New Approaches to Screening for Barrett Esophagus

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Abstract: Current screening methods for Barrett esophagus (BE), the precursor to esophageal adenocarcinoma (EAC), are inadequate with less than one-third of screen-eligible patients currently undergoing screening. In addition to low screening rates, key issues include overemphasis on gastroesophageal reflux disease symptoms and lack of provider awareness, owing in part to heterogeneous guidelines. To address these challenges, several new approaches are being explored: swallowable cell collection devices, exhaled volatile organic compounds analysis, blood-based molecular biomarkers, microbiome analysis, and alternative visualization methods such as transnasal and capsule endoscopy. Proposed strategies to improve BE screening integrate enhanced risk stratification tools using machine learning and electronic health record data, noninvasive screening for low-risk patients, traditional endoscopy for high-risk patients, primary care education, and public health initiatives to increase awareness. This article highlights the latest developments in BE detection, including noninvasive screening methods and strategies to improve risk stratification, that have the potential to reduce EAC incidence and mortality.

Keywords
Barrett esophagus, esophageal adenocarcinoma, noninvasive screening, molecular biomarkers, esophageal mucosal visualization

The incidence of esophageal adenocarcinoma (EAC) has continued to rise over the past several decades.[1] Barrett esophagus (BE) is the only known precursor to EAC and is thought to develop from a dysplasia-to-carcinoma sequence.[2] The current model to prevent deaths from EAC is to perform endoscopic screening in patients who are at high risk for BE, based on studies that suggest that screening and surveillance programs may reduce mortality associated with EAC.[3] Most guidelines recommend screening patients with chronic gastroesophageal reflux disease (GERD) as well as additional risk factors for BE.[4-7] Despite the longstanding existence of endoscopic screening and surveillance programs geared toward earlier detection and prevention of EAC, a vast majority of patients with either EAC or esophagogastric junction adenocarcinoma

Table 1. Current BE Screening Recommendations

Year	2012	2014	2019	2022	2022	2023
Society	**American College of Physicians**	**British Society of Gastroenterology**	**American Society for Gastrointestinal Endoscopy**	**American College of Gastroenterology**	**American Gastroenterological Association**	**European Society of Gastrointestinal Endoscopy**
Defined screening population	Men >50 years with chronic GERD symptoms (>5 years) + additional risk factors: • Nocturnal reflux • Hiatal hernia • Elevated BMI • Tobacco use • Intra-abdominal distribution of fat	Chronic GERD symptoms + ≥3 risk factors (fewer risk factors needed if patient has first-degree relative with BE or EAC): • Age ≥50 years • White race • Male sex • Obesity	All patients with family history of BE or EAC OR Chronic GERD + 1 risk factor: • Age >50 years • Male sex • Obesity/central adiposity • Smoking history	Chronic GERD symptoms + ≥3 risk factors: • Age >50 years • White race • Male sex • Obesity • Smoking history • First-degree relative with BE or EAC	≥3 risk factors: • Age >50 years • Chronic GERD • White race • Male sex • Obesity • Smoking history • First-degree relative with BE or EAC	Age ≥50 years, chronic GERD symptoms + ≥1 risk factors: • White race • Male sex • Obesity • Smoking • First-degree relative with BE or EAC
Recommended screening modality	EGD with biopsies	EGD with biopsies	EGD with biopsies	EGD with biopsies OR Swallowable cell collection device	EGD with biopsies OR Swallowable cell collection device	EGD with biopsies OR Swallowable cell collection device

BE, Barrett esophagus; BMI, body mass index; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease.

do not have a known diagnosis of BE before their cancer diagnosis.[8] This indicates that current cancer prevention strategies, which focus on performing sedated upper endoscopy in individuals with known GERD and additional risk factors for BE, are not optimal. This article outlines the current approach to BE screening and why it is inadequate and describes alternate nonendoscopic screening modalities and risk stratification tools to help identify patients at the highest risk for developing BE and EAC.

Current Criteria for Barrett Esophagus Screening

Risk factors for BE include chronic GERD, age greater than 50 years, family history of BE or EAC, central obesity, male sex, White race, and tobacco use. Of these, GERD is the most commonly known and well-recognized risk factor for BE. Studies have shown a nearly 3 times increased odds of having BE in patients with known GERD.[9] However, it is important to highlight that approximately 40% of patients with BE or EAC do not have typical symptoms of chronic GERD.[10,11] Currently, a number of societal guidelines use GERD as a predicating factor for BE screening, and 2 guidelines recommend esophagogastroduodenoscopy (EGD) in patients with chronic GERD symptoms and at least 3 other risk factors.[4,5] The American Society for Gastrointestinal Endoscopy BE screening guidelines[6] and the American Gastroenterological Association clinical practice update[12] differ, as they include GERD as one of the risk factors but do not require it as an essential criterion for screening. Including GERD as one of a number of risk factors, as opposed to a requisite for screening, will likely decrease the proportion of patients deemed not screen-eligible who later develop cancer but has the downside of qualifying as much as 80% of the US population for screening.[13] The various screening guidelines from the American College of Physicians and the major gastroenterological organizations all differ somewhat in how the BE screening population is defined, making implementation of these recommendations challenging (Table 1).

Reasons for Suboptimal Barrett Esophagus Screening

Given the heterogeneity of the screening guidelines for BE among different societies, it is not surprising that BE screening rates are low. Multiple studies have shown that one-third or less of patients who are eligible for BE screening undergo an upper endoscopy. One study of 182 veterans with EAC showed that only 24.7% had an EGD prior to their cancer diagnosis despite having established risk factors for BE.[14] Two other retrospective studies reported similar rates in the primary care setting, with one showing that only 38.7% of 1127 screen-eligible patients had an EGD, and another showing that only 30.5% of 3535 at-risk patients were screened, demonstrating opportuni-

Table 2. Summary of Studies Evaluating Swallowable Cell Collection Devices for BE

Study design	Patient #	Key findings	Sensitivity	Specificity	Limitations	Reference
Cytosponge-TFF3						
Prospective cohort study of 12 general practices in the United Kingdom	504 participants on a PPI or H2-receptor antagonist	Safe, well tolerated, effective in BE detection	1-2 cm segment: 73.3% Long segment ≥2 cm: 90.0%	1-2 cm segment: 93.8% Long segment ≥2 cm: 93.5%	None reported	Kadri et al[20]
Case-control study of patients with BE and controls with GERD/ dyspepsia	463 controls, 647 BE cases	Showed high efficacy for BE detection in multicenter setting	79.9% Long segment BE: 87.2%	92.4%	None reported	Ross-Innes et al[22]
Pragmatic RCT in GERD patients in primary care to detect BE	6834 in intervention group and 6388 in usual care group	Cytosponge group had a 10.6× higher rate of BE detection than usual care	Not reported	Not reported	4% sore throat; 1 device detachment requiring endoscopy	Fitzgerald et al[23]
EsoCheck and EsoGuard						
Initial pilot study using DNA methylation biomarkers for BE neoplasia and dysplasia detection	86 patients	Showing an efficient, well-tolerated, sensitive, and specific method for BE screening	90.3%	91.7%	17% failed swallowing; 14% insufficient DNA samples	Moinova et al[25]
Multicenter prospective study combining EsoCheck with EsoGuard DNA testing for BE detection	88 BE cases, 155 controls	High sensitivity for BE detection and 100% cancer detection	85%	85%	None reported	Moinova et al[26]
EsophaCap						
Pilot study using 2-MDM panel for BE detection	62 BE cases, 30 controls	2-MDM panel accurate for BE detection	100%	100%	2% unable to swallow device	Iyer et al[29]
Multicenter case-control validation of 5-MDM panel for BE detection	112 BE cases, 89 controls	High sensitivity and specificity in training and test cohorts; well tolerated; 95% preferred test over EGD	92%	94%	None reported	Iyer at al[30]
Multicenter case-control recalibration and validation of 5-MDM panel and test of 3-MDM panel for BE detection	Training set: 110 BE cases, 89 controls Test set: 60 BE cases, 29 controls	High accuracy of 5-MDM panel for BE detection and similar accuracy with 3-MDM panel; well tolerated and safe; 73-95% preferred test over EGD	Training set: 93% Test set: 93%	Training set: 90% Test set: 93%	Minimal trauma; 1 sponge detachment	Iyer et al[31]
Prospective multicenter training and testing of 3-MDM panel for BE detection	Training set: 154 BE cases, 198 controls Test set: 81 BE cases, 41 controls	Excellent sensitivity of 3-MDM panel with cell collection device for high-risk BE in independent validation samples	Training set: 82% Test set: 88%	Training set: 90% Test set: 84%	Superficial mucosal tear with bleeding in 2 cases and 2 controls; 2 with incomplete expansion of cell collection device; 1 detachment in training and test sets	Iyer et al[32]

BE, Barrett esophagus; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; H2, histamine-2; MDM, methylated DNA marker; PPI, proton pump inhibitor; RCT, randomized controlled trial; TFF3, trefoil factor 3.

ties for improved BE screening measures in this setting.[15,16] Multiple factors likely contribute to the poor uptake of screening practices in primary care. First, as mentioned, there is heterogeneity in the screening recommendations among different gastrointestinal societies. Given the lack of unified recommendations, primary care clinicians may be justly confused as to who the ideal screening population is. Additionally, there is limited guidance in the internal medicine literature regarding BE screening, other than the American College of Physicians best practice advice from 2012.[17] The fact that screening for BE is not endorsed by the US Preventive Services Task Force could play a role in how BE screening is prioritized in the primary care setting. Second, BE screening criteria are complex with both the need for knowledge and identification of multiple pertinent risk factors to determine screening eligibility, unlike colonoscopy screening, which primarily relies on age. Finally, given that upper endoscopy is the current gold standard for screening, there may be issues of widespread access and patient tolerability to sedation.

Another reason why only a small proportion of EAC patients undergo an EGD is that most societal guidelines prioritize chronic GERD as a key factor in selecting patients for BE screening.[8] However, GERD symptoms are neither sensitive nor specific for the identification of BE, as nearly half of the patients with BE do not have or report typical GERD symptoms, thus excluding them from the current BE screening paradigm. In fact, in a recent study[18] comparing BE patients with and without GERD symptoms, the prevalence of EAC was nearly 40% in the non-GERD group, higher than that in the group with GERD symptoms. The results of this study support prior data demonstrating that patients without GERD symptoms were more likely to present with advanced stages of EAC than those with GERD symptoms who tend to have a known diagnosis of BE or earlier-stage EAC.[11] Although deemphasizing GERD symptoms for BE screening can help in better capturing the at-risk population for EAC, it leads to a larger proportion of the population who are screen eligible.[19] Because endoscopic screening for the entire population is neither practical or cost-effective, the use of novel nonendoscopic screening modalities and widely accessible risk stratification tools integrated into electronic health records (EHRs) to help identify high-risk individuals might be the answer to help curb the rising deaths from EAC.

Swallowable Cell Collection Devices for Barrett Esophagus Screening

Swallowable cell collection devices have been evaluated in clinical trials, and their efficacy and safety continue to be evaluated in the diagnosis of BE. These nonendoscopic devices are lower in cost, do not require sedation, and have the potential to offer screening to a wider population compared with traditional upper endoscopy. The evidence for 3 of these devices, Cytosponge (Medtronic), EsophaCap (PAVmed), and EsoCheck (Lucid Diagnostics), is summarized in Table 2. Of note, EsophaCap has been recalled owing to sponge detachment and is therefore not currently available.

Cytosponge With Trefoil Factor 3

Cytosponge with trefoil factor 3 (TFF3) analysis is a nonendoscopic test for BE that utilizes a 3-cm spherical sponge compressed in a gelatin capsule attached to a string. Once swallowed, the gelatin capsule dissolves within 5 to 8 minutes of reaching the stomach. The expanded sponge is then pulled back up the gastroesophageal junction and the esophagus with the attached tether collecting cells along the way from the gastric cardia and the entire length of the esophagus. These cells are then analyzed with immunohistochemical staining for TFF3, a protein marker expressed in the goblet cells. The Cytosponge-TFF3 test was shown in multiple clinical trials to be safe, well tolerated, acceptable, and to have good efficacy for BE detection.[20,21] Sensitivity and specificity for BE detection was reported to be 80% and 92%, respectively, with a higher sensitivity of 87% in patients with long-segment BE.[22] Cytosponge-TFF3 was also tested in a multicenter, pragmatic, randomized controlled trial in patients taking acid suppressive treatment for GERD in a primary care setting.[23,24] During an average of 12 months of follow-up, 140 (2%) of 6834 participants in the intervention group and 13 (<1%) of 6388 participants in the usual care group were diagnosed with BE with an adjusted rate ratio of 10.6 (95% CI, 6.0-18.8; P<.0001). Among 1654 participants in the intervention group who swallowed the Cytosponge device successfully, 221 (13%) underwent endoscopy after testing positive for TFF3, and 131 (8%) were diagnosed with BE or EAC. In this study, the sponge was also well tolerated with the most common side effect being sore throat in 4% (n=63), and 1 patient had a detachment of the Cytosponge from the thread requiring endoscopic removal. Therefore, this trial demonstrated a real-world utility of using this nonendoscopic sponge as a cost-effective, well-tolerated, acceptable, and effective method of screening for a larger at-risk population, which has led to its wider-spread adoption in routine clinical care in the United Kingdom. However, Cytosponge is currently not available for routine clinical use in the United States.

EsoCheck and EsoGuard

The EsoCheck nonendoscopic cell collection device is an encapsulated, inflatable, surface-textured balloon that is swallowed as a 16×9-mm capsule attached to a thin

silicone catheter. After the pill enters the stomach, the balloon is inflated by injecting air through the catheter and then withdrawn 5 cm to sample the distal esophagus. The balloon is then deflated and pulled back into the capsule prior to being withdrawn. The DNA from the balloon surface then undergoes molecular analysis using EsoGuard (Lucid Diagnostics), a 2-biomarker panel consisting of methylation of cyclin-A1 DNA and vimentin DNA, which when combined had a sensitivity of 90.3% and specificity of 91.7% for detecting BE neoplasia and dysplasia in an initial pilot study of 86 patients.[25] In a subsequent multicenter study of 88 patients with BE and/or EAC and 155 controls who underwent EsoCheck sampling, the sensitivity of EsoCheck combined with EsoGuard had a sensitivity of 85% (95% CI, 0.78-0.93) and specificity of 85% (95% CI, 0.79-0.90). Sensitivity for nondysplastic BE was 84%. EsoCheck/EsoGuard detected 100% of cancers (n=18).[26] These studies demonstrated the operating characteristics of EsoCheck combined with EsoGuard; however, there were a few limitations. In the initial study, 17% of patients were unable to successfully swallow the balloon device, and approximately 14% of the samples demonstrated insufficient DNA.[25,26] However, an interim analysis of real-world data from a 275-patient BE screening cohort showed a 96% success rate in EsoCheck administration and a 97% success rate of samples yielding adequate DNA for the EsoGuard assay.[27] This was achieved using trained personnel and enhanced sample processing in the laboratory, suggesting increased success of this intervention in high throughput targeted centers. EsoCheck combined with EsoGuard is currently available in the United States, both in dedicated testing centers and in some clinicians' offices.

EsophaCap and DNA Methylation Biomarkers

EsophaCap operated in a similar way to Cytosponge but with a smaller 25-mm sponge and a thicker cord-like string. Samples obtained from EsophaCap were evaluated for epigenetic changes using a methylated DNA marker (MDM) panel.[28] An initial pilot study using EsophaCap with a 2-MDM panel demonstrated 100% sensitivity and specificity for BE detection.[29] A multicenter case-control validation study of a 5-MDM panel showed 93% sensitivity in both training and test cohorts, the test cohort also had 93% specificity, and the training cohort had 90% specificity.[30,31] A more recent study[32] of a trained 3-MDM panel that was tested in an independent cohort showed a sensitivity of 82%, with 90% specificity, in the training set, and a sensitivity of 88%, with 84% specificity, in the test set. The area under the receiver operating characteristic curve (AUC) for BE detection was 0.92 and 0.94 in the training and test sets, respectively. Moreover, studies showed that EsophaCap was well tolerated and accepted by patients, and 91% were able to swallow the device successfully.[30]

Exhaled Volatile Organic Compounds

The analysis of volatile organic compounds (VOCs) in exhaled gases may be another promising screening technique for detecting BE. VOCs are gaseous metabolic end-products that can reflect various metabolic changes such as inflammation, necrosis, cancer, and alterations in the microbiome. VOCs can be detected through a handheld electronic nose (eNose, The eNose Company) device as well as mass spectrometric analysis. In an initial study[33] of 513 patients whose breath samples were collected with no adverse events, there were significant differences in VOC profiles noted among patients with BE, GERD, and controls. A subsequent study developed and cross-validated a BE prediction model to analyze the VOCs and demonstrated that eNose could differentiate between patients with and without BE with good diagnostic accuracy (sensitivity, 91%; specificity, 74%; AUC, 0.91).[34] Although eNose may be an efficient, well-tolerated, sensitive, and specific screening method for BE, it is limited by the need for standardized sampling protocols and accounting for variability owing to medications and diet.

Peripheral Blood-Sample Molecular Biomarkers

Currently, there are no clinically available blood- or serum-based biomarkers for detection of BE or EAC. An accurate blood-based biomarker could be used as a non-invasive screening tool with clinical utility comparable to that of a diagnosis by endoscopy and histology. Circulating microRNAs (miRNAs), which are endogenous non-coding RNA molecules between 18 and 25 nucleotides long that can be measured in both tissue and serum, have been studied for their potential use in detection of BE and EAC. At least 105 miRNAs are differentially regulated in BE and EAC vs controls.[35,36] MiRNAs 133a-3p, 136-5p, 194-5p, 382-5p, and 451a are dysregulated in serum from patients with BE and can be differentiated from the miRNA of controls and patients with EAC.[37,38] A recent study demonstrated the utility of miR-92a-3p, a specific type of miRNA, as both a serum-circulating marker of BE and an epithelial-specific miRNA.[39] Studies have also evaluated the utility of using a combination of circulating miRNAs. One study using a 4-miRNA panel (95-3p, 136-5p, 194-5p, and 451a) had a sensitivity and specificity of 78% and 86%, respectively, for distinguishing patients with BE from controls.[35] In the same study, when

a 3-miRNA panel (133a-3p, 382-5p, and 451a) was used, sensitivity was 86% and specificity was 80% in identifying EAC from controls. Although circulating biomarkers could provide an innovative approach to overcome histologic-based sampling issues, further prospective studies are needed to validate these biomarkers.

Esophageal Microbiome

The esophageal microbiome has also been studied as a possible mechanism to potentially identify patients with BE. The normal distal esophagus has a distinct microbiome of predominantly oral flora, which is altered in BE and reflux esophagitis with a predominance of Gram-negative bacteria and reduced *Streptococcus*. Studies have found that a greater diversity—less abundant *Streptococcus* (30%) and a predominance of Gram-negative taxa (53%)—was strongly linked to reflux esophagitis (odds ratio, 15.4) and BE (odds ratio, 16.5) compared with controls.[40-42] There also appears to be a higher risk of EAC with the presence of *Tannerella forsythia* and *Lactobacillus fermentum* and lower risk with number of the genus *Neisseria* and species *Streptococcus pneumoniae*.[43,44] Studies have also shown an increased yield of microbiome DNA retrieved with the use of cell collection devices, such as Cytosponge, compared with traditional upper endoscopy.[45] Although these data are promising for the use of the oral microbiome for BE screening, the prevalent use of proton pump inhibitors in this population can affect the results, and additional work is needed to validate the existing data in prospective cohorts. Also, given the natural variability in microbiomes among individuals, how reproducible these findings will be from population to population is unclear.

Alternate Approaches to Esophageal Mucosal Visualization

Transnasal Endoscopy

Currently, high-definition white-light endoscopy is the standard modality for BE screening, which has associated costs and sedation risks. Therefore, alternate methods of esophageal mucosal visualization for BE screening have been studied. One such method is transnasal endoscopy (TNE) that uses an ultra-thin endoscope (diameter <6 mm) and can be performed in an office-based setting without the need for sedation. Multiple studies have shown that TNE has comparable accuracy to conventional endoscopy in detecting BE. The sensitivity and specificity for BE diagnosis are generally high, often above 90%.[46,47] TNE has been shown to be well tolerated and accepted by patients,[48] as more than 80% of patients who underwent TNE were willing to undergo the procedure again in one randomized controlled trial.[49] TNE also allows for obtaining biopsies, which is an added benefit compared with other capsule devices that can only visualize the esophageal mucosa. TNE has a good safety profile and is cost-effective owing to the procedure's shorter duration compared with traditional upper endoscopy and ability to be performed in office-based settings without sedation. Despite these advantages and data supporting its efficacy as an alternative for EGD for BE screening, TNE is not routinely used owing to its limited availability and uptake. One common concern is insurance coverage for the in-office procedure. Additionally, some endoscopists may be concerned that introducing unsedated TNE in their offices would diminish the caseloads of standard peroral endoscopy, which may be both disruptive to their office practices and financially disadvantageous to their ambulatory surgery centers.

Esophageal Capsule Endoscopy

Esophageal capsule endoscopy (ECE) utilizes a wireless capsule with a camera, similar to small bowel capsule endoscopy, which has been studied for esophageal investigation. In a meta-analysis that included 9 studies, the pooled sensitivity of ECE to detect BE was found to be lower than with standard EGD.[50] This lower sensitivity was thought to be secondary to rapid esophageal transit time, which has subsequently led to the development of ECE with a higher number of frames per second rate. In a multicenter study, sensitivity, specificity, positive predictive value, and negative predictive value of ECE to diagnose BE were 97%, 99%, 97%, and 99%, respectively.[51] Subsequent iterations of the capsule device (eg, PillCam ESO [Medtronic]) that have cameras at both ends of the capsule,[52] wider angle of view (174°), and higher recording rate (35 fps) have been tested in pilot studies[53] but have been shown to be inferior to upper endoscopy for BE detection. A more recent innovation, detachable string magnetically controlled capsule endoscopy, has been shown to be feasible, well tolerated, and efficacious in detecting esophageal pathology, but it has not been specifically tested for the detection of BE.[54-56]

Tethered Capsule Endomicroscopy

Tethered capsule endomicroscopy (TCE) is an alternate ECE technology that incorporates in vivo microscopy based on optical coherence tomography (OCT) technology. OCT uses low-coherence interferometry to obtain microscopic, cross-sectional tissue images. TCE obtains 3-dimensional microscopic images as the capsule advances down the esophagus by peristalsis and can also be maneuvered with the attached tether. One multicenter study[57] of 147 BE patients showed that 94% successfully completed the procedure with a mean duration of 5.55 minutes and a strong correlation (r=0.77-0.79) between

the maximal BE extent noted on TCE vs EGD. Although the study showed that the TCE technology is feasible, the enthusiasm for this technology is dampened by the need for decontamination protocol for this reusable device and difficulties with swallowing the capsule in approximately 20% of the cases.

All told, none of the currently available capsule imaging devices are ready to be used in the clinical setting, and further refinement and studies are needed to prove them to be an acceptable screening alternative to standard endoscopy.

Strategies to Improve Risk Stratification to Identify Screen-Eligible Patients

Given that GERD is neither a sensitive nor specific screening criterion for identifying patients with BE and EAC, incorporating epidemiologic risk factors for these conditions to identify patients at the highest risk would be valuable. Previous research has proposed several risk prediction models for BE and EAC.[58-62] However, most of these models rely on data that are not easily accessible from EHRs, such as GERD symptom details, waist-to-hip ratio, smoking history, and education level. These datapoints often require patient questionnaires or specific measurements not routinely performed, making them difficult to implement in clinical practice. A recent Swedish case-control study[63] did create a simplified EAC risk model with the potential to use EHR data, incorporating body mass index, smoking status, and the presence of GERD symptoms or acid-suppressant medication use. However, the study found that EHR-derived GERD symptoms were not strong predictors of BE or high-risk BE, highlighting the challenges in developing accurate, EHR-based risk prediction models for these conditions.

In response to these challenges, one study used established BE risk factors readily extracted from an EHR to develop a logistic regression model.[64] The model included GERD, sex, body mass index, and ever-smoker status and identified BE patients with an AUC of 0.71 (95% CI, 0.64-0.77), with similar accuracy to that of prior risk models with reported AUC of 0.68 to 0.70. A more recent study developed and internally validated 2 novel predictive machine learning models to predict the risk of incident BE and EAC using an EHR database incorporating both temporal and nontemporal features such as demographics, medications, comorbidities, laboratory tests, and symptoms.[65] The BE model achieved a sensitivity of 76%, specificity of 76%, and AUC of 0.84, whereas the EAC model had a sensitivity of 84%, specificity of 70%, and AUC of 0.84. These models outperformed previous risk prediction tools based on conventional risk factors. In addition to established risk factors, the machine learning models identified potential novel predictors such as metabolic and vascular consequences of obesity, hormonal medications, and serum electrolytes. Further external validation, clinical testing, and consideration of implementation challenges are needed before these models can be integrated into clinical practice.

Conclusion

Despite guidelines recommending screening for BE and EAC in high-risk individuals, the majority of patients with EAC do not undergo prior screening with upper endoscopy. Only approximately one-third of screen-eligible patients in the primary care setting undergo EGD for any reason, with just 9% referred specifically for screening.[16] Although multiple societal guidelines recommend screening in patients with chronic and symptomatic GERD, given that only approximately 60% of EAC patients report significant prior GERD symptoms, the current screening model is insufficient to capture the larger at-risk group. These findings suggest that current referral patterns for EGD are not effectively targeting patients at highest risk for EAC. Therefore, moving beyond a GERD-centric screening strategy and not depending on conventional upper endoscopy for screening is needed to help move the needle toward earlier EAC detection.

A future model of BE screening should integrate multiple methods, including enhanced risk stratification tools based on clinical risk factors that are readily integrated into EHR systems, possibly coupled with biomarkers to categorize patients into high or low risk for BE or EAC. This risk categorization would then inform the screening modality with the low-risk group being screened with noninvasive screening tools such as cell collection devices coupled with biomarkers for BE detection and high-risk patients undergoing standard upper endoscopy with biopsies. The roles of VOCs and microbiome profiling for BE detection, while holding promise, are currently not close to clinical use and require further refinement. Finally, integrating screening strategies into primary care practices and educating primary care physicians on the importance of BE screening could address the gap in screening rates. Public health initiatives should aim to increase awareness of BE and EAC risks among both patients and health care providers. Additionally, research into cost-effective, noninvasive screening methods and reliable biomarkers should be prioritized as part of a new integrated approach to BE screening.

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