

Novel Screening Alternatives for Barrett Esophagus

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Abstract: Barrett esophagus (BE) is the only known premalignant precursor to esophageal adenocarcinoma (EAC), a deadly malignancy that carries a dismal prognosis. Guidelines currently recommend screening for BE only in high-risk populations, such as patients with chronic gastroesophageal reflux disease (GERD) and 1 or more additional risk factors. A GERD-centered approach to BE screening likely leads to a large number of missed EAC cases, as the true population prevalence of BE is thought to be much higher than current estimates. Mass screening for BE has been proposed but is fraught with challenges. Esophagogastroduodenoscopy screening is the current gold standard for BE detection, but it is expensive and cumbersome and carries a small potential for unwanted harms. Transnasal endoscopy is simple, cost-effective, and well tolerated, but it has not found widespread acceptance among physicians and patients. Esophageal capsule endoscopy, despite being well tolerated and accepted, has not been shown to be cost-effective. Newer minimally invasive, nonendoscopic techniques for BE screening have shown promise in prospective clinical trials. Pragmatic head-to-head trials comparing these techniques will help determine the path forward and could herald a new future for population-based BE screening.

Barrett esophagus (BE) is a precancerous condition of the distal esophagus in which a specialized intestinal-type columnar epithelium replaces the stratified squamous epithelium. This metaplastic transformation likely occurs as a reparative response to injury caused by chronic exposure to gastric refluxate.¹ BE is the only known precursor to esophageal adenocarcinoma (EAC), a deadly malignancy whose prognosis remains extremely poor.² EAC has been one of the fastest-growing cancers in the United States, increasing 6-fold (from 4 to 23 cases per 1 million) between 1975 and 2001.³ Through a Surveillance, Epidemiology, and End Results database analysis, it has been estimated that the overall incidence of EAC increased from 0.4 per 100,000 in 1973 to 2.8 per 100,000 in 2012.⁴ Despite the 5-year survival rate of EAC showing some improvement, from 5% in the 1970s to almost 20% currently,⁵ the

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prognosis remains dismal. Over 40% of EAC patients still have distant metastasis at the time of diagnosis.⁴

Screening is defined as the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations, or other procedures that can be applied rapidly and easily to the target population.⁶ The basic tenet of a screening program is early detection of disease before the onset of noticeable symptoms, thereby allowing for treatment that would be more effective than it would be after the development of signs and symptoms. An ideal screening program is one that is capable of detecting a high proportion of disease in its preclinical state, is safe to administer, is acceptable to the population being screened, is cost-effective, leads to demonstrably improved health outcomes, and can be made widely available.^{6,7}

Need for Population-Based Barrett Esophagus Screening

Screening and surveillance of BE are of particular importance, as patients with BE have a 10-fold or higher risk of progressing to EAC compared to the general population.⁸ The major risk factor for BE is gastroesophageal reflux disease (GERD), and individuals with chronic GERD have a higher risk of BE than individuals without GERD.⁹ Additionally, male sex, age older than 50 years, white race, smoking history, central obesity, and family history of BE or EAC have all been implicated as risk factors for BE.¹⁰ Unsurprisingly, the risk of BE increases additively with each additional risk factor in patients with GERD symptoms.⁹

Major gastroenterology societies in the United States and Europe recognize that there is insufficient evidence to support mass screening for BE, as there are no randomized, controlled trials (RCTs) investigating the effectiveness of screening.¹¹⁻¹⁴ However, these societies suggest that BE screening should be considered in individuals with chronic (≥ 5 years) GERD who have multiple other risk factors. In general, the high-risk group is white men with chronic or frequent GERD with 1 or more additional risk factors, such as age older than 50 years, history of smoking, waist-to-hip circumference greater than 0.9, and a family history of BE or EAC. However, not every person with BE has symptomatic GERD, and heartburn is an imperfect marker to identify individuals at risk for developing cancer. It has been estimated that there are nearly as many BE patients with GERD as there are patients with GERD. Approximately 40% of patients with EAC have no previous symptoms of GERD, indicating that a GERD-centric screening strategy may have limited effectiveness.^{15,16} True population-based prevalence estimates of BE are rarely available, and studies have

shown a high proportion of BE detected in asymptomatic patient populations.^{17,18} This not only points to a Barrett iceberg, but also gives pause regarding current screening recommendations.

BE is the ideal disease candidate for the application of widespread, population-based screening. It is (presumably) a disease with a high prevalence and is an important health risk given the often-delayed detection and poor outcomes associated with EAC. There is also a recognizable latent or early symptomatic stage before EAC develops, and there are well-recognized and evidence-based treatment modalities in the form of endoscopic surveillance and endoscopic eradication therapies for patients with diagnosed BE.

The success of a BE screening program largely depends upon the ability to detect BE before it develops into incurable EAC. However, current strategies are suboptimal, as a majority of patients with EAC are not known to have a prior diagnosis of BE and over 90% do not appear to have had prior esophagogastroduodenoscopy (EGD).¹⁹⁻²¹ A survival advantage may be conferred when BE is detected early, which would then allow for endoscopic surveillance at regular intervals.²² Furthermore, the success and widespread availability of endoscopic eradication therapies, such as radiofrequency ablation, make early detection of dysplastic BE and early EAC even more attractive.^{23,24} Therefore, it is imperative that efforts are directed at detecting BE in its nascent stages.

Conventional EGD in combination with histopathology verification is considered the gold standard for detecting BE. Endoscopy is generally a safe procedure, but there may be complications beyond 72 hours that are missed or go unseen by endoscopists.²⁵ The need for sedation prohibits the use of EGD in the primary care setting as well as adds direct costs (medication administration, monitoring, personnel, and recovery time) and indirect costs (day off work for both the patient and a companion who is needed to drive or accompany the patient home, as well as avoidance of the operation of heavy machinery for the subsequent 24 hours).²⁶ Hence, conventional sedated EGD might not be a suitable option for population screening of BE. Innovations in the space of minimally invasive and noninvasive screening techniques, such as transnasal endoscopy (TNE), esophageal capsule endoscopy (ECE), Cytosponge (Medtronic), Esophacap (CapNostics), and EsoCheck (Lucid Diagnostics), have shown promising results in clinical trials (Table). These and other novel screening tools are discussed further.

Transnasal Endoscopy

TNE is performed with an ultrathin endoscope (< 6 mm in diameter) using topical nasal or oral anesthetic

Table. Summary of BE Screening Methods or Tools

Screening Method or Tool	Advantages	Disadvantage(s)	Comment(s)
EGD	<ul style="list-style-type: none"> • Widely available • Allows physicians to visualize the BE segment with white-light and narrow-band imaging, to take jumbo biopsies, and to resect if a nodule is detected during screening 	<ul style="list-style-type: none"> • Costly • Inefficient • Requires additional personnel, anesthesia or sedation, training (gastroenterology fellowship), and skill • Not portable • Endoscope disinfection process is cumbersome and time-consuming and usually requires special equipment • Unsuitable for use in the primary care setting 	<ul style="list-style-type: none"> • Current gold standard for BE screening • Gastroenterology societies recommend BE screening in high-risk populations using EGD
TNE	<ul style="list-style-type: none"> • Can be used without sedation through the nasopharyngeal or peroral route • Can be combined with a disposable sheath, which helps to forgo complicated endoscope reprocessing • Can be performed by physician extenders • A portable version with a disposable probe is available • Cost-effective • Has a high sensitivity and specificity for BE detection 	<ul style="list-style-type: none"> • Ultrathin endoscopes can be floppy • Visualization potential is not as good as with conventional EGD, but still allows physicians to visualize the BE segment with white-light and narrow-band imaging • Few accessories beyond pediatric biopsy forceps are available • Procedure is slightly less tolerated than EGD or ECE • Risk of epistaxis (although rare and usually self-limited) 	<ul style="list-style-type: none"> • The American College of Gastroenterology suggests the use of TNE as an alternative to EGD for BE screening • This method has not gained widespread traction in the physician or patient community despite low cost and advantages
ECE	<ul style="list-style-type: none"> • Safe • Portable • Physician extenders can be trained to perform and read capsule images • Has a high tolerance and acceptability 	<ul style="list-style-type: none"> • Time of transit through esophagus cannot be controlled • Image quality may be suboptimal compared to EGD or TNE • Is not cost-effective 	<ul style="list-style-type: none"> • Not recommended for BE screening because it is not cost-effective and is only moderately sensitive and specific for the detection of BE
Cytosponge	<ul style="list-style-type: none"> • Safe • Quick • Portable • Can be performed by nonphysicians in the primary care setting • Does not require sedation 	<ul style="list-style-type: none"> • Abrasions are more severe than with EsoCheck (but not severe enough to require intervention) • Requires cytopathology expertise because it uses IHC 	<ul style="list-style-type: none"> • Can be combined with TFF3 IHC • Has been tested in several large clinical trials in the United Kingdom and the United States • A large prospective, cluster-randomized trial is currently underway in the United Kingdom
EsophaCap	<ul style="list-style-type: none"> • Safe • Quick • Portable • Can be performed by nonphysicians in the primary care setting • Does not require sedation or cytopathology expertise (relies on methylated DNA biomarkers and not on IHC) 	<ul style="list-style-type: none"> • Has limited data 	<ul style="list-style-type: none"> • Device is similar to Cytosponge but is slightly smaller • Two methylated DNA biomarkers have shown promise in a small clinical trial • Larger trials are currently underway

(Table continues on next page)

Table. (Continued) Summary of BE Screening Methods or Tools

Screening Method or Tool	Advantages	Disadvantage(s)	Comment(s)
EsoCheck	<ul style="list-style-type: none"> • Faster procedure time than Cytosponge • Safe • Portable • Easily performed by nonphysicians in the primary care setting • Does not require sedation or the use of IHC • Has a high tolerance and acceptability • Does not cause abrasions 	<ul style="list-style-type: none"> • Has limited data • A small proportion of patients might experience uncontrollable gag due to the attached silicone catheter • The DNA yield is occasionally low 	<ul style="list-style-type: none"> • Combined with EsoGuard (which has 2 methylated DNA biomarkers, vimentin and cyclin-A1), EsoCheck has shown high sensitivity and specificity • A large multicenter, prospective BE detection trial is currently underway in the United States

BE, Barrett esophagus; ECE, esophageal capsule endoscopy; EGD, esophagogastroduodenoscopy; IHC, immunohistochemistry; TFF3, trefoil factor 3; TNE, transnasal endoscopy.

pretreatment, thereby obviating the need for sedation. The procedure can be performed with endoscopes that have 2-mm accessory channels that permit pediatric biopsies. In a large prospective, multicenter, cross-sectional study conducted by Peery and colleagues, 426 patients with predominant GERD symptoms underwent TNE without sedation with 99% success, with few failures that were largely attributable to patient discomfort.²⁷ Four percent of patients were found to have BE.²⁷ In a blinded RCT performed by Jobe and colleagues, TNE compared favorably to EGD in terms of BE detection (30% vs 26%).²⁸ Procedure time ranged from 3.7 ± 1.8 minutes to 5.5 ± 1.7 minutes, and the mean recovery time was quicker with TNE compared to EGD. Seventy-one percent of patients preferred TNE. However, patients undergoing EGD had less anxiety compared to patients undergoing TNE, presumably due to the unsedated nature of the TNE procedure.²⁸ Shariff and colleagues compared TNE to EGD in a single-center, prospective, randomized, crossover study.²⁹ They found that TNE had a sensitivity of 98% and a specificity of 100% for detecting BE. Of note, the population selected in this study was either consecutive patients with BE or patients who were referred for diagnostic assessment; thus, there was a high prevalence of patients with a BE length of more than 2 cm. Nearly 60% of patients preferred TNE. Complications were few, and included choking, gagging, anxiety, nasal pain, sore throat, and minor epistaxis.²⁹ In a large prospective RCT, Sami and colleagues observed that TNE compared favorably to EGD.³⁰ Mean recovery times were significantly longer for EGD (67.3 minutes) compared with TNE (15.5-18.5 minutes, depending on whether TNE was performed in a hospital outpatient endoscopy laboratory or in a mobile

research van in the community). Approximately 80% of TNE patients were willing to undergo the procedure again in the future.³⁰ The main attractiveness of TNE is its ability to be combined with a disposable sheath, such as EndoSheath (Cogentix Medical), which reduces costs associated with conventional endoscope reprocessing. However, the ultrathin endoscope still needs to be cleaned with alcohol-based sanitizer and an enzymatic detergent after every use.

A similar technology is the transnasal video esophagoscope (E.G. Scan II, IntroMedic), which uses a highly compact and portable system in combination with a disposable ultrathin probe that eliminates the need for scope disinfection.³¹ As it is portable, the esophagoscope can be used in the clinic or in a community setting. In a prospective, multicenter, cohort study conducted at 3 tertiary care referral centers in the United Kingdom and the United States, 200 patients with and without BE were recruited to undergo TNE using the transnasal video esophagoscope.³¹ The results were compared to EGD. There were 22 (11%) failures, as the TNE probe could not be passed through the nasopharynx. No serious adverse events were reported, and a significantly higher proportion of patients preferred E.G. Scan II to EGD. Compared to EGD, the sensitivity and specificity for detecting BE with E.G. Scan II were 90% and 91%, respectively.³¹

A key benefit of TNE is that physician extenders, such as nurse practitioners and physician assistants, can perform the procedure with minimal training.^{26,32} However, TNE is not without disadvantages. Ultrathin endoscopes, which are used for TNE, can be floppy, which potentially limits their use in patients with atypical anatomy.³³ Ultrathin endoscopes also have limited suction

power compared to adult gastroscopes. Moreover, few accessories beyond pediatric biopsy forceps are available for ultrathin endoscopes.³³ Epistaxis is a well-recognized complication associated with TNE, but bleeding episodes are usually self-limited and can easily be avoided by using the peroral route, especially in patients with altered nasal anatomy. The American College of Gastroenterology guideline for BE states that TNE can be considered as an alternative to EGD for BE screening.¹¹ The sensitivity of TNE for diagnosing very short BE segments remains unclear, although the risk of progression for ultrashort BE may be minimal.²⁶ Despite high-quality evidence for the use of TNE over conventional sedated EGD for BE screening, its use and uptake remain low due to perceived physician and patient barriers.³⁴

Esophageal Capsule Endoscopy

ECE is a noninvasive, unsedated imaging technique that allows visualization of the esophagus using wireless or tethered cameras without obtaining a biopsy. With this technique, the patient ingests a capsule using a standard simplified ingestion protocol.³⁵ Real-time visualization allows the physician to determine the passage of the capsule into the stomach. Videotapes of the ECE examination can be reviewed by both physicians and physician extenders, who can be easily trained. ECE is a safe procedure and has a high acceptance rate and high tolerability compared to sedated EGD. An RCT comparing TNE to ECE in veterans, which was not powered for detecting BE, showed that both procedures were almost equally acceptable to most primary care patients who were interested in being screened for BE.³⁶ TNE was found to be moderately less tolerable than ECE; approximately 12.6% of patients randomized to undergo TNE found it intolerable compared with 0.0% of the ECE group.³⁶ In a meta-analysis of 9 studies including 618 patients, the pooled sensitivity and specificity for detecting BE using ECE were low (78% and 73%, respectively, using sedated EGD as a standard reference).³⁷ Another disadvantage of ECE is its inability to obtain biopsies, thereby adding another step if BE were to be visualized during the capsule study. Furthermore, ECE was not found to be more cost-effective than conventional EGD.^{38,39} These shortcomings limit the application of ECE as a mass screening tool for BE.

Sponge-on-String Devices

Cytosponge

Cytosponge is a 3-cm polyurethane sponge that is encapsulated in gelatin, tethered to a string, and easily swallowed. When combined with trefoil factor 3, a cellular marker that highlights early goblet cells,⁴⁰ Cytosponge

has shown promising results in detecting BE in large clinical trials.⁴¹ The procedure is relatively simple; the patient swallows the gelatin capsule, which dissolves in the stomach over the course of 7 to 8 minutes, and the device is then withdrawn from the stomach using the tethered string, allowing for sampling of exfoliated cells at the esophagogastric junction and from the entire length of the esophagus.⁴⁰

Collecting cells for immunohistochemistry examination has been attempted in multiple clinical trials both in the United Kingdom and the United States. A screening trial (BEST 1) performed across 12 primary care practices in the United Kingdom enrolled 504 patients between the ages of 50 and 70 years to swallow the sponge device.⁴² Of these, 501 (99%) successfully swallowed the sponge. Compared to conventional EGD, the sensitivity and specificity of the sponge device were 73.3% and 93.8%, respectively, for detecting circumferential BE of 1 cm or more. The sensitivity increased to 90% when the BE length cutoff was increased to 2 cm or more. This trial was not powered for diagnostic accuracy. No major adverse events were reported.⁴² A second large multicenter, case-control study (BEST 2) performed in 11 secondary care centers across the United Kingdom enrolled 647 patients with BE (cases) and 463 patients with GERD referred for endoscopy (controls) to swallow the sponge device.⁴³ Of the 1110 patients, 1042 (93.9%) successfully swallowed the sponge. Compared to EGD, the sensitivity and specificity of the sponge device were 79.9% and 92.4%, respectively. The sensitivity increased to 87.2% as the circumferential length of BE increased to 3 cm. There were 34 false positives in the control group, but none of these patients had intestinal metaplasia of the gastric cardia. Overall, 16.7% of patients had oozing of blood from a sponge abrasion site on subsequent endoscopy, but these abrasions did not require any intervention and were described as no worse than the oozing from a biopsy collection site.⁴³ Of note, both of these trials^{42,43} excluded short-segment, noncircumferential BE, which is considered important in the United States.

A cost-effectiveness model showed that using the sponge device to screen GERD patients and then using EGD to confirm positive results would reduce the cost of screening by 27% to 29% compared to screening with EGD alone, but would also result in 1.8 to 5.5 (per 1000 patients) fewer quality-adjusted life years.⁴⁴ Another microsimulation model found that using Cytosponge to screen 50-year-old men with GERD symptoms would be cost-effective and reduce mortality from EAC compared with no screening.⁴⁵ The results of a large, primary care-based, cluster-randomized pragmatic clinical trial (BEST 3) in the United Kingdom using Cytosponge are awaited.⁴⁶

EsophaCap

EsophaCap, a sponge-on-string device that is similar to but slightly smaller than Cytosponge, has been used in combination with methylated DNA biomarkers for diagnosing BE. A pilot trial by Iyer and colleagues demonstrated the feasibility of using panels of multiple methylated DNA biomarkers with EsophaCap to detect BE.⁴⁷ In this trial, 41 patients (20 with known BE and 21 controls) were randomized to swallow the sponge-on-string device with either 10 or 20 pores per inch. Ninety-eight percent of patients were able to successfully swallow the device. A number of methylated DNA biomarkers were tested in this study; 2 markers (vav guanine nucleotide exchange factor 3 and zinc finger protein 682) showed 100% sensitivity and specificity for diagnosing BE and were proposed for further testing in larger validation studies. No major adverse events were reported, and there was minimal abrasion without bleeding in 32% of patients who swallowed the device. The sponge with 10 pores per inch was better tolerated, safer, and had similar DNA yield when compared to the sponge with 20 pores per inch.⁴⁷ Another study reported a complex model, which included clinical factors plus a methylated DNA biomarker panel to detect BE using EsophaCap.⁴⁸ Eighty-five percent (80/94) of patients were successful in swallowing the device, and there was no evidence of any sponge-related abrasions on endoscopy.⁴⁸ Zhou and colleagues used combined cytology and mucin 2 immunohistochemistry on 136 specimens obtained from a cohort of 169 patients who swallowed the EsophaCap.⁴⁹ In this study, the sensitivity and specificity were 68% and 91%, respectively, compared to endoscopically obtained biopsies.⁴⁹

Encapsulated Balloon Device

EsoCheck is a novel nonendoscopic diagnostic test that uses a swallowable encapsulated balloon device to sample the distal esophagus. In this technique, a collapsible encapsulated balloon tethered to a silicone catheter is swallowed by the patient with sips of water. The balloon inflates with air when it crosses the lower esophageal sphincter into the stomach and then is slowly withdrawn, allowing the textured balloon to pick up exfoliated cells from the distal esophagus. The balloon is inverted back into the capsule to prevent contamination from the proximal esophagus and mouth as the sample is withdrawn. The theoretical advantage to this design is that it improves the signal-to-background-noise ratio, as it samples only the distal esophagus. BE and EAC are detected by assaying DNA extracted from the distal esophagus for methylated vimentin (VIM) and cyclin-A1 (CCNA1). In a pilot study conducted at 2

tertiary care hospitals involving 156 patients, balloon-based esophageal sampling combined with the methylated biomarkers had a sampling success rate of 82% and high patient tolerance.⁵⁰ The balloon device combined with methylated VIM and CCNA1 had a sensitivity of 90.3% and a specificity of 91.7% for the detection of intestinal metaplasia.⁵⁰

EsoCheck is easily performed by nonphysicians with minimal training. In the pilot study, the sampling balloon reached the stomach in 3.3 minutes (range, 1.0-7.7 minutes).⁵⁰ A newer generation of the EsoCheck device with the methylated VIM and CCNA1 biomarker panel (EsoGuard, Lucid Diagnostics) is currently being tested at 7 tertiary care hospitals across the United States.⁵¹

Limitations of the Sponge-on-String and Encapsulated Balloon Devices

Limitations of both the sponge and balloon devices include nonvisualization of the device during sampling, inability to collect mucosal biopsies, occasional low yield of cells necessitating a second swallow, and limited control over its passage through the lower esophageal sphincter. The sponge is more abrasive than the balloon and thus obtains a deeper sample. The balloon device has the advantage of selectively targeting the distal esophagus. The sponge procedure can take up to 10 minutes for the gelatinized capsule to dissolve. Cytosponge uses an immunohistochemistry assay, which requires cytopathology interpretation and expertise. The other techniques use methylated DNA biomarkers, similar to stool DNA assays, which are quantifiable and can be automated. Whether these differences in techniques and assays will translate to one method being adopted over another remains to be seen.

MicroRNAs

MicroRNAs (miRNAs) are short noncoding regulatory RNAs approximately 21 to 25 nucleotides long. They are tissue- and disease-specific, and therefore can serve as markers for disease detection and progression. Several miRNAs have been discovered that are frequently upregulated or downregulated in BE and are thought to play a key role in the onset of BE and its subsequent progression to EAC.⁵² Several circulating miRNA panels (MIR-192, MIR-194, MIR-203, MIR-205, and MIR-215) have shown promise in the detection of BE.⁵³ Li and colleagues identified 15 miRNAs that were significantly upregulated in BE patients when compared to controls; 11 of these were validated on Cytosponge samples.⁵⁴ Li and colleagues also combined trefoil factor 3 with 3 of the 15 miRNAs (MIR-192, MIR-196a, and MIR-199a).⁵⁴ This

combination identified BE with a sensitivity of 93.1% and a specificity of 93.7%.⁵⁴

Cabibi and colleagues used quantitative real-time polymerase chain reaction to compare miRNA expression levels in blood samples from 30 patients diagnosed with esophagitis, columnar-lined esophagus, or BE.⁵⁵ The authors found that expression levels of circulating MIR-143, MIR-194, and MIR-215 were upregulated in the serum of patients with BE compared to patients with columnar-lined esophagus and esophagitis. Similarly, using quantitative real-time polymerase chain reaction in plasma samples, Bus and colleagues found that 4 miRNAs (MIR-95-3p, MIR-136-5p, MIR-194-5p, and MIR-451a) were elevated in BE and had a sensitivity of 78.4% and a specificity of 85.7% for the detection of BE compared to controls.⁵⁶

Alternative Novel Approaches

Optical coherence tomography provides near-microscopic resolution of epithelial surfaces. Although commercially available devices have primarily been applied to surveillance of BE, a tethered capsule device has been developed for imaging the gastroesophageal junction.⁵⁷ Technical advances have allowed this device to be operated cost-effectively with a laptop, making it an attractive method for potentially imaging and screening the distal esophagus if it proves to be accurate in clinical testing. Another novel approach is based on assaying volatile organic compounds (VOCs) by detecting conductance changes in the patient's breath (Aeonose, The eNose Company). The e-nose device works with exhaled VOCs in aggregate and creates a breath profile for the patient. These breath profiles are then modified to remove individual differences in comorbidities, diet, medications, and other factors to create a Barrett breath profile, which can then be possibly used as a non-invasive screening tool for identifying BE. A preliminary study using VOCs comparing 66 patients with dysplastic BE to 56 controls showed a sensitivity and specificity of 82% and 80%, respectively, for BE detection.⁵⁸ The results of this study may have been confounded by the use of proton pump inhibitors in the patients with BE. Larger controlled, clinical studies on both of these techniques as potential alternatives to EGD for BE screening are awaited.

Conclusion

Current prevalence estimates of BE might be underestimating the true population prevalence. This underestimation is compounded by the fact that prognosis for EAC continues to be abysmal.⁹ BE screening, or the lack thereof, has been called the biggest missed opportunity for the reduction of EAC mortality.⁵⁹ Major gastroenterology

societies currently recommend BE screening in high-risk populations using conventional EGD, but it is a costly and cumbersome process that carries with it the potential for unwanted harms.

Recent years have seen tremendous advances in the development of minimally invasive and noninvasive screening tools for BE. The use of physician extender-reliant, office-based, simple, fast, and reasonably priced BE screening devices, such as Cytosponge, EsophaCap, and EsoCheck, may make mass screening of BE a reality in the near future. The discovery of highly sensitive and specific DNA- and RNA-based biomarkers further adds to the attractiveness of these emerging screening technologies. Large clinical trials involving Cytosponge and EsoCheck are ongoing, and their results are eagerly awaited. Ultimately, pragmatic head-to-head RCTs comparing these newer minimally invasive screening technologies will help guide patients, physicians, and guideline committees toward the large-scale adoption of 1 or more of these screening methods.

Dr Chak has founders shares and stock options in Lucid Diagnostics, serves as a consultant to Lucid Diagnostics, has sponsored research with Lucid Diagnostics, and has a royalty interest in patents licensed to Lucid Diagnostics. He is also a consultant for Interpace Diagnostics and receives research support from C2 Therapeutics/Pentax Inc. He is supported by National Institutes of Health grants U54CA163060 and P50CA150964. The other authors have no relevant conflicts of interest to disclose.

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