tortuous. Throughout this book, you will learn about traditional methods of evaluating the small bowel, as well as the newer techniques that have revolutionized the way we approach the small bowel today.

Traditional imaging methods, such as the barium small bowel follow through, have been limited in their ability to detect small or subtle abnormalities. Enteroclysis provided more detail but was difficult to perform and associated with significant patient discomfort. Whereas small bowel follow through or enteroclysis is relatively safe and noninvasive, the yield is low [1, 2], especially for mucosal lesions such as angioectasias. Endoscopy is useful for the most proximal and distal aspects of the small bowel but failed to investigate the majority of this organ. Although the yield of intraoperative endoscopy is very good, this test is very invasive and carries significant risks including serosal tears, perforation, mortality, and postoperative complications.

In the "olden days," circa 2000, the evaluation of suspected small bowel disease, particularly obscure gastrointestinal bleeding, was therefore inefficient and not cost effective. Patients would often require multiple hospitalizations, extensive diagnostic testing, and repeated blood transfusions without identifying a source. Patients would undergo repeat upper and lower endoscopy, push enteroscopy, small bowel follow through, or enteroclysis followed by angiography or intraoperative endoscopy. The historical challenges related to these tests included a high miss rate for small bowel lesions, limited availability, and accuracy of these older diagnostic tests, and thus the need for more invasive intraoperative enteroscopy and exploratory laparotomy to adequately examine the small bowel.

We are now in a "new age" with regard to imaging the small bowel. With the introduction of capsule endoscopy (CE) in 2001 and balloon-assisted enteroscopy in 2004, there was a true paradigm shift in the approach to suspected small bowel disease. This was followed by the development of more sophisticated software for

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cross-sectional imaging and the introduction of CT enterography and MR enterography. Together, these new modalities are seen as "disruptive technology" in that they led to a complete change in how we view the small bowel. Prior to these new techniques, the gastrointestinal tract was viewed as the upper tract, proximal to the ligament of Treitz, and the lower tract, distal to the ligament of Treitz. With the advent of these technologies, we can now view not only the upper and lower tract, but also the middle tract, i.e., the small bowel. Obscure gastrointestinal bleeding is no longer so obscure. The small bowel is no longer the "black box" of the gastrointestinal tract thanks, in particular, to capsule endoscopy and deep enteroscopy.

Capsule Endoscopy

In the following chapters, you will become more familiar with CE and its indications. Capsule endoscopy is truly an archetypical example of "disruptive" technology. It allows for a direct, noninvasive visual examination of the small bowel mucosa without discomfort or the need for sedation. Capsule endoscopy is an elegant solution in that the camera is not tethered to an apparatus, and thus is able to travel the entire length of the small bowel. The capsule measures from 24 mm to 31 mm × 11 mm to 13 mm, and is propelled through the small bowel by peristalsis. It is ingested orally or delivered into the small bowel by endoscopic assistance. It can visualize the entire small intestine in 79–90 % of cases [3]. As such, CE has become the gold standard in the evaluation of suspected small bowel disease.

Studies have shown that its diagnostic yield for small bowel lesions is superior to most other modalities [4, 5]. Its main utility lies in its high positive and negative predictive value as well as its ability to direct further therapeutic intervention and/or surgery [6]. While CE has had a huge impact in gastroenterology, we must recognize its limitations. These include a lack of therapeutic capabilities, inability to control movement, a high rate of incidental findings, and difficulty in localizing lesions. Finally, there is a potential to miss single-mass lesions and for capsule retention in high-risk individuals. In most situations, the benefits of CE outweigh these limitations.

Deep Enteroscopy

In addition to the development of CE, deep enteroscopy techniques have also added to our armamentarium for evaluating the small bowel. These new devices include double-balloon and single-balloon enteroscopy, as well as spiral enteroscopy. The main concept of all three techniques is to plicate the intestine over the endoscope, using a series of push-and-pull maneuvers. Unlike CE, therapeutic interventions such as biopsy, cauterization, and polypectomy can be performed and are undertaken in approximately 33 % of deep enteroscopies [7]. The major drawback of deep enteroscopy is the high resource utilization, with procedures lasting upwards of 60 min, and the need for anesthesia, assistants, and fluoroscopy. Its overall diagnostic yield is comparable to CE [8], but deep enteroscopy is more invasive, requires sedation or anesthesia, and is associated with higher resource utilization. The new device-assisted enteroscopy techniques can achieve a total enteroscopy by combined oral and anal approach in 8–63 % of cases, depending on the experience of the endoscopist [5]. As you will learn in the following chapters, all forms of deep enteroscopy are comparable in terms of yield, safety, and learning curve. The advent of this new technology has indeed brought the small bowel within the reach of the endoscopist.

Indications for Evaluating the Small Bowel

Although gastroenterologists most often are called to evaluate the stomach and colon, there are many reasons to image the small bowel (Table 1.1). The main ones can be divided into vascular, inflammatory, and neoplastic disorders. Overall, the single most common reason to evaluate the small bowel is for obscure gastrointestinal bleeding. Other indications include suspected

Table 1.1 Reasons to image the small bowel

Vascular	Inflammatory	Neoplastic	Other
• Angioectasia	• Peptic ulcer disease	• Carcinoid	• Abnormal imaging study
• Arteriovenous malformation	• Inflammatory bowel disease	• GIST	• Symptom evaluation
• Dieulafoy lesion	• NSAID enteropathy	• Adenocarcinoma	
• Varices	• Celiac disease	• Lymphoma	
• Hemorrhoids		• Ampullary carcinoma	
• Radiation enteritis		• Metastases	

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small bowel disease, tumors and polyposis syndromes, Crohn's disease, and malabsorptive disorders. As you will see throughout this book, the approach to these different disorders may vary depending on the individual scenario and there is, to date, very little evidence-based medicine to determine specific practice guidelines. Imaging of the small bowel is done for obscure gastrointestinal bleeding, tumors and/or polyps, inflammatory bowel disease (IBD), malabsorptive syndromes, as well as symptomatology.

Obscure Gastrointestinal Bleeding

The most common indication for CE and deep enteroscopy is the evaluation of suspected small bowel bleeding. Obscure gastrointestinal bleeding (OGIB) is persistent bleeding from the gastrointestinal tract after negative esophagogastroduodenoscopy, colonoscopy, and small bowel radiologic test. It can be either overt (visible bleeding) or occult (iron-deficiency anemia without visible bleeding) [9]. The differential diagnosis is quite extensive and includes vascular, inflammatory, and neoplastic lesions, as well as hemobilia, hemosuccus pancreaticus, and vasculitis.

The diagnosis may be straightforward, as in the patient with multiple, bleeding, arteriovenous malformations or an ulcerated mass seen on capsule endoscopy. However, of all indications for evaluating the small bowel, obscure gastrointestinal bleeding can also be the most challenging because lesions can be located anywhere throughout the small bowel and, in the case of certain vascular lesions, may be difficult to identify when they are not bleeding. Lesions may be missed due to patient conditions (e.g., hypotension), the fleeting nature of the lesion (e.g., Dieulafoy), or human error. Lesions include, in order of decreasing prevalence, angiodysplasia, ulcer, varices, bleeding polyp, tumor, and other rare causes [10].

While many lesions are ultimately found in the distal small bowel, a significant amount can be located in regions accessible with standard endoscopes [11]. As such, this bleeding can be caused by lesions proximal to the ligament of Treitz or in the colon that were missed on initial endoscopic evaluation. Thus, second-look endoscopy is recommended prior to embarking on an extensive small bowel evaluation. It is also important to rule out other causes of anemia such as bone marrow diseases and malabsorption, before concluding that the cause is gastrointestinal bleeding. Once gastrointestinal bleeding has been documented or iron-deficiency anemia confirmed and malabsorption and hematologic causes have been excluded, and second-look endoscopy is negative, then one can proceed with a small bowel evaluation.

In most cases, Capsule endoscopy will be the next best test. Depending on results, deep enteroscopy may be indicated to follow up on suspicious lesions. Deep enteroscopy complements CE. One study showed that there is excellent concordance between deep enteroscopy and CE [12]. The results of CE can be used to identify a lesion and guide further management. Generally, if the lesion is present within the first 75 % of small bowel transit time, we use an antegrade approach, and otherwise use a retrograde approach. Cost-effectiveness models suggest that DBE is the most

cost-effective approach for obscure overt gastrointestinal bleeding; however, CE-guided DBE may be associated with better long-term outcomes due to decreased risk for complications and appropriate resource utilization [13]. Cross-sectional imaging techniques including CT angiography and CT enterography can also be used to localize a source of bleeding with a diagnostic yield of 10–40 % [12, 13], which is lower than CE and deep enteroscopy. However, in difficult cases of OGIB, cross-sectional imaging, capsule endoscopy, and deep enteroscopy can be complementary. That is, complex cases will require all three modalities for diagnosis and treatment of the condition.

Tumors and Polyposis Syndromes

Tumors of the small bowel often present with OGIB. In the USA in 2014, cancers of the small intestine represented 0.5 % of total cancer cases and 0.2 % of cancer deaths [14]. Primary small bowel tumors comprise approximately 2–5 % of all primary gastrointestinal neoplasms [15, 16]. The most common malignant small intestine malignant neoplasms, in decreasing order of incidence, are carcinoid, adenocarcinoma, lymphoma, and stromal tumors [17].

Capsule endoscopy now plays an important role in the diagnosis and management of small bowel tumors. A meta-analysis found CE to be superior to push enteroscopy and small bowel follow through, in the setting of OGIB [4]. CE can provide initial diagnosis, estimated location, characteristics (size, shape, ulceration, etc.), and extent/number of mass lesions present. It can also be used for surveillance after polypectomy. However, CE can miss single-mass lesions in the small intestine at a rate approximating 19 % [18]. Factors that can affect the visualization in CE include rapid transit and poor/lack of preparation. In one study, most (74 %) missed lesions were located in the proximal small bowel [19]. Thus, CE and push enteroscopy may be complementary studies in this setting. CE is superior to MRE for evaluation of tumors in patients with Peutz-Jeghers syndrome (PJS) and familial adenomatous polyposis (FAP) [20, 21]. However, one study did suggest that MRE may be better at estimating the size of large polyps [22].

Deep enteroscopy also plays a role in the evaluation of small bowel tumors, particularly because of the ability to attain a tissue diagnosis. DBE has a diagnostic yield between 94 and 100 % for all small bowel tumors. Thus, this test may be helpful in cases where CE is negative but suspicion for a tumor remains high. It also has the advantage of being able to obtain a histopathologic diagnosis and, potentially, treat with polypectomy. However, DBE is more invasive and has a risk of perforation (1.3 %) and pancreatitis (0.6 %) [19].

At this time, there are limited evidence-based guidelines for small bowel imaging for suspected tumors. We suggest capsule endoscopy, in most cases, as the initial test of choice. It is suggested to perform CE prior to deep enteroscopy due to increased patient tolerance, ability to visualize the entire small intestine, and less invasive nature of the test. If a tumor is identified on CE, it can help direct the approach to deep enteroscopy. Thus these two tests work well together in the diagnosis and management of small bowel tumors.

Two polyposis syndromes with increased risk of small intestinal malignancy are PJS and FAP. In patients with PJS the risk ratio of small intestinal tumors is 520 [23], and thus some have recommended capsule endoscopy every 3 years starting at age 8 [24]. Most patients with FAP will have duodenal adenomas and it is estimated that they occur in 54–74 %. By age 75, >95 % of patients with FAP will have duodenal adenomas [25].

Regarding polyposis syndromes, there are limited studies on the benefits of CE, either for diagnosis or surveillance. Research in this area is limited mostly by the rarity of each condition. It has been suggested to screen patients with Peutz-Jeghers syndrome and others [26, 27], and can be justified in patients presenting with gastrointestinal bleeding. The role of deep enteroscopy in these patients is to sample and/or remove polyps. Deep enteroscopy can also be combined with surgery when very large polyps are identified.

Inflammatory Bowel Disease

Small bowel imaging can play an important role in the evaluation of patients with IBD with also have small bowel involvement. The diagnosis of IBD, particularly Crohn's disease, can be challenging because there is no single gold standard test. The disease involves the small bowel in approximately 70 % of patients and up to 30 % of patients have disease confined to the small bowel, usually the distal ileum [28]. Furthermore, even when the disease is not confined to the small intestine, involvement of this part of the GI tract can confer a worst prognosis and higher likelihood of recurrence [29]. In a subgroup of patients, identification of small bowel inflammation proximal to the terminal ileum can be difficult. Cross-sectional imaging has become popular for evaluation and monitoring of Crohn's disease due to its noninvasive nature and relative ease of use (especially when compared to deep enteroscopy). The role of CE and deep enteroscopy in this area remains controversial and has yet to be determined. Notably, cross-sectional imaging is helpful in assessing transmural inflammation and fistulae; however, it probably does not assess mucosal disease as well as CE and deep enteroscopy.

Capsule endoscopy can be used to evaluate the small bowel, particularly when colonoscopy with ileoscopy is negative. The advent of capsule technology has facilitated the evaluation of suspected CD, allowing for a more thorough assessment of the mucosa. The technology appears to have additional diagnostic yield of up to 70 % for CD isolated to the small bowel following a negative ileocolonoscopy. CE has the potential to be used not only in the diagnosis of IBD, but also in assessing the severity and extent of disease, postsurgical recurrence, and, perhaps, response to therapy. Findings of aphthous ulcers, fissuring ulcers, granularity, loss of vascular patter, and mucosal edema are similar on CE as on traditional endoscopy.

Capsule endoscopy may also be of benefit in patients with established CD. It may be complementary to ileocolonoscopy and upper endoscopy and has been shown to affect medical and surgical decision making [30]. In particular, CE may be useful in assessing the extent and severity of small bowel inflammation, particularly in patients with unexplained symptoms. In addition, CE may be useful for assessing mucosal healing once therapy has been initiated. There are studies to suggest that it may play a role in the evaluation of postoperative recurrence when ileocolonoscopy is not successful or needs to be avoided [29]. Finally, CE may be of value in assessing indeterminate colitis and reclassifying a subgroup as CD.

There are definite concerns and unanswered issues with CE in CD. The risk of capsule retention, due to stricturing disease, is higher in patients with known Crohn's disease, and in one study was reported to be 13 % [31]. Although CE has a high sensitivity (83–93 %), it has a low specificity (53–84 %) for diagnosing small bowel Crohn's disease [32, 33]. Furthermore, it remains to be seen whether or not CE is cost effective in the diagnosis of Crohn's disease [34].

The role of deep enteroscopy in IBD is less clear due to limited randomized controlled trials assessing the utility of this modality for CD. Deep enteroscopy has the advantage of obtaining tissue samples and being able to perform therapeutic interventions such as stricture dilatation. Histological evaluation can be particularly helpful in confirming active IBD, both for initial diagnosis and monitoring of IBD. Regarding the diagnostic yield, a meta-analysis of 11 studies comparing CE and DBE showed that they were comparable for small bowel disease, including inflammatory lesions [12]. However, DBE is more invasive and should be reserved for cases where CE is contraindicated, to obtain a tissue diagnosis after a positive study, to perform endotherapy, or to retrieve a retained capsule.

In contrast to obscure gastrointestinal bleeding, radiologic imaging can be particularly useful in the assessment of patients with CD. On cross-sectional imaging, transmural inflammation manifests as bowel wall thickening and enhancement. Both magnetic resonance enterography (MRE) and computed tomography enterography (CTE) have a good accuracy (0.86–0.93) compared to

endoscopic evaluation with a sensitivity (0.81–0.90) and specificity (0.88–1.0) for assessing disease activity by bowel wall thickening and enhancement [35]. However, both CTE and MRE lack the ability to visualize the mucosa and false-positive results can be seen if the bowel is underdistended.

In the majority of cases, ileocolonoscopy is the first test of choice in the assessment of patients with CD. However, it is reasonable to evaluate the small bowel, with either cross-sectional imaging or CE when suspicion of CD is high despite negative ileocolonoscopy. These new methods for evaluating the small bowel disease can assist clinicians in making a more timely and accurate diagnosis in patients with IBD, and can assist in determining prognosis and likelihood of recurrence. Armed with this information, the clinician can make better recommendations for treatment. Then, these methods can be used for monitoring response to treatment or disease recurrence.

Celiac Disease and Other Autoimmune Enteropathies

The exact role of small bowel imaging in celiac disease is evolving. Celiac disease is an immune reaction to eating gluten manifesting as inflammation of the small intestine that affects 1 % of the white American population [36]. Other enteropathies include autoimmune, hypogammaglobulinemic sprue and drug-induced (e.g., olmesartan). Typically, patients present with chronic diarrhea, postprandial abdominal pain, bloating, and weight loss. For diagnosis of celiac disease, initial testing with serology (i.e., tissue transglutaminase antibodies) is followed by duodenal biopsies. Macroscopically, enteropathy appears as villous atrophy, nodularity, fissures, scalloping, layered or stacked folds, and a mosaic appearance of the mucosa [37, 38]. Duodenal biopsies show intraepithelial lymphocytes, crypt hyperplasia, and/or villous atrophy.

Although histology is the gold standard for diagnosing celiac disease, CE may play a role in evaluating those patients with positive serology and negative histology, for patients unwilling or unable to undergo upper endoscopy, and for complicated or refractory celiac disease. In patients who are symptomatic despite a gluten-free diet, especially if they have alarm symptoms such as weight loss, fever, and pain, up to 60 % may have evidence of ongoing villous atrophy, ulcers or erosions, or cancer [39–41]. Capsule endoscopy has a sensitivity of 89 % and specificity of 95 % for detecting enteropathy [42].

Deep enteroscopy techniques may also be useful in patients with refractory or complicated celiac disease. In one study of 21 patients who were symptomatic and had villous flattening on duodenal biopsies despite maintaining a strict gluten-free diet, referred for double-balloon enteroscopy, 5 patients were diagnosed with enteropathy-associated T cell lymphoma (EATL) and 2 with ulcerative jejunitis. CT scan of these patients only detected EATL in four patients and did not detect ulcerative jejunitis in any. The authors conclude that deep enteroscopy should be reserved for patients with refractory celiac disease or those with a history of EATL [43]. In another study of 12 patients with unexplained malabsorption, double-balloon enteroscopy with small bowel biopsies yielded a diagnosis in 8 patients (including amyloidosis and Crohn's disease) even though duodenal biopsies were normal [44].

The role of radiologic evaluation is limited. Small bowel barium studies may show decreased jejunal folds, jejunal dilation, increased ileal fold thickness, and intussusceptions; however, this cannot reliably differentiate celiac disease or malabsorption from irritable bowel syndrome [45]. MRE, enteroclysis, and CTE, in contrast, can be useful in evaluating complicated celiac disease (malignancy, ulceration) [46].

Although upper endoscopy is usually sufficient for diagnosis and evaluation of celiac disease, small bowel imaging can be useful in complicated or refractory cases or when lymphoma is suspected. Capsule endoscopy can also be used for patients who cannot tolerate upper endoscopy. There is little role for cross-sectional imaging in this disease, other than to look for complications.

Symptom Evaluation and Abnormal Imaging Studies

The role of CE and deep enteroscopy in the evaluation of nonspecific symptoms is not clear. Small bowel imaging in patients with gastrointestinal symptoms is most useful when "alarm" features are present. Such "alarm" symptoms include weight loss, elevated erythrocyte sedimentation rate or C-reactive protein, thrombocytosis, anemia, and/or fevers. In patients with abdominal pain and diarrhea alone without these "alarm" symptoms, the yield tends to be quite low.

In a study of 165 nonbleeding patients referred for CE, the most common indications were diarrhea and abdominal pain. Among the 30 patients with diarrhea alone, only 8 (27 %) had positive findings [47]. In a study of 72 patients with chronic abdominal pain, with or without diarrhea, the diagnostic yield of CE was poor (21 and 0 %) in patients with normal inflammatory markers but was 67 and 90 % in patients with positive inflammatory markers. Diagnoses included IBD, small bowel tumors, enteritis, and NSAID enteropathy [48]. Similarly, in another group of 50 patients with chronic abdominal pain, the only additional sign that was associated with positive findings on CE was evidence of inflammation [49].

Conclusion

New endoscopic techniques, including CE and deep enteroscopy, in conjunction with cross-sectional imaging, have revolutionized our approach to the evaluation of small bowel disorders. Physicians are now armed with several methods of investigating the small intestine. These advances in technology have also improved patients' tolerance to testing and may reduce their exposure to radiation and complications by using less invasive methods.

These new techniques have transformed our approach to patients with OGIB. In many ways, OGIB is no longer "obscure" because of our ability to adequately image the small bowel. With the arrival of these new methods, patients previously labeled "OGIB" may be further subdivided into missed lesions (within reach of the upper endoscope or colonoscope), small bowel bleeding, and truly "obscure" gastrointestinal bleeding. With this ease of access, we may increase the diagnosis of small bowel tumors and enteropathy, and more accurately assess for disease activity in IBD.

In the twentieth century, no one would have imagined being able to reach the entire length of the small intestine endoscopically. What will come next? Research is currently under way with remote-controlled capsules using magnets, which could quickly be guided to a point of interest for more detailed inspection, and capsules that release gas to distend the lumen for better visualization. The logical next step would be to have that capsule take samples of the mucosa or deliver drugs to a specific lesion as well. Research in this area is also under way. The future is bright for imaging of the small bowel and evaluating small bowel diseases.

References

1. Rondonotti E, Villa F, Mulder CJ, Jacobs MA, de Franchis R. Small bowel capsule endoscopy in 2007: indications, risks and limitations. World J Gastroenterol. 2007;13(46):6140–9 [Review].
2. Delvaux M, Fassler I, Gay G. Clinical usefulness of the endoscopic video capsule as the initial intestinal investigation in patients with obscure digestive bleeding: validation of a diagnostic strategy based on the patient outcome after 12 months. Endoscopy. 2004;36(12):1067–73 [Validation Studies].
3. Gerson LB, Batenic MA, Newsom SL, Ross A, Semrad CE. Long-term outcomes after double-balloon enteroscopy for obscure gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2009;7(6):664–9.
4. Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol. 2005;100(11):2407–18 [Comparative Study Meta-Analysis].
5. Pennazio M, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology. 2004;126(3):643–53 [Clinical Trial Multicenter Study Research Support, Non-U.S. Gov't].
6. Nakamura M, Niwa Y, Ohmiya N, Miyahara R, Ohashi A, Itoh A, et al. Preliminary comparison of capsule endoscopy and double-balloon enteroscopy in

patients with suspected small-bowel bleeding. Endoscopy. 2006;38(1):59–66 [Comparative Study].
7. Gross SA, Stark ME. Initial experience with double-balloon enteroscopy at a U.S. Center. Gastrointest Endosc. 2008;67(6):890–7 [Comparative Study].
8. Raju GS, Gerson L, Das A, Lewis B. American Gastroenterological A. American gastroenterological association (aga) institute technical review on obscure gastrointestinal bleeding. Gastroenterology. 2007;133(5):1697–717 [Review].
9. Zaman A, Katon RM. Push enteroscopy for obscure gastrointestinal bleeding yields a high incidence of proximal lesions within reach of a standard endoscope. Gastrointest Endosc. 1998;47(5):372–6 [Clinical Trial].
10. Marmo R, Rotondano G, Casetti T, Manes G, Chilovi F, Sprujevnik T, et al. Degree of concordance between double-balloon enteroscopy and capsule endoscopy in obscure gastrointestinal bleeding: a multicenter study. Endoscopy. 2009;41(7):587–92 [Clinical Trial Comparative Study Multicenter Study].
11. Somsouk M, Gralnek IM, Inadomi JM. Management of obscure occult gastrointestinal bleeding: a cost-minimization analysis. Clin Gastroenterol Hepatol. 2008;6(6):661–70.
12. Pasha SF, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol. 2008;6(6):671–6 [Comparative Study Meta-Analysis Research Support, Non-U.S. Gov't].
13. Gerson L, Kamal A. Cost-effectiveness analysis of management strategies for obscure GI bleeding. Gastrointest Endosc. 2008;68(5):920–36.
14. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9–29.
15. Giuliani A, Caporale A, Teneriello F, Alessi G, Serpieri S, Sammartino P. Primary tumors of the small intestine. Int Surg. 1985;70(4):331–4.
16. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol. 2009;19(1): 58–69 [Research Support, N.I.H., Extramural Review].
17. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the united states: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1): 63–71 [Research Support, Non-U.S. Gov't].
18. Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. Endoscopy. 2005;37(10):960–5 [Comparative Study Evaluation Studies].
19. Honda W, Ohmiya N, Hirooka Y, Nakamura M, Miyahara R, Ohno E, et al. Enteroscopic and radiologic diagnoses, treatment, and prognoses of small-bowel tumors. Gastrointest Endosc. 2012;76(2):344–54 [Comparative Study Evaluation Studies Research Support, Non-U.S. Gov't].
20. Urquhart P, Grimpen F, Lim GJ, Pizzey C, Stella DL, Tesar PA, et al. Capsule endoscopy versus magnetic resonance enterography for the detection of small bowel polyps in Peutz-Jeghers syndrome. Fam Cancer. 2014;13:249–55.
21. Akin E, Demirezer Bolat A, Buyukasik S, Algin O, Selvi E, Ersoy O. Comparison between capsule endoscopy and magnetic resonance enterography for the detection of polyps of the small intestine in patients with familial adenomatous polyposis. Gastroenterol Res Pract. 2012;2012:215028.
22. Gupta A, Postgate AJ, Burling D, Ilangovan R, Marshall M, Phillips RK, et al. A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. AJR Am J Roentgenol. 2010;195(1):108–16 [Comparative Study Research Support, Non-U.S. Gov't].
23. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53 [Meta-Analysis Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.].
24. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59(7):975–86 [Consensus Development Conference].
25. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (fap): results of a 10 year prospective study. Gut. 2002;50(5):636–41.
26. Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol. 2006;4(4):408–15 [Research Support, N.I.H., Extramural Research Support, Non--U.S. Gov't Review].
27. Dunlop MG. Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polypolis, juvenile polyposis, and Peutz-Jeghers syndrome. Gut. 2002;51 Suppl 5:V21–7 [Guideline Practice Guideline].
28. Farmer RG, Hawk WA, Turnbull Jr RB. Clinical patterns in Crohn's disease: a statistical study of 615 cases. Gastroenterology. 1975;68(4 Pt 1):627–35.
29. Pons Beltran V, Nos P, Bastida G, Beltran B, Arguello L, Aguas M, et al. Evaluation of postsurgical recurrence in Crohn's disease: a new indication for capsule endoscopy? Gastrointest Endosc. 2007;66(3):533–40 [Comparative Study].
30. Cotter J, Dias de Castro F, Moreira MJ, Rosa B. Tailoring Crohn's disease treatment: the impact of small bowel capsule endoscopy. J Crohn's Colitis. 2014;8:1610–5.
31. Cheifetz AS, Kornbluth AA, Legnani P, Schmelkin I, Brown A, Lichtiger S, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol. 2006;101(10):2218–22.
32. Solem CA, Loftus Jr EV, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small-bowel imaging

in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointest Endosc. 2008;68(2): 255–66 [Clinical Trial Comparative Study Research Support, Non-U.S. Gov't].
33. Girelli CM, Porta P, Malacrida V, Barzaghi F, Rocca F. Clinical outcome of patients examined by capsule endoscopy for suspected small bowel Crohn's disease. Dig Liver Dis. 2007;39(2):148–54 [Clinical Trial].
34. Levesque BG, Cipriano LE, Chang SL, Lee KK, Owens DK, Garber AM. Cost effectiveness of alternative imaging strategies for the diagnosis of small-bowel Crohn's disease. Clin Gastroenterol Hepatol. 2010;8(3):261–7. 267 e261–264 [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.].
35. Fiorino G, Bonifacio C, Peyrin-Biroulet L, Minuti F, Repici A, Spinelli A, et al. Prospective comparison of computed tomography enterography and magnetic resonance enterography for assessment of disease activity and complications in ileocolonic Crohn's disease. Inflamm Bowel Dis. 2011;17(5):1073–80 [Clinical Trial Comparative Study Validation Studies].
36. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163(3):286–92 [Multicenter Study Research Support, Non-U.S. Gov't].
37. Cellier C, Green PH, Collin P, Murray J. Icce consensus for celiac disease. Endoscopy. 2005;37(10):1055–9 [Consensus Development Conference Research Support, Non-U.S. Gov't].
38. Green PH, Rubin M. Capsule endoscopy in celiac disease. Gastrointest Endosc. 2005;62(5):797–9 [Comment Editorial].
39. Culliford A, Daly J, Diamond B, Rubin M, Green PH. The value of wireless capsule endoscopy in patients with complicated celiac disease. Gastrointest Endosc. 2005;62(1):55–61 [Comparative Study Research Support, Non-U.S. Gov't].
40. Joyce AM, Burns DL, Marcello PW, Tronic B, Scholz FJ. Capsule endoscopy findings in celiac disease associated enteropathy-type intestinal t-cell lymphoma. Endoscopy. 2005;37(6):594–6 [Case Reports].
41. Apostolopoulos P, Alexandrakis G, Giannakoulopoulou E, Kalantzis C, Papanikolaou IS, Markoglou C, et al. M2a wireless capsule endoscopy for diagnosing ulcerative jejunoileitis complicating celiac disease. Endoscopy. 2004;36(3):247 [Case Reports].
42. Rokkas T, Niv Y. The role of video capsule endoscopy in the diagnosis of celiac disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2012;24(3):303–8 [Evaluation Studies Meta-Analysis].
43. Hadithi M, Al-toma A, Oudejans J, van Bodegraven AA, Mulder CJ, Jacobs M. The value of double-balloon enteroscopy in patients with refractory celiac disease. Am J Gastroenterol. 2007;102(5):987–96.
44. Fry LC, Bellutti M, Neumann H, Malfertheiner P, Monkemuller K. Utility of double-balloon enteroscopy for the evaluation of malabsorption. Dig Dis. 2008;26(2):134–9 [Clinical Trial].
45. Kumar P, Bartram CI. Relevance of the barium follow-through examination in the diagnosis of adult celiac disease. Gastrointest Radiol. 1979;4(3):285–9 [Comparative Study].
46. Tennyson CA, Semrad CE. Small bowel imaging in celiac disease. Gastrointest Endosc Clin N Am. 2012;22(4):735–46 [Review].
47. Katsinelos P, Tziomalos K, Fasoulas K, Paroutoglou G, Koufokotsios A, Mimidis K, Terzoudis S, Maris T, Beltsis A, Geros C, Chatzimavroudis G. Can capsule endoscopy be used as a diagnostic tool in the evaluation of nonbleeding indication in daily clinical practice? A prospective study. Med Princ Pract. 2011;20:362–7.
48. Katsinelos P, Fasoulas K, Beltsis A, Chatzimavroudis G, Paroutoglou G, Maris T, et al. Diagnostic yield and clinical impact of wireless capsule endoscopy in patients with chronic abdominal pain with or without diarrhea: a Greek multicenter study. Eur J Intern Med. 2011;22(5):e63–6.
49. May A, Manner H, Schneider M, Ipsen A, Ell C. Prospective multicenter trial of capsule endoscopy in patients with chronic abdominal pain, diarrhea and other signs and symptoms (cedap-plus study). Endoscopy. 2007;39(7):606–12.