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Novel Screening Tests for Barrett's Esophagus

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Abstract

Purpose of Review There has been an exponential increase in the incidence of esophageal adenocarcinoma (EAC) over the last half century. Barrett's esophagus (BE) is the only known precursor lesion of EAC. Screening for BE in high-risk populations has been advocated with the aim of identifying BE, followed by endoscopic surveillance to detect dysplasia and early stage cancer, with the intent that treatment can improve outcomes. We aimed to review BE screening methodologies currently recommended and in development.

Recent Findings Unsedated transnasal endoscopy allows for visualization of the distal esophagus, with potential for biopsy acquisition, and can be done in the office setting. Non-endoscopic screening methods being developed couple the use of swallowable esophageal cell sampling devices with BE specific biomarkers, as well as trefoil factor 3, methylated DNA markers, and microRNAs. This approach has promising accuracy. Circulating and exhaled volatile organic compounds and the foregut microbiome are also being explored as means of detecting EAC and BE in a non-invasive manner.

Summary Non-invasive diagnostic techniques have shown promise in the detection of BE and may be effective methods of screening high-risk patients.

Keywords Barrett's esophagus · Esophageal adenocarcinoma · Screening tests

Introduction

Esophageal adenocarcinoma (EAC) is a lethal cancer with exponentially increasing incidence in the West. In 2012, the global incidence of EAC was 0.7 per 100,000 persons, with the highest rates found in Europe (1.9/100,000 persons), Oceania (2.5/100,000 persons), and North America (2.8/100,000 persons) [1, 2]. In the USA, esophageal cancer caused over 15,000 deaths in 2017, mostly accounted for by EAC [3]. The incidence of EAC has risen considerably over the last half century, with an average annual percentage increase of 6.0% from 1975 to 2009 in the USA [4]. Overall, EAC survival has not considerably improved with the exception of those with early stage disease, which can be managed by surgical and endoscopic means [46]. This subset unfortunately constitutes less than 20% of all EAC cases. However, the improvement in survival has not translated to improved outcomes for patients with advanced stages of malignancy, who typically present with symptoms of dysphagia and weight loss. Less than 15% of patients with advanced stage disease at diagnosis live past 5 years from diagnosis [5, 79].

Barrett's esophagus (BE), intestinal metaplasia involving the esophagus, is the only known precursor for EAC [6]. Given that the improvement in EAC survival is most pronounced in patients with early stage disease, screening for BE followed by surveillance may mitigate the burden of EAC by allowing for the detection of early stage cancers that are amenable to definitive management [7]. Treatment of dysplastic BE can both prevent the progression to EAC and induce remission of intestinal metaplasia [8–11]. Further supporting the role for screening, EAC patients previously diagnosed with BE have increased survival compared to those who present without a prior history of BE [12]. Unfortunately, despite guidelines, greater than 90% of patients who present with EAC continue to be diagnosed outside of BE surveillance programs, highlighting the need for targeted BE screening [13].

Widespread screening programs must be cost-effective, safe, tolerable, and equitable [14]. Furthermore, it is important for

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screening to potentially alter the course of a disease. While controversy exists regarding what the appropriate target population for BE screening is, guidelines generally recommend that patients with multiple risk factors for BE, including male gender, older age, chronic gastroesophageal reflux symptoms, smoking history, visceral obesity, and family history of BE or EAC, should be screened [15–18]. This review will discuss BE screening methodologies currently recommended and in development.

Currently Recommended and Available Screening Methods

Endoscopy

Conventional Endoscopy

Conventional high-definition per-oral esophagogastroduodenoscopy (EGD) is the current gold standard for the diagnosis of BE, allowing for the visualization and biopsy of salmon-colored mucosa that extends at least 1 cm proximally from the gastroesophageal junction, with histology confirming the presence of intestinal metaplasia [17]. Several gastroenterology society guidelines currently suggest that EGD be utilized in screening for BE in high-risk populations [15–17, 19].

However, endoscopy is an expensive and invasive procedure and typically in the USA involves the use of sedation or anesthesia, with its associated cardiopulmonary risks, in order to decrease patient discomfort [20, 21]. There is also a small, though not inconsequential, risk of bleeding and perforation with sedated EGD [22]. The exposure to sedation usually requires patients to take time off from work and mandates a companion to transport them to and from the procedure leading to additional indirect costs [23, 24].

There is also a degree of operator dependence to EGD-based screening, as a thorough examination is needed to evaluate for BE, and there is a chance of sampling error if biopsies are not obtained from the correct area. Despite being the "gold standard," conventional endoscopic evaluation of the esophageal mucosa carries a sensitivity and specificity of 82% and 81%, respectively, with a positive predictive value of only 34%, in the detection of BE when endoscopists' initial interpretation during endoscopy is judged against pathology results [25]. Indeed, approximately 25% of patients are diagnosed with EAC within 1 year of their initial endoscopic BE diagnosis (i.e. "missed" dysplasia and cancer), demonstrating the potential of missed cancers at index endoscopy [26, 27].

Unsedated Transnasal Endoscopy

Given concerns regarding sedation risk, cost, time, and invasiveness of conventional endoscopy, unsedated transnasal endoscopy (uTNE) has been explored as an alternative method for BE screening. An ultrathin endoscope, typically less than 6 mm in diameter, is passed through the nares into the upper GI tract. uTNE can be safely done in the office without need for sedation or extended monitoring [28]. uTNE has comparable rates of technical success (defined as achieving the intended extent of examination) and tolerability as compared to conventional transoral endoscopy [29••, 30]. In clinical trials, patients preferred uTNE over conventional endoscopy, and recovery times were significantly shorter for uTNE [29••, 31, 32]. The yield of uTNE compared to conventional endoscopy in the detection of BE also appeared to be equivalent [30].

The sensitivity and specificity of detecting BE on uTNE is high when compared to conventional endoscopy. A meta-analysis of 5 studies (439 patients) showed a sensitivity and specificity of 91% and 96%, respectively, in detecting BE when compared to conventional endoscopy [33]. However, with an approximately 10–11% rate of inability to intubate the nares and smaller biopsy specimens (due to the use of pediatric biopsy forceps given the smaller channel size), the histologic sensitivity of detecting BE may be lower with uTNE (66.7%) than with conventional endoscopy [32]. Endoscopes with smaller diameters (less than 5.9 mm) are better tolerated and have better rates of technical success as well [29••].

More recently, a uTNE system utilizing a disposable probe has been developed, with the advantage that this system does not require any reprocessing that would occur with a reusable scope. In a clinical trial with this esophagoscope, technical success, defined as complete visualization of the entire esophagus, was similar compared to patients undergoing traditional per-oral endoscopy (98.3% vs 99.4%, respectively). The sensitivity and specificity for detecting BE were 90% and 91%, respectively [34].

Conventional endoscopy may provide superior image quality compared to uTNE. However, in a post-hoc analysis of videos collected from a randomized trial, the overall imaging quality with uTNE was comparable to that of sedated EGD, particularly with reference to visualization of the gastroesophageal junction (GEJ) [35]. The direct and indirect costs of uTNE also are substantially lower than that of standard EGD, making it a cost-effective tool for BE screening in those with chronic GERD symptoms [36, 37]. Due to this substantial body of evidence, current gastroenterology society guidelines suggest that uTNE may be used as an alternative to conventional endoscopy in screening for BE [17]. However, limitations of uTNE include the need for a specifically trained health care provider and continued lack of utilization by practitioners despite evidence of its effectiveness [38].

Swallowable Imaging Capsules

Video capsule endoscopy (VCE) has been explored as a method for screening of BE. Early studies for the detection

of BE in patients with chronic gastroesophageal reflux showed sensitivities ranging from 64 to 100%, and specificities ranging from 87 to 100%, respectively, when compared to conventional endoscopy [39–41]. However, a systematic review and meta-analysis, incorporating 618 patients from 9 studies, showed an overall sensitivity of only 78% and specificity of 73% for the detection of BE in patients with GERD [42]. Other studies have shown high inter-observer variability for the detection of short segment (< 3 cm) BE by capsule [43]. A variation of this technique, wherein a string is attached to the video capsule allowing it to more carefully examine the GEJ, has also been described but is not currently widely used [44, 45]. Hence, VCE is not currently recommended for BE screening.

Screening Tools in Development

Video Capsule Endomicroscopy

A resonant fiber-optic laser scanner can be used in conjunction with an optical fiber and imaging software to produce high-definition, wide-field color images of the esophageal mucosa. This technology has been incorporated into a tethered capsule that can be swallowed and withdrawn, with real-time imaging allowing the operator to assess for the presence of BE, utilizing the differences in imaging characteristics of normal squamous and BE epithelium [46].

Gora et al. created a tethered capsule measuring 12.8 mm × 24.8 mm that incorporates optical frequency domain imaging (OFDI) and near-infrared wavelength to create high-resolution cross-sectional images of the esophagus. Findings consistent with BE include irregular luminal surface, heterogeneous backscattering, and glands within the mucosa [47]. In a pilot study of 13 patients, of which 6 had confirmed BE, 12 of 13 preferred tethered capsule endomicroscopy to traditional per-oral endoscopy [47]. The safety and tolerability of tethered capsule endomicroscopy (TCE) appeared to be similar to traditional per-oral endoscopy, and in a study of 38 patients, TCE was able to effectively image the extent of BE when compared to endoscopic assessment, with high correlation ($r = 0.77$–0.78, $p < 0.01$) [48]. TCE incorporating OFDI and VLE principles remains a promising tool for BE screening, but further research is required to validate the use of this technology in BE screening [47].

Swallowable Non-endoscopic Sampling Devices Combined with Biomarkers

A number of non-endoscopic esophageal cell collection devices are currently being used in research studies. The Cytosponge (Medtronic, Minneapolis, MN) is a tethered polyurethane foam sphere enclosed in a gelatin capsule, attached to a suture that is swallowed with sips of water (Fig. 1). The gelatin shell dissolves in the stomach over 5 min, releasing a compressible 30 mm spherical sponge. This sponge is pulled out using the attached string, sampling the entire esophageal mucosal surface [50]. Similar devices include the EsophaCap (Capnostics, Doylestown, PA) (Fig. 1) and the EsoCheck balloon (Lucid Diagnostics, New York, NY) (Fig. 1). Unlike the first two devices, the EsoChek balloon is inflated (to 18 mm diameter) and deflated by the operator. Using all these devices, esophageal cytology samples are obtained, which can be combined with biomarkers thought to be specific for Barrett's esophagus. A number of biomarkers have been utilized for detecting BE (Table 1).

Trefoil Factor 3

Trefoil factor-3 (TFF3) is a protein biomarker hypothesized to recruit healthy epithelial cells from the edges of wounds in order to facilitate healing of ulcers and other disruptions of the mucosal barrier [60]. TFF3 is upregulated in BE mucosa and hence has been used for the non-endoscopic diagnosis of BE in two trials (one in a primary care population and in one large case control study) conducted in the UK. The sensitivity of the Cytosponge-TFF3 system in detecting BE ranged from 73.3 to 79.9%%, with 93.8% specificity compared to endoscopy [51, 52••]. Patients tolerated this device well [49, 51, 52••, 61]. In an exploratory study, the addition of a biomarker panel (including protein markers, methylation markers, the presence of glandular atypia, and TP53 mutation status) could also identify BE patients who are at risk of progression to dysplasia [50].

Compared to conventional endoscopy, the Cytosponge avoids sedation risks and is a simple and quick procedure that can be done in the office by a nurse. Approximately 94% of patients were able to successfully swallow the Cytosponge with no adverse events reported [51]. This device has been shown to be safe and well tolerated in a systematic review and meta-analysis of clinical studies which studied over 2600 patients [62]. Microsimulation models have shown that this approach for BE screening in patients with GERD may be cost-effective and decrease mortality from EAC [63, 64]. A large, prospective trial utilizing Cytosponge screening in patients on long-term acid suppressing medications is currently being conducted in a primary care setting [65].

Methylated DNA Markers

Aberrantly methylated genes can lead to oncogenesis by two proposed mechanisms. Hypermethylation of cytosine-phosphate-guanine (CpG) island gene promoters can silence tumor suppressor genes, while hypomethylation of repetitive genetic elements can lead to genomic instability or oncogene activation [66]. These alterations are promising targets for screening purposes and have been used in the development

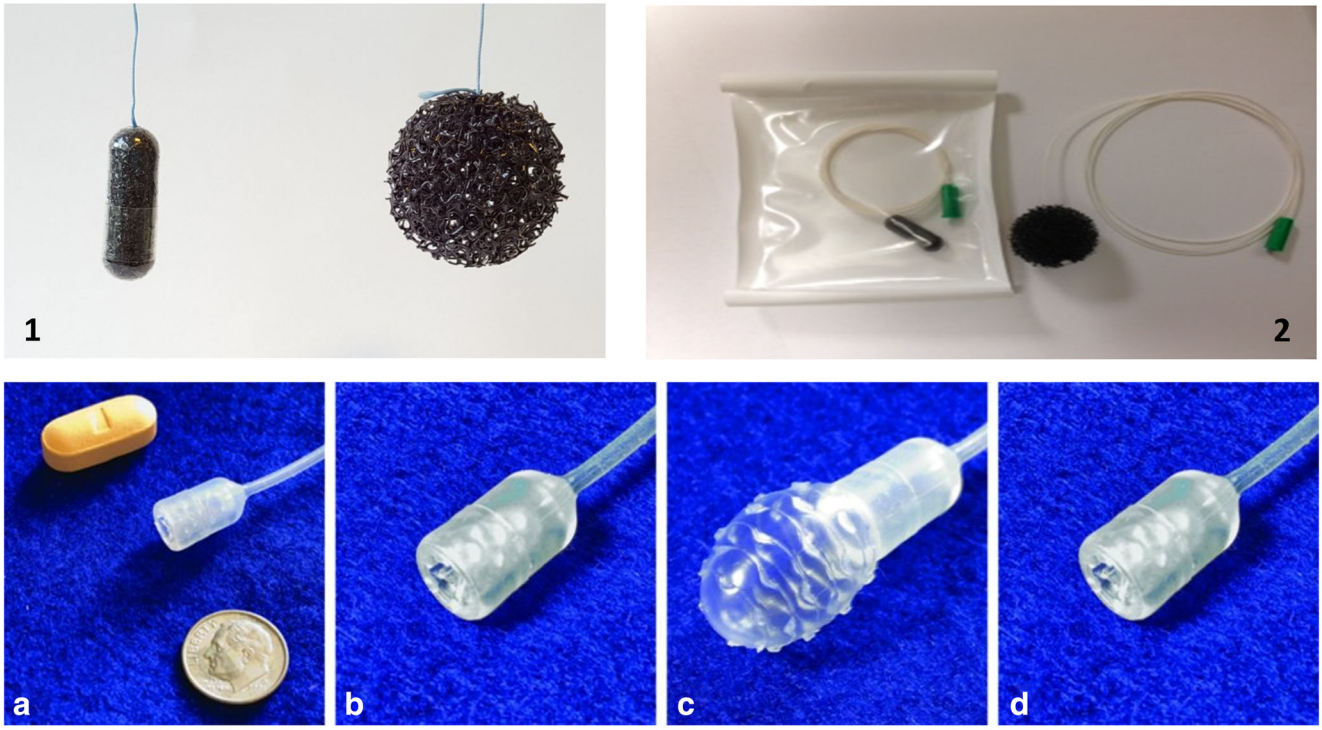

Fig. 1 Swallowable non-endoscopic sampling devices. (1) Cytosponge: intact (left) and expanded (right). Taken, with permission, from Freeman et al. (BMJ Open 2017) [49]. (2) EsophaCap: intact (left) and expanded (right). Photo courtesy of P.G. Iyer. (A) + (B) EsoCheck device: the device is swallowed with sips of water, inflated with 5 cm^3 of air (C), pulled 5 cm proximal to the GEJ and then deflated into a cap (D) before withdrawal to avoid contamination by the squamous epithelium. Picture courtesy of Lucid Diagnostics (New York, NY)

of stool-based DNA tests for colorectal cancer screening [67]. Aberrant methylation has been studied in the diagnosis of BE by many investigators. As opposed to protein markers such as TFF3, methylated DNA markers (MDMs) are less susceptible to subjectivity in interpretation (being reported quantitatively as opposed to protein markers, which are reported using immunohistochemistry) and are more scalable for widespread use. MDMs have been investigated for BE detection in combination with esophageal sampling devices by many investigators.

MDMs discovered by reduced representation bisulfite sampling (RRBS) and subsequently validated on brush samples were pilot tested on cytology samples obtained by a sponge-on-a-string (SOS) device (EsophaCap, Capnostics, Doylestown, PA), which is quite similar to the Cytosponge device (releasing a 25 mm sponge instead of a 30-mm sponge) on 20 BE patients and 20 controls [54••]. Ninety-eight percent of subjects were able to successfully swallow the device. Nineteen MDMs were tested, and areas under the curve (AUC) were greater than 0.9 for nine markers (Table 2). A combination of two markers (VAV3 and ZNF 682) was able to identify BE with an AUC of 1.0 [54••]. Preliminary results from a subsequent larger multicenter validation trial continued to show promising results, with an AUC of 0.97 using a combination of two markers (VAV3 and DOCK10 [54••].

In a prospective cohort of 80 patients, quantitative methylation-specific polymerase chain reaction (msPCR) found 5 biomarkers (p16, HPP1, NELL1, TAC1, and

Table 1 Reported sensitivity and specificity for detection of BE in novel screening tests

Method	Sensitivity* (%)	Specificity* (%)
Traditional per-oral endoscopy		
Eloubeidi 1999 [25]	82+	81+
Unsedated transnasal endoscopy		
Shariff 2016 [32]	66.7	100
Sami 2019 [34]	90	91
Video capsule endoscopy		
Lin 2007 [39]	67	84
Galmiche 2008 [40]	60	100
Sharma 2008 [41]	67	87
Bhardwaj 2009 [42]	78	73
Cytosponge-TFF3 system		
Kadri 2010 [51]	90	93.8
Ross-Innes 2015 [52••]	79.9	92.4
MDM panels		
Chettouh 2018 [53]	82.2	95.7
Iyer 2018 [54••]	100	100
Moinova 2018 [55]	90.3	91.7
Wang 2019 [56]	78.6	92.8
miRNA panels		
Li 2018 [57••]	86.2	91.6
Exhaled VOCs		
Chan 2017 [58••]	82	80
Oral microbiome analysis		
Snider 2018 [59]	96.9	88.2

TFF3 trefoil-factor 3, *miRNA* microribonucleic acid, *MDM* methylated deoxyribonucleic acid markers, *VOCs* volatile organic compounds

*Compared to gold standard (per oral endoscopy or biopsy)

+ Based on suspicion of BE during endoscopy and final pathologic diagnosis

Table 2 Area under the curve (AUC) of various non-invasive tests for BE screening

Test	AUC
2 MDM panel—EsophaCap System [54••]	0.97
5 MDM panel—EsophaCap System [56]	0.93
11 miRNA target—Cytosponge System [57••]	0.89
Exhaled VOCs with machine learning algorithm [58••]	0.79
Microbiome changes (in saliva) [59]	0.94
2 Circulating VOCs panel [68]	0.83*
4 Exhaled VOC panel [69]	0.91*

MDM methylated DNA markers, *miRNA* microribonucleic acid, *VOC* volatile organic compound

*Detection of esophageal adenocarcinoma

AKAP12) that were expressed in significantly higher proportions in cytology samples obtained using the EsophaCap device from 14 patients with BE and 14 controls. This study also showed a relatively high accuracy with an AUC of 0.93 and sensitivity and specificity of 78.6% and 92.8%, respectively [56].

The EsoCheck (Lucid Diagnostics, New York, NY) is a novel non-endoscopic esophageal sampling device in which patients swallow a tethered collapsed balloon (with a textured outer surface), which, once in the stomach, is inflated and withdrawn to retrieve exfoliated cells. After withdrawing for 5–6 cm (to adequately sample the distal esophagus), the balloon is deflated and inverted into the outer capsule, avoiding any contamination with the proximal squamous epithelium (Fig. 1) [55]. Moinova and colleagues used this device to collect samples from 156 patients; of these, 128 (82%) were able to successfully swallow the capsule. In 86 of the above 128 patients without a history of BE dysplasia and/or ablation history, a two marker panel consisting of CCNA1 and VIM DNA methylation had a sensitivity and specificity of 90.3% and 91.7% respectively for BE diagnosis [55].

Chettouh et al. identified differentially methylated genes in whole methylome datasets from esophageal, gastric, and BE tissue. These markers were then analyzed, initially against a pilot cohort, and subsequently against a validation cohort of 149 BE patients and 129 controls from a prior Cytosponge study. Hypermethylation of four genes (TFPI2, TWIST1, ZNF345 and ZNF569) was observed in BE biopsies compared to normal esophagus and stomach samples. TFPI2 showed a sensitivity and specificity of 82.2% and 95.7%, respectively, in the diagnosis of BE on Cytosponge samples [53].

MicroRNAs

Several micro-RNA (miRNA) panels have been investigated in the diagnosis of BE [70]. A microarray expression analysis of tissue samples from 38 BE patients and 26 controls identified 15 miRNAs that were significantly upregulated in BE patients. Of these, 11 miRNA targets were validated on cytology samples obtained using the Cytosponge, and after the creation of an optimized multivariable logistic regression model, this panel demonstrated an AUC of 0.89 and sensitivity and specificity of 86.2% and 91.6%, respectively, in diagnosing BE [57••]. Furthermore, specific miRNA sequences may be able to distinguish EAC from BE. A panel identifying miR-663b, miR-421, and miR-502-5p was present in greater than 80% of EAC patients, but found in less than 20% of BE patients [71]. A blood based test would greatly increase the acceptability and tolerability of BE screening. Cabibi et al. utilized quantitative real-time PCR to compare miRNA expression profiles in 30 patients with esophagitis, columnar lined esophagus, and BE. This study revealed a significant upregulation of circulating miRNA-143 in BE patients compared to the other cohorts

[72]. A pilot study of 8 BE patients, 8 EAC patients, and 6 controls identified miRNA expression profiles in peripheral blood samples. miRNA profiles were then validated in an independent cohort of 41 BE patients, 59 EAC patients, and 15 controls. Bus et al. found that four miRNAs (miRNA-95-3p, miRNA-136-5p, miRNA-194-5p, and miRNA-451a) showed an AUC of 0.832 with a sensitivity of 78.4% and specificity of 85.7% for the diagnosis of BE [73].

Volatile Organic Compounds

Volatile organic compounds (VOCs) have also been used in the diagnosis of esophageal cancer. An analysis of 17 VOCs isolated from the breath of patients with gastroesophageal junction cancers, non-malignant conditions of the upper gastrointestinal tract, and healthy controls showed that 4 VOCs (hexanoic acid, phenol, methyl phenol, and ethyl phenol) were associated with cancer, with an AUC of 0.91 [69]. Follow-up studies have demonstrated novel exhaled VOCs that can discriminate EAC from premalignant lesions and normal tissue [74].

Chan et al. utilized an "E-nose" device, in which breath samples from patients with dysplastic BE were analyzed by an artificial neural network and compared to those of patients who had undergone successful ablation eliminating BE. Results were promising and showed a sensitivity of 82%, a specificity of 80%, an accuracy of 81%, and an AUC of 0.79 compared to biopsies obtained by conventional per-oral endoscopy [58••]. While exhaled VOCs represent an exciting prospect for future screening, significant research is required prior to this method's widespread adoption.

Circulating plasma VOCs have also been studied for their potential role in the non-invasive diagnosis of EAC. Analysis of plasma from 39 patients (20 with biopsy confirmed EAC, 19 with typical clinical gastroesophageal reflux disease) identified 9 VOCs with reduced levels in EAC patients. A discriminatory model found the highest AUC in a combination VOC profile of acrylonitrile and carbon disulfide, with an AUC of 0.83 in identifying EAC. An internal validation of this model found an AUC of 0.80 in differentiating EAC from gastroesophageal reflux disease patients [68].

Alterations in the Esophageal Microbiome

Broad range 16S PCR and pyrosequencing from 12 subjects in the Seattle Barrett's Esophagus Research cohort has shown that Streptococcus and Prevotella species are abundant in the upper GI tract of patients with BE and that an increasing ratio of Streptococcus to Prevotella is correlated with high waist-to-hip ratio and hiatal hernia risk, which are risk factors in BE/EAC [75]. Cytosponge samples from the upper GI tract of 86 patients subjected to 16S rRNA gene amplicon sequencing showed that BE patients have a higher proportion of Proteobacteria compared to controls without BE or EAC [76]. Interestingly, salivary samples of patients with BE showed a decreased proportion of Proteobacteria but higher abundance of Firmicutes compared to controls [59]. A model utilizing the presence of several phyla in salivary samples showed a sensitivity of 96.9%, specificity of 88.2%, and an AUC of 0.94 in distinguishing BE from controls [59]. As we come to better understand the oral and gut microbiome changes typical of BE, these profiles could become attractive targets for non-invasive screening.

Conclusion

Screening for BE has traditionally involved sedated endoscopy in high-risk populations. Logistical barriers limited widespread adoption of this practice, and recent research has focused on non-invasive methods for BE screening. There has been a shift in focus to molecular biomarkers that can be easily applied using minimally invasive methods in an outpatient setting, opening the door to widespread implementation, with the potential to alter favorably the rising incidence of esophageal adenocarcinoma. In addition to the detection of Barrett's esophagus, efficient and accurate detection of dysplasia and adenocarcinoma as well as risk stratification in those without dysplasia will be important to establish a more effective screening and surveillance paradigm.

Compliance with Ethical Standards

Conflict of Interest Prasad G. Iyer declares research funding from Exact Sciences, Medtronic, Pentax Medical, Nine Point Medical, Consulting: Pentax Medical, CSA Medical, and Medtronic.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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