New Techniques to Screen for Barrett Esophagus

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Abstract: Barrett esophagus (BE) is the only known precursor to esophageal adenocarcinoma (EAC), a cancer that continues to have a poor 5-year survival rate of 20%. Current BE screening strategies aim to detect BE and EAC at early, curable stages, but the majority of patients with EAC are diagnosed outside of BE screening and surveillance programs. Guidelines around the world suggest screening for BE in patients with gastroesophageal reflux disease (GERD) and additional demographic and clinical risk factors using high-definition white-light endoscopy (HDWLE). However, current strategies relying on HDWLE are problematic with high direct and indirect costs, procedural risks, and limitations in patient selection owing to the low sensitivity of GERD as a risk factor for detection of BE. In an effort to address these shortcomings, a variety of other screening strategies are under investigation, including risk prediction algorithms, noninvasive cell collection devices, and other new technologies to make screening more efficient and cost-effective. At this time, only cell collection devices have been integrated into professional guidelines, and clinical implementation of alternatives to endoscopy has lagged. In the future, screening may be personalized using a combination of different screening modalities. This article discusses the current state of BE screening and new approaches that may alter the future of screening.

Keywords
Barrett esophagus, esophageal adenocarcinoma, screening, Cytosponge, surveillance

Esophageal adenocarcinoma (EAC) remains a lethal disease with an overall survival rate of 20% at 5 years, and its incidence has increased over time.[1,2] The clinical impact of undiagnosed EAC highlights the importance of early detection of the disease and its only known precursor, Barrett esophagus (BE). Population-based studies suggest that endoscopic surveillance of BE leads to detection of EAC at an earlier, curable stage.[3] Furthermore, minimally invasive endoscopic eradication therapies are effective for the treatment of dysplasia and early EAC.[3] Current professional society guidelines suggest screening for BE in high-risk patients using high-definition white-light endoscopy

Table 1. Summary of the Current Professional Society Guidelines for BE Screening

BSG 2014, ESGE 2017, ACG 2022[5,7,11]	ASGE 2019[4]	AGA 2022[6]
Consider or suggest BE screening if patient has chronic GERD (or GERD >5 years per ESGE) AND ≥3 risk factors: • Male • Age >50 years • White race • Central obesity • Tobacco smoking[a] • First-degree relative with BE or EAC[b] [a]BSG does not include tobacco smoking as a risk factor. [b]BSG does not include family history of BE or EAC as a risk factor but states that it should lower the screening threshold.	Risk stratify and recommend BE screening if patient has: • Family history of BE or EAC Patient may benefit from BE screening if has GERD + ≥1 risk factor: • Age >50 years • Male • Obesity • Smoking	Suggest BE screening if patient has ≥3 risk factors: • Male • White race • Age >50 years • History of smoking • Chronic GERD • Obesity • Family history of BE or EAC

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett esophagus; BSG, British Society of Gastroenterology; EAC, esophageal adenocarcinoma; ESGE, European Society of Gastrointestinal Endoscopy; GERD, gastroesophageal reflux disease.

(HDWLE) with the goal of increasing the early diagnosis of EAC.[4-7] However, in contrast to colorectal cancer, the incidence of EAC is much lower, bringing into question the concept of widespread screening using an invasive and costly technology such as endoscopy.[8] Although the incidence of EAC is low, screening for BE remains an important opportunity to reduce the morbidity and mortality of EAC; studies have shown that EAC patients with a prior diagnosis of BE have enhanced survival as well as lower tumor stage and grade.[9] The current approach to BE screening has significant limitations, as the majority of patients with EAC are diagnosed outside of screening programs.[10] New technologies are being developed to address these limitations and may change the approach to screening in the future. This article discusses the current state of BE screening and reviews new approaches that may alter screening in the coming years.

The Challenge: Limitations of Current Barrett Esophagus Screening

Current professional society guidelines inform clinical practice for BE screening, and all recommend that screening should be considered for patients with multiple risk factors using HDWLE.[4-7,11] Although there are many similarities among the current guidelines, there is also some variation as outlined in Table 1. Of note, the American Gastroenterological Association (AGA) Clinical Practice Update recommends consideration of screening in patients with multiple risk factors for BE, whereas the American Society for Gastrointestinal Endoscopy (ASGE), European Society of Gastrointestinal Endoscopy (ESGE), and American College of Gastroenterology (ACG) rely on the presence of gastroesophageal reflux disease (GERD) plus additional risk factors such as male sex, age greater than 50 years, White race, tobacco smoking, obesity, and family history of BE or EAC.[4-7,11] However, there are limitations to how well the current guidelines perform in clinical practice. A study looking at primary care clinic patients who were offered esophagogastroduodenoscopy (EGD) at the time of screening colonoscopy demonstrated that more than 50% of patients diagnosed with BE did not have frequent GERD symptoms.[12] As such, guidelines that required GERD symptoms plus additional risk factors (ASGE, ESGE, and ACG) had low sensitivity in this population, but guidelines that did not require GERD (AGA) had low specificity.[12] A study looking at the ACG and British Society of Gastroenterology guidelines in cohorts in the United States and the United Kingdom found that 38.9% to 54.9% of EAC cases were missed by the guideline criteria owing to a lack of heartburn in the majority of patients with EAC.[13]

As these studies demonstrate, there are significant limitations in patient selection for screening, and research suggests that more than 50% of BE in the community is undiagnosed.[14] As discussed, chronic GERD symptoms are integrated into the indications for endoscopic screening, but the prevalence of BE in patients with GERD is relatively low. Based upon 2 meta-analyses, it is estimated that 5% to 12% of patients globally with chronic GERD will have BE, and the pooled prevalence for BE in patients with GERD in North America was reported to be 14.3%.[15,16] At the same time, GERD is very common with a recent meta-analysis showing a pooled prevalence

of 19.6% in North America.[17] In addition, up to 25% of patients with BE are asymptomatic, and 20% to 50% of patients with EAC do not have prior GERD symptoms.[16,18] Thus, reliance on GERD symptoms as an entry criterion for screening would miss a substantial number of patients with BE, and the high prevalence of GERD would place further demand for endoscopic procedures on already strained systems.[19]

Importantly, all of these guidelines target the field of gastroenterology and are not widely disseminated within the primary care community, where the majority of patients with GERD are encountered. Notably, the last practice guideline for the role of upper endoscopy in GERD in internal medicine, published in 2012, recommended consideration of upper endoscopy in men older than age 50 years with GERD and additional risk factors.[20] However, there is still no recommendation from the US Preventive Services Task Force to screen for BE or EAC. Research on primary care referral patterns demonstrated that only a small subset (30%) of patients with GERD were referred to see a gastroenterologist, and the indications were typically for alarm symptoms such as melena, dysphagia, or weight loss.[21] Similarly, several recent studies of primary care health care networks found that only 30% to 39% of patients who were eligible for BE screening underwent an EGD.[22,23] A large case-control study showed that many patients diagnosed with EAC had not undergone a previous endoscopy, but had potential opportunities where screening could have been offered.[24] In one survey, 70% of primary care providers (PCPs) and gastroenterologists thought that BE screening was effective for early EAC detection, but few thought there was a reduction in all-cause mortality, and PCPs noted concerns about cost-effectiveness.[25] As with other screening tests, buy-in from the primary care community is crucial to ensure the inclusion of at-risk patients. Furthermore, as described in a later section, implementation of future nonendoscopic screening modalities may be most important in the primary care setting.

Other limitations to endoscopy include the direct procedural cost as well as the cost of time away from work, risks of sedation, and the procedure's invasive nature. There is also considerable variability in endoscopic quality. EAC can be missed during index endoscopy, with recent studies noting that 13.7% to 21% of patients with BE had postendoscopy EACs, which are EACs diagnosed within 30 to 365 days following index endoscopy.[26-28] Overall, the current guidelines and PCP referral patterns are imperfect when identifying patients who may benefit from BE screening, and HDWLE has limitations related to cost, risk, and variable quality. These gaps create opportunities to utilize new and existing technologies to identify and screen patients more effectively.

Patient Selection: Risk Prediction Tools

Because current guidelines are limited in their ability to identify high-risk patients, further work to optimize BE screening patient selection focuses on BE risk assessment tools. Rubenstein and colleagues developed the M-BERET tool, which includes GERD, age, waist-to-hip ratio, and cigarette pack use in a logistic regression model (https://mberet.umms.med.umich.edu).[29] The Kunzmann model, developed in the United Kingdom, utilizes age, sex, body mass index (BMI), smoking status, and presence of an esophageal condition in a logistic regression model for risk of EAC.[30] The HUNT model, developed in Norway, incorporates age, sex, GERD symptoms, obesity, and tobacco smoking status using a competing risk regression model to predict the presence of EAC.[31] These 3 models were compared in 1241 patients presenting for either their first EGD or their first endoscopic eradication treatment for BE. All of the models were superior to using GERD alone (area under the receiver operating characteristic curve [AUROC], 0.579) with similar predictive values: HUNT (0.6649), Kunzmann (0.6674), and M-BERET (0.6951).[32] Although each of these models is superior to using GERD alone as a threshold for screening, the precision of each of them is still not optimal. In an effort to improve upon these models, the MARK-BE study examined 40 risk factors and symptoms of patients from the BEST-2 Cytosponge case-control study to create another prediction model.[33] They used machine learning to create a multivariate model with 8 factors (age, sex, waist circumference, stomach pain, acid-suppressing medications, duration of acidic taste, duration of heartburn, and smoking) with an AUROC of 0.87. More recently, the Houston-BEST model, which utilizes electronic medical record information such as sex, age greater than 50 years, race/ethnicity, smoking status, BMI, GERD, and family history of esophageal cancer, had an AUROC of 0.65 to 0.70.[34] Overall, all models performed better than GERD alone for predicting BE and EAC, but MARK-BE had the highest predictive value. Each of these risk prediction models has the potential to change current screening practice. However, to operationalize these models, they will need to be integrated into electronic health records in order to identify and flag patients who are at higher risk for BE.[35]

Currently, patients who meet criteria for screening are offered a onetime endoscopy, and a normal examination requires no further evaluation. Because the risk of having BE and EAC varies significantly among subsets of the population, a re-evaluation of this once-in-a-lifetime concept has been performed. Recent work by Rubenstein and colleagues modeled BE endoscopic screening in varied populations and found differences among sex and

Table 2. Novel Nonendoscopic Screening Techniques for Barrett Esophagus

Device	Mode	Biomarker(s)	Reference(s)	Sensitivity	Specificity
Cytosponge	Swallowable tethered capsule	TFF3	Ross-Innes et al[38]	79.9%	92.4%
EsophaCap	Swallowable tethered capsule	MUC2-IHC 5-MDM 4-MDM 2-MDM	Zhou et al[68] Iyer et al[46] Wang et al[44] Iyer et al[69]	68% 93% 94.4% 100%	91% 90% 62.2% 100%
EsoCheck	Swallowable tethered balloon	VIM, CCNA1	Moinova et al[47]	90.3%	91.7%
eNose	Electronic nose device	Exhaled VOCs	Peters et al[49]	91%	74%
	Magnetically assisted capsule endoscopy	None	Beg et al[59]	93.8%	100%
	Esophageal capsule endoscopy	None	Park et al[70]	78%	86%
	Tethered capsule endomicroscopy	None	Dong et al[62]	N/A	N/A

IHC, immunohistochemistry; MDM, methylated DNA marker; N/A, not available; TFF3, trefoil factor family; VOCs, volatile organic compounds.

race. From their analysis, White men with GERD should be considered for screening at both ages 45 and 60 years and Black men once at age 55 years, and women of both races should not be screened at all.[36] In addition, another study found that patients with higher risk and younger age had the highest yields of repeat endoscopies and that the risk of a new diagnosis increased with the duration of time from index endoscopy.[37] Further work is needed to evaluate the optimal timing and frequency of screening and whether demographics should be factored in as outlined previously.

Barrett Esophagus Screening: The Future

Given the limitations of traditional sedated endoscopy as the primary tool for screening patients for BE, a variety of alternative strategies are now under study (Table 2). These can be categorized broadly as cell collection devices, breath tests, image-based testing, and blood-based testing.

Cell Collection Devices

Swallowable esophageal cell collection devices represent a novel category of minimally invasive technology. Each of the devices is tethered and can be withdrawn after swallowing to sample the esophageal mucosa. The samples can be analyzed using a variety of different methods, including cytology, immunohistochemistry (IHC), and molecular or epigenetic markers, to improve detection of BE.

Of all the swallowable cell collection devices, Cytosponge (Medtronic) is the best studied to date. Cytosponge is a compacted polyurethane mesh sponge encapsulated in a gelatin delivery pill with an attached tether that is swallowed by the patient. When the capsule reaches the stomach, the gelatin capsule dissolves and the compressed sponge expands and is then pulled back through the esophagus by the attached tether. The sponge collects cells that can be used for IHC analysis for trefoil factor family (TFF3), which is expressed on goblet cells that are characteristic of intestinal metaplasia. Based on a case-control study of 1110 patients with GERD, Cytosponge and TFF3 have a sensitivity of 79.9% that increased to 87.2% when including only BE greater than 3 cm with a specificity of 92.4%.[38] A recent landmark randomized controlled trial examined the use of Cytosponge in patients with symptoms of GERD on acid suppression therapy in the United Kingdom.[39] Patients were randomized to either a usual care group that was comprised of standard management of GERD with EGD performed only if clinically indicated or to a Cytosponge group with subsequent EGD if the sample detected TFF3-positive cells. Of the 6834 patients in the intervention group, 1654 successfully swallowed the Cytosponge. Two percent (n=140) of patients in the intervention group were diagnosed with BE on endoscopy compared with less than 1% (n=13) of patients in the usual care arm. Of the 221 patients who had positive TFF3 on Cytosponge findings, 59% were found to have BE on endoscopy, leading to an estimated specificity of 94%. Furthermore, 9 patients in the intervention group were identified with dysplastic BE or stage I cancer, whereas no cases of dysplasia and 1 case each of stage II, III, and IV cancer were diagnosed in the usual care group. This study added to the emerging evidence in

support of Cytosponge as a potential screening technique for the general population.

The Cytosponge device is well tolerated, and throat discomfort is the most common adverse effect, described in 4% of patients. Sponge detachment occurs in fewer than 1 in 2000 procedures and is managed with prompt endoscopic retrieval.[39] Several modeling studies have found Cytosponge-based screening to be cost-effective when compared with endoscopic screening for BE.[40,41] However, one challenge is patient acceptance. In the randomized trial cited previously, 61% of patients did not express interest in Cytosponge and only 24% of all patients in the intervention group actually used it.[39] Although gagging occurred in 60% of patients who used Cytosponge, 80% stated that they would be willing to use it again or recommend it to friends.[42] High levels of anxiety, failed swallow at first attempt, female sex, shorter height, frequent alcohol intake, and higher education attainment were identified as factors that predicted a less positive patient experience.[43]

Similar to Cytosponge, EsophaCap (PAVmed) is a swallowable capsule sponge made of a polyurethane foam sphere attached to a tethered cord. EsophaCap analysis combines cytology samples with methylated DNA markers (MDMs) associated with increased cancer risk.[44,45] Compared with TFF3, MDMs do not require IHC analysis. This leads to quantitative interpretations without the need for a pathologist's expertise, thereby reducing subjectivity associated with IHC. A multicenter case-control study using EsophaCap combined with 5-MDM in 110 patients with BE and 89 control patients showed a sensitivity of 93% and specificity of 90% for BE diagnosis.[46]

EsoCheck (Lucid Diagnostics) is an oval, deflated balloon that is swallowed by the patient and then inflated to a diameter of 18 mm after reaching the stomach. The balloon is then pulled to 5 cm above the gastroesophageal junction and inverted within the cap to reduce squamous cell contamination, and analysis is again combined with MDMs to detect BE. The methylated biomarkers used with EsoCheck are VIM and CCNA1. In a pilot study of 86 patients, EsoCheck and the MDM assay had a sensitivity of 90.3% and specificity of 91.7%.[47] There is currently a multicenter trial evaluating the performance characteristics of EsoCheck (NCT04293458) in a larger population.

Breath Tests

Volatile organic compounds (VOCs) are exhaled gases that represent end products of digestion, metabolism, the microbiome, and disease states. An electronic nose (eNose) device is a potential new BE screening method that detects disease-specific patterns of VOCs in exhaled breath using metal oxide sensors.[48] eNose consists of a handheld device that has been programmed to recognize a VOC profile associated with BE and EAC. In a study of 401 patients, eNose was able to distinguish VOCs between patients with and without BE with encouraging diagnostic accuracy (sensitivity of 91%, specificity of 74%) that was not affected by a history of proton pump inhibitor use, GERD, or a hiatal hernia.[49] This technology still requires further validation in a primary care setting, along with a better understanding of factors that may affect VOCs such as medications and diet.

Image-based Testing

Transnasal unsedated endoscopy for screening has been extensively studied but not widely embraced in clinical practice. As an alternative to sedated endoscopy, it involves a smaller endoscope that is introduced through the nasal cavity of an unsedated patient after administration of a topical anesthetic. It has been well described for evaluation of BE with a pooled sensitivity of 98% and pooled specificity of 99% for detection of columnar epithelium.[50-52] Functionally, it has many similarities with sedated endoscopy, including the need for air insufflation, biopsy capability, comparable maneuverability, and high-definition imaging. Because patients do not receive sedation, this technique has a favorable safety profile. In addition, both direct and indirect costs are reduced, with no anesthesia costs and less time needed away from work for both the patient and potential chaperone.[50-52] Transnasal unsedated endoscopy can also be performed in an office-based setting with minimal additional staff compared with an endoscopy unit. Moriarty and colleagues modeled 30-day costs of screening in the United States and found higher direct costs associated with sedated EGD (mean $1821) compared with transnasal unsedated endoscopy (mean $406). The mean indirect costs of missed work were also higher: $113.35 for sedated EGD, $84.55 for hospital-based transnasal unsedated endoscopy, and $64.55 for mobile-based transnasal unsedated endoscopy.[53] A randomized trial found comparable rates of participation and clinical effectiveness for transnasal unsedated endoscopy compared with sedated endoscopy.[54] In addition, disposable endosheaths could minimize the need for scope reprocessing.[55] Although considered an alternative for screening in previous guidelines, implementation of transnasal unsedated endoscopy has been limited by patient interest and provider experience.

Esophageal capsule endoscopy (ECE) is a minimally invasive technique that utilizes a swallowed encapsulated camera to visualize the esophagus. Rapid esophageal transit time presents a significant barrier to the quality of the examination, and a recent third-generation device was tested and found to have suboptimal performance characteristics.[56-58] Magnetically assisted capsule endoscopy

(MACE) utilizes an external magnet to slow esophageal transit time. A small proof-of-principal study of 47 patients (16 with BE) using MACE showed an increased sensitivity of 93.8% and specificity of 100%, and MACE was considered more comfortable by patients compared with conventional endoscopy.[59] With MACE, the capsule was held within the esophagus for a mean duration of 190 seconds and up to a maximum of 634 seconds. Of note, 3 of the 47 patients (6.38%) were unable to swallow the capsule. Cost modeling suggests that ECE does not have a significant advantage when compared with sedated endoscopy, but this was prior to further optimization with magnetic augmentation.[60] Although significant technological advances have been made in ECE, it has yet to be integrated into BE screening, and this technique does not obtain any cell-based samples.

Tethered capsule endomicroscopy (TCE) is a promising new screening modality that utilizes optical coherence tomography (OCT) technology in a reusable swallowable capsule to obtain cross-sectional imaging of the esophageal mucosa to detect features specific for BE.[61] Patients swallow the capsule, which is approximately the size of a video capsule. It continuously obtains 10 μm resolution cross-sectional images of the esophagus while it is manually adjusted by the operator using a tether. A recent multicenter trial evaluated TCE in 116 BE patients and found high-quality OCT images in 93.7% and strong correlation with EGD measurement of BE length (r=.77-.79; P<.001).[62] Of note, only 79% of patients were able to successfully swallow the capsule, and the capsule malfunctioned in 5 studies. Similar to other noninvasive screening methods, TCE can be performed in unsedated patients, and nurses and physicians were equally capable of performing the test after training. A study evaluating TCE for BE screening in a primary care population is currently underway (NCT04561791).

Blood-based Testing

Blood-based testing looks for DNA or RNA in peripheral blood samples to screen for BE and is an exciting but unproven technology. Circulating microRNAs (miRNAs) are short noncoding RNAs that regulate gene expression by inhibiting messenger RNA translation or increasing degradation and can be dysregulated in neoplastic tissue. In BE, several miRNAs have abnormal expression that can be tested using quantitative real-time polymerase chain reaction in both tissue and serum.[63-65] However, there is considerable variation in the miRNAs of interest based upon current literature. Circulating tumor DNA (ctDNA) is fragmented DNA originating from tumor cells that is found in serum. Multicancer detection projects have evaluated ctDNA via blood-based testing that could detect cancer types and cancer cell origin, with a large multicenter study currently ongoing; however, this approach may have limited sensitivity for BE or early EAC.[66,67] The idea of testing for BE based upon peripheral blood samples is appealing as a noninvasive alternative, but further studies that demonstrate consistent findings on larger patient populations are needed.

Conclusions

BE is the only known precursor to EAC, and studies have shown that early detection of EAC leads to improved outcomes. Current practice relies on utilizing risk factors to identify patients suitable for screening with HDWLE, but this strategy has many limitations. Professional society guidelines that rely on GERD (ASGE, ESGE, and ACG) have low sensitivity but high specificity, whereas guidelines that do not require GERD (AGA) have low specificity but high sensitivity. The HUNT, Kunzmann, Houston-BEST, and M-BERET models have calculators that can be applied to better identify patients who would benefit from BE screening. The integration of risk calculators within an electronic medical record has the potential to streamline patient selection for screening in both the primary care and gastroenterology settings.

Many new strategies are under development that have the potential to revolutionize screening for BE, including cell collection devices (Cytosponge, EsophaCap, EsoCheck), image-based screening (including transnasal unsedated endoscopy, MACE, TCE), exhaled VOCs, and blood-based testing. Of the novel modalities for BE screening, only swallowable cell collection devices have become integrated into practice guidelines by the AGA and ACG.[5,6] However, there has been minimal uptake of these devices into clinical practice in the United States, and there are several current barriers to implementation. Test administrators need to be trained to use these devices, and systems must be created for testing. Insurance companies will also need to demonstrate a willingness to reimburse for these procedures. Most importantly, the population for these interventions is likely to come from PCPs and not from within gastroenterology. As such, there is a considerable unmet need for education of the primary care community and implementation of systems to identify patients who may benefit from screening. Patient education will also be needed to explain the testing options for BE screening. Future screening efforts may mirror colorectal cancer screening, where many options are presented to patients that allow for patient-centered and individualized choices weighing the risks and benefits.

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References

1. Codipilly DC, Sawas T, Dhaliwal L, et al. Epidemiology and outcomes of young-onset esophageal adenocarcinoma: an analysis from a population-based database. *Cancer Epidemiol Biomarkers Prev*. 2021;30(1):142-149.
2. Arnold M, Laversanne M, Brown LM, Devesa SS, Bray F. Predicting the future burden of esophageal cancer by histological subtype: international trends in incidence up to 2030. *Am J Gastroenterol*. 2017;112(8):1247-1255.
3. Codipilly DC, Chandar AK, Singh S, et al. The effect of endoscopic surveillance in patients with Barrett's esophagus: a systematic review and meta-analysis. *Gastroenterology*. 2018;154(8):2068-2086.e5.
4. Qumseya B, Sultan S, Bain P, et al; ASGE Standards of Practice Committee; ASGE Standards of Practice Committee Chair. ASGE guideline on screening and surveillance of Barrett's esophagus. *Gastrointest Endosc*. 2019;90(3):335-359.e2.
5. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and management of Barrett's esophagus: an updated ACG guideline. *Am J Gastroenterol*. 2022;117(4):559-587.
6. Muthusamy VR, Wani S, Gyawali CP, Komanduri S; CGIT Barrett's Esophagus Consensus Conference Participants. AGA Clinical Practice Update on new technology and innovation for surveillance and screening in Barrett's esophagus: expert review. *Clin Gastroenterol Hepatol*. 2022;20(12):2696-2706.e1.
7. Fitzgerald RC, di Pietro M, Ragunath K, et al; British Society of Gastroenterology. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut*. 2014;63(1):7-42.
8. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(3):233-254.
9. Bhat SK, McManus DT, Coleman HG, et al. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study. *Gut*. 2015;64(1):20-25.
10. Spechler SJ, El-Serag HB. Why has screening and surveillance for Barrett's esophagus fallen short in stemming the rising incidence of esophageal adenocarcinoma? *Am J Gastroenterol*. 2023;118(4):590-592.
11. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. 2017;49(2):191-198.
12. Nguyen TH, Thrift AP, Rugge M, El-Serag HB. Prevalence of Barrett's esophagus and performance of societal screening guidelines in an unreferred primary care population of U.S. veterans. *Gastrointest Endosc*. 2021;93(2):409-419.e1.
13. Sawas T, Zamani SA, Killcoyne S, et al. Limitations of heartburn and other societies' criteria in Barrett's screening for detecting de novo esophageal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2022;20(8):1709-1718.
14. Hammad TA, Thrift AP, El-Serag HB, Husain NS. Missed opportunities for screening and surveillance of Barrett's esophagus in veterans with esophageal adenocarcinoma. *Dig Dis Sci*. 2019;64(2):367-372.
15. Qumseya BJ, Bukannan A, Gendy S, et al. Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. *Gastrointest Endosc*. 2019;90(5):707-717.e1.
16. Eusebi LH, Cirota GG, Zagari RM, Ford AC. Global prevalence of Barrett's oesophagus and oesophageal cancer in individuals with gastro-oesophageal reflux: a systematic review and meta-analysis. *Gut*. 2021;70(3):456-463.
17. Nirwan JS, Hasan SS, Babar ZUD, Conway BR, Ghori MU. Global prevalence and risk factors of gastro-oesophageal reflux disease (GORD): systematic review with meta-analysis. *Sci Rep*. 2020;10(1):5814.
18. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340(11):825-831.
19. Rubenstein JH. Gastroesophageal reflux disease is not a great screening criterion: time to move on to other strategies for controlling the burden of esophageal adenocarcinoma. *Am J Gastroenterol*. 2022;117(11):1759-1761.
20. Shaheen NJ, Weinberg DS, Denberg TD, Chou R, Qaseem A, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. *Ann Intern Med*. 2012;157(11):808-816.
21. Vajravelu RK, Kolb JM, Gellad WF, et al. Patient factors associated with gastroesophageal reflux disease diagnostic evaluation strategies: a retrospective cohort study using real-world evidence from a large U.S. medical claims database. *Gastro Hep Adv*. 2022;1(4):563-572.
22. Eluri S, Reddy S, Ketchem CC, et al. Low prevalence of endoscopic screening for Barrett's esophagus in a screening-eligible primary care population. *Am J Gastroenterol*. 2022;117(11):1764-1771.
23. Stewart M, Menon A, Akbar U, Garg S, Jang HJ, Trindade AJ. Missed opportunities for screening for Barrett's esophagus in the primary care setting of a large health system [published online March 12, 2023]. *Gastrointest Endosc*. doi:10.1016/j.gie.2023.03.010.
24. Rubenstein JH, Evans RR, Burns JA, Arasim ME, Zhu J, Waljee AK; Harnessing Opportunities to Screen for Esophageal Adenocarcinoma Group. Patients with adenocarcinoma of the esophagus or esophagogastric junction frequently have potential screening opportunities. *Gastroenterology*. 2022;162(4):1349-1351.e5.
25. Kolb JM, Chen M, Tavakkoli A, Singal AG, Vajravelu RK, Wani S; SCREEN-BE Study Group. Understanding compliance, practice patterns and barriers among gastroenterologists and primary care providers is crucial for developing strategies to improve screening for Barrett's esophagus. *Gastroenterology*. 2022;162(6):1568-1573.e4.
26. Vajravelu RK, Kolb JM, Thanawala SU, et al. Characterization of prevalent, post-endoscopy, and incident esophageal cancer in the United States: a large retrospective cohort study. *Clin Gastroenterol Hepatol*. 2022;20(8):1739-1747.
27. Desai M, Lieberman D, Srinivasan S, et al. Post-endoscopy Barrett's neoplasia after a negative index endoscopy: a systematic review and proposal for definitions and performance measures in endoscopy. *Endoscopy*. 2022;54(9):881-889.
28. Sawas T, Majzoub AM, Haddad J, et al; Post-Endoscopy Esophageal Adenocarcinoma Consensus Panel. Magnitude and time-trend analysis of postendoscopy esophageal adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2022;20(2):e31-e50.
29. Rubenstein JH, Morgenstern H, Appelman H, et al. Prediction of Barrett's esophagus among men. *Am J Gastroenterol*. 2013;108(3):353-362.
30. Kunzmann AT, Thrift AP, Johnston BT, et al. External validation of a model to determine risk of progression of Barrett's oesophagus to neoplasia. *Aliment Pharmacol Ther*. 2019;49(10):1274-1281.
31. Xie SH, Ness-Jensen E, Medefelt N, Lagergren J. Assessing the feasibility of targeted screening for esophageal adenocarcinoma based on individual risk assessment in a population-based cohort study in Norway (the HUNT Study). *Am J Gastroenterol*. 2018;113(6):829-835.
32. Rubenstein JH, McConnell D, Waljee AK, et al. Validation and comparison of tools for selecting individuals to screen for Barrett's esophagus and early neoplasia. *Gastroenterology*. 2020;158(8):2082-2092.
33. Rosenfeld A, Graham DG, Jevons S, et al; BEST2 study group. Development and validation of a risk prediction model to diagnose Barrett's oesophagus (MARK-BE): a case-control machine learning approach. *Lancet Digit Health*. 2020;2(1):E37-E48.
34. Wenker TN, Rubenstein JH, Thrift AP, Singh H, El-Serag HB. Development and validation of the Houston-BEST, a Barrett's esophagus risk prediction model adaptable to electronic health records [published online August 17, 2022]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2022.08.007.
35. Murphy DR, Meyer AND, Vaghani V, et al. Development and validation of trigger algorithms to identify delays in diagnostic evaluation of gastroenterological cancer. *Clin Gastroenterol Hepatol*. 2018;16(1):90-98.
36. Rubenstein JH, Omidvari AH, Lauren BN, et al. Endoscopic screening program for control of esophageal adenocarcinoma in varied populations: a comparative cost-effectiveness analysis. *Gastroenterology*. 2022;163(1):163-173.
37. Rubenstein JH, Burns JA, Arasim ME, et al. Yield of repeat endoscopy for Barrett's esophagus after normal index endoscopy [published online March 27, 2023]. *Am J Gastroenterol*. doi:10.14309/ajg.0000000000002204.
38. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al; BEST2 Study Group. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. *PLoS Med*. 2015;12(1):e1001780.
39. Fitzgerald RC, di Pietro M, O'Donovan M, et al; BEST3 Trial team. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. *Lancet*. 2020;396(10247):333-344.
40. Offman J, Muldrew B, O'Donovan M, et al; BEST3 Trial team. Barrett's oesophagus trial 3 (BEST3): study protocol for a randomised controlled trial comparing the Cytosponge-TFF3 test with usual care to facilitate the diagnosis of oesophageal pre-cancer in primary care patients with chronic acid reflux. *BMC Cancer*. 2018;18(1):784.
41. Heberle CR, Omidvari AH, Ali A, et al. Cost effectiveness of screening patients

with gastroesophageal reflux disease for Barrett's esophagus with a minimally invasive cell sampling device. *Clin Gastroenterol Hepatol*. 2017;15(9):1397-1404.e7.
42. Maroni R, Barnes J, Offman J, et al; BEST3 Consortium. Patient-reported experiences and views on the Cytosponge test: a mixed-methods analysis from the BEST3 trial. *BMJ Open*. 2022;12(4):e054258.
43. Ghimire B, Landy R, Maroni R, et al; BEST3 Consortium. Predictors of the experience of a Cytosponge test: analysis of patient survey data from the BEST3 trial. *BMC Gastroenterol*. 2023;23(1):7.
44. Wang Z, Kambhampati S, Cheng Y, et al. Methylation biomarker panel performance in EsophaCap cytology samples for diagnosing Barrett's esophagus: a prospective validation study. *Clin Cancer Res*. 2019;25(7):2127-2135.
45. Zou H, Molina JR, Harrington JJ, et al. Aberrant methylation of secreted frizzled-related protein genes in esophageal adenocarcinoma and Barrett's esophagus. *Int J Cancer*. 2005;116(4):584-591.
46. Iyer PG, Taylor WR, Slettedahl SW, et al. Validation of a methylated DNA marker panel for the nonendoscopic detection of Barrett's esophagus in a multisite case-control study. *Gastrointest Endosc*. 2021;94(3):498-505.
47. Moinova HR, LaFramboise T, Lutterbaugh JD, et al. Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. *Sci Transl Med*. 2018;10(424):eaao5848.
48. Chan DK, Zakko L, Visrodia KH, et al. Breath testing for Barrett's esophagus using exhaled volatile organic compound profiling with an electronic nose device. *Gastroenterology*. 2017;152(1):24-26.
49. Peters Y, Schrauwen RWM, Tan AC, Bogers SK, de Jong B, Siersema PD. Detection of Barrett's oesophagus through exhaled breath using an electronic nose device. *Gut*. 2020;69(7):1169-1172.
50. Huibertse LJ, Peters Y, Westendorp D, Siersema PD. Unsedated transnasal endoscopy for the detection of Barrett's esophagus: systematic review and meta-analysis. *Dis Esophagus*. 2023;36(2):doac045.
51. Peery AF, Hoppo T, Garman KS, et al; Barrett's Esophagus Risk Consortium. Feasibility, safety, acceptability, and yield of office-based, screening transnasal esophagoscopy (with video). *Gastrointest Endosc*. 2012;75(5):945-953.e2.
52. Sami SS, Subramanian V, Ortiz-Fernández-Sordo J, et al. Performance characteristics of unsedated ultrathin video endoscopy in the assessment of the upper GI tract: systematic review and meta-analysis. *Gastrointest Endosc*. 2015;82(5):782-792.
53. Moriarty JP, Shah ND, Rubenstein JH, et al. Costs associated with Barrett's esophagus screening in the community: an economic analysis of a prospective randomized controlled trial of sedated versus hospital unsedated versus mobile community unsedated endoscopy. *Gastrointest Endosc*. 2018;87(1):88-94.e2.
54. Sami SS, Dunagan KT, Johnson ML, et al. A randomized comparative effectiveness trial of novel endoscopic techniques and approaches for Barrett's esophagus screening in the community. *Am J Gastroenterol*. 2015;110(1):148-158.
55. Shariff MK, Varghese S, O'Donovan M, et al. Pilot randomized crossover study comparing the efficacy of transnasal disposable endosheath with standard endoscopy to detect Barrett's esophagus. *Endoscopy*. 2016;48(2):110-116.
56. Bhardwaj A, Hollenbeak CS, Pooran N, Mathew A. A meta-analysis of the diagnostic accuracy of esophageal capsule endoscopy for Barrett's esophagus in patients with gastroesophageal reflux disease. *Am J Gastroenterol*. 2009;104(6):1533-1539.
57. Duvvuri A, Desai M, Vennelaganti S, et al. Diagnostic accuracy of a novel third generation esophageal capsule as a non-invasive detection method for Barrett's esophagus: a pilot study. *J Gastroenterol Hepatol*. 2021;36(5):1222-1225.
58. Chen WS, Zhu LH, Li DZ, Chen L, Wu YL, Wang W. String esophageal capsule endoscopy with real-time viewing improves visualization of the distal esophageal Z-line: a prospective, comparative study. *Eur J Gastroenterol Hepatol*. 2014;26(3):309-312.
59. Beg S, Card T, Warburton S, et al. Diagnosis of Barrett's esophagus and esophageal varices using a magnetically assisted capsule endoscopy system. *Gastrointest Endosc*. 2020;91(4):773-781.e1.
60. Rubenstein JH, Inadomi JM, Brill JV, Eisen GM. Cost utility of screening for Barrett's esophagus with esophageal capsule endoscopy versus conventional upper endoscopy. *Clin Gastroenterol Hepatol*. 2007;5(3):312-318.
61. Gora MJ, Sauk JS, Carruth RW, et al. Tethered capsule endomicroscopy enables less invasive imaging of gastrointestinal tract microstructure. *Nat Med*. 2013;19(2):238-240.
62. Dong J, Grant C, Vuong B, et al. Feasibility and safety of tethered capsule endomicroscopy in patients with Barrett's esophagus in a multi-center study. *Clin Gastroenterol Hepatol*. 2022;20(4):756-765.e3.
63. Cabibi D, Caruso S, Bazan V, et al. Analysis of tissue and circulating microRNA expression during metaplastic transformation of the esophagus. *Oncotarget*. 2016;7(30):47821-47830.
64. Clark RJ, Craig MP, Agrawal S, Kadakia M. microRNA involvement in the onset and progression of Barrett's esophagus: a systematic review. *Oncotarget*. 2018;9(8):8179-8196.
65. Craig MP, Rajakaruna S, Paliy O, et al. Differential microRNA signatures in the pathogenesis of Barrett's esophagus. *Clin Transl Gastroenterol*. 2020;11(1):e00125.
66. Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*. 2021;32(9):1167-1177.
67. Nadauld LD, McDonnell CH III, Beer TM, et al. The PATHFINDER study: assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. *Cancers (Basel)*. 2021;13(14):3501.
68. Zhou Z, Kalatskaya I, Russell D, et al. Combined EsophaCap cytology and MUC2 immunohistochemistry for screening of intestinal metaplasia, dysplasia and carcinoma. *Clin Exp Gastroenterol*. 2019;12:219-229.
69. Iyer PG, Taylor WR, Johnson ML, et al. Highly discriminant methylated DNA markers for the non-endoscopic detection of Barrett's esophagus. *Am J Gastroenterol*. 2018;113(8):1156-1166.
70. Park J, Cho YK, Kim JH. Current and future use of esophageal capsule endoscopy. *Clin Endosc*. 2018;51(4):317-322.