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GI ONCOLOGY (R BRESALIER, SECTION EDITOR)

Barrett's Esophagus and Esophageal Carcinoma: Can Biomarkers Guide Clinical Practice?

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Abstract

Purpose of Review Despite gastrointestinal societal recommendations for endoscopic screening and surveillance of Barrett's esophagus, the rates of esophageal adenocarcinoma continue to rise. Furthermore, this current practice is costly to patients and the medical system without clear evidence of reduction in cancer mortality. The use of biomarkers to guide screening, surveillance, and treatment strategies might alleviate some of these issues.

Recent Findings Incredible advances in biomarker identification, biomarker assays, and minimally-invasive modalities to acquire biomarkers have shown promising results.

Summary We will highlight recently published, key studies demonstrating where we are with using biomarkers for screening and surveillance in clinical practice, and what is on the horizon regarding novel non-invasive and minimally invasive methods to acquire biomarkers. Proof-of principle studies using in silico models demonstrate that biomarker-guided screening, surveillance, and therapeutic intervention strategies can be cost-effective and can reduce cancer deaths in patients with Barrett's esophagus.

Keywords Screening · Surveillance · Gastroesophageal reflux disease · Endoscopic · Imaging · Tissue

Introduction

It is estimated that 5.6% of adults in the USA have Barrett's esophagus, a condition in which a metaplastic columnar mucosa replaces normal squamous mucosa that has been damaged by gastroesophageal reflux disease (GERD) [1]. Barrett's esophagus is clinically important because it predisposes to esophageal adenocarcinoma, a tumor with a 5-year survival rate of < 20% [2]. To prevent death from this lethal tumor, gastrointestinal societies recommend conventional endoscopic screening for and surveillance of Barrett's esophagus [3–5]. Data from observational studies suggest that patients with Barrett's-associated cancers diagnosed during surveillance endoscopy have earlier-stage tumors and higher survival rates than those found when patients present with symptoms such as weight loss and dysphagia [6]. However, a recent retrospective, case-control study found that endoscopic surveillance had no benefit in preventing death from esophageal adenocarcinoma [7]. Moreover, more than 90% of esophageal adenocarcinomas are discovered in patients without a prior diagnosis of Barrett's esophagus and thus are not enrolled in surveillance programs [8, 9]. Needless to say, our current screening and surveillance strategies for patients with Barrett's esophagus are woefully ineffective, as rates of esophageal adenocarcinoma still continue to rise [10, 11].

Two promising areas that may help to alleviate some of the issues with screening and surveillance of these patients are using biomarkers to predict the presence of Barrett's esophagus or esophageal neoplasia and to risk stratify neoplastic progression in those with Barrett's esophagus. Although investigators have been searching for these elusive "Barrett's biomarkers" for years, the quest for these biomarkers has intensified due to incredible advances in biomarker detection techniques, advances in minimally-invasive modalities to screen for Barrett's esophagus, and successes in endoscopic eradication therapies to treat dysplasia and early carcinoma arising in established Barrett's esophagus [12–14]. So, is it just wishful

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thinking to imagine that we are any closer to identifying those slippery Barrett's biomarkers or for that matter that they can actually guide clinical practice? The following sections will focus on recently published, key studies demonstrating where we are with using biomarkers for screening and surveillance in clinical practice, and what is on the horizon using novel non-invasive and minimally invasive methods of biomarker detection in patients with Barrett's esophagus or even the general population at large. Furthermore, proof-of-principle in silico models demonstrate that yes, it is conceivable that biomarkers can guide clinical practice and even be cost-effective for screening and surveillance of patients with Barrett's esophagus.

Biomarkers and Their Detection: Where We Are Now and What Lies Ahead

Extensive research into the use of biomarkers, on endoscopically obtained tissue specimens, has focused primarily on risk stratification of patients with non-dysplastic and low-grade dysplastic Barrett's esophagus. Requiring the use of endoscopically obtained tissue specimens entails risk, expense, and inconvenience to patients. In recent years, the identification of potential biomarkers has exploded due to incredible advances in genomics techniques such as whole-genome sequencing which can be performed on whole-blood DNA (Table 1). The increase in biomarker identification has led to the use of biomarker panels rather than a single biomarker to determine the risk of neoplasia in patients with Barrett's esophagus (Table 1) [15, 16]. New modes of biomarker sampling are being developed (i.e., sponge on a string and breath tests) and, if proven to be reliable, are non-endoscopic methods that may reduce or eliminate the risk, cost, and inconvenience to patients of endoscopic surveillance as well as become a cost-effect approach to endoscopic screening (Table 1). Also, technologic advances in endoscopic imaging allow biomarker detection in real-time in vivo (Table 1). The studies discussed below highlight recently identified biomarkers, their novel methods of detection, and how they can be used as guides to identify patient with Barrett's esophagus who can be placed in surveillance programs (Fig. 1a) or to identify patients at high-risk for cancer progression for endoscopic eradication therapy (Fig. 1b). Currently, however, the American College of Gastroenterology and American Gastroenterological Association recommend against the *routine* use of biomarkers in the management of Barrett's esophagus [3, 4].

Blood-Based Biomarkers

Recent data from the genomics (r)evolution has revealed potential biomarkers of inherited genetic susceptibility that may predict the risk of developing Barrett's esophagus and esophageal adenocarcinoma. These biomarkers are usually genetic variants of a single-nucleotide polymorphism (SNP) located at a specific region in the genome that can be mapped to a specific gene. SNP detection can be performed on whole-blood DNA to identify these germline (i.e., inherited) alterations, and genome-wide association studies (GWAS) are used to compare SNPs between individuals who have the disease of interest and control subjects. Ek et al. performed GWAS on a subset of subjects from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) dataset, which contains clinical information and blood samples from subjects enrolled in 14 epidemiological studies from three countries [17]. All subjects were of white-European ancestry; 1509 patients had esophageal adenocarcinoma; 2383 patients had Barrett's esophagus, and 2170 subjects were used as controls in this GWAS study. Following a complex series of bioinformatics analyses, they estimated that 35% of Barrett's esophagus cases and 25% of esophageal adenocarcinoma cases have a polygenic component (i.e., influenced by many genes) underlying disease risk [17]. Moreover, these unrelated subjects with Barrett's esophagus and esophageal adenocarcinoma

Table 1 Clinical considerations for biomarker testing

Method	Marker type	Requires endoscopy	Patient tolerability	Availability	Cost
GWAS	Blood	No	****	No	–
P53 Immunostaining	Tissue	Yes	***	Yes	*
Flow cytometry	Tissue	Yes	***	Yes	**
Tissue systems pathology assay	Tissue	Yes	***	Yes	***
Sponge on a string	Cells	No	**	Yes	**
Confocal laser endomicroscopy	Imaging	Yes	***	Yes	****
Volumetric laser endomicroscopy	Imaging	Yes	***	Yes	****
Tethered OCT capsule	Imaging	No	**	No	–
OCT angiography	Imaging	Yes	***	No	–
Electronic nose	VOCs	No	*****	No	–

Patient tolerability: ****, most tolerable; *, least tolerable

Cost: ****, most costly; *, least costly

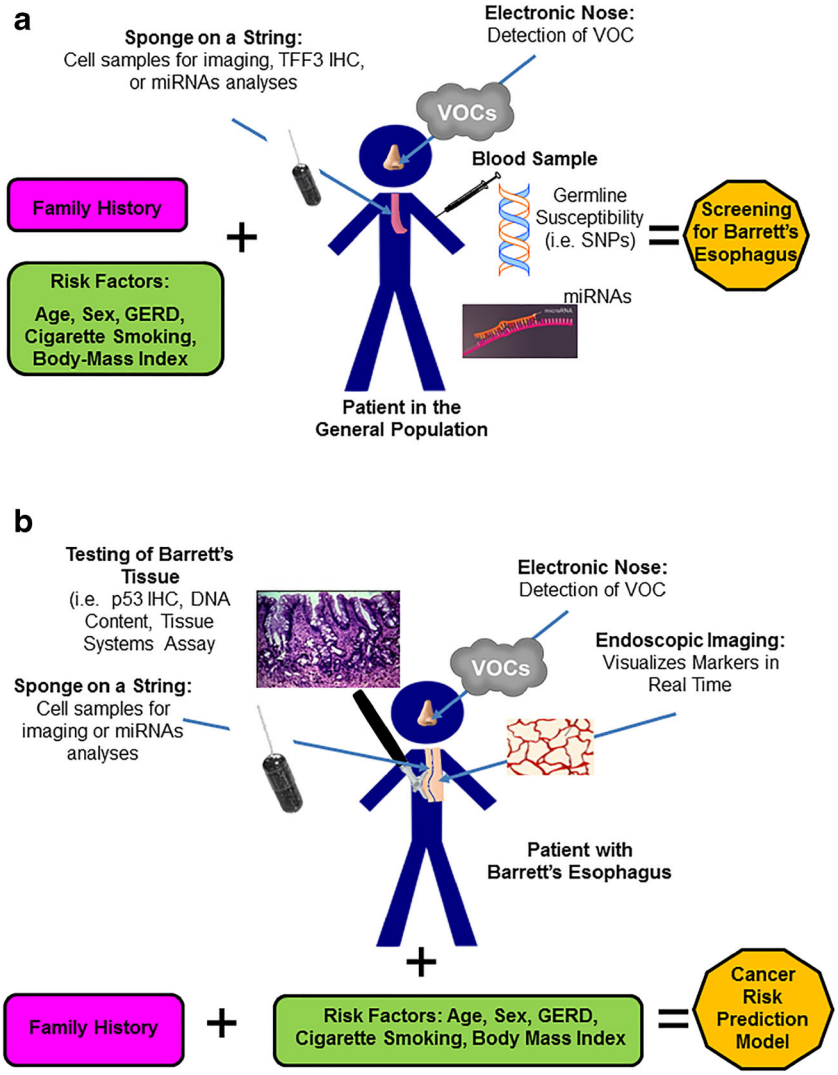

Fig. 1 The Future of biomarkers in screening and surveillance for Barrett's esophagus. **a** The potential sources for interrogation of biomarkers to screen for Barrett's esophagus includes esophageal cell sampling via sponge on a string for use in histologic diagnosis or detection of biomarkers such as trefoil factor 3 (TFF3) by immunohistochemistry (IHC) or microRNAs (miRNAs). Patients may have testing for molecular markers available in the whole body and sources include blood samples which can provide information on inherited genetic susceptibility or miRNAs and volatile organic compounds (VOCs) which can be detected via the novel electronic nose. It is conceivable that these screening biomarkers combined with a family history and risk factors for Barrett's esophagus will be synthesized into a single, screening evaluation. **b** Traditionally, biomarker testing to risk stratify cancer progression in patients with Barrett's esophagus has been done on esophageal tissues obtained by endoscopic biopsy, and biomarkers such as p53 IHC, DNA content, or tissue system analyses are performed on these specimens. More recently, biomarker testing can now be performed on esophageal cell samples obtained via a sponge on a string for use in histologic diagnosis or miRNAs testing, directly imaging molecular markers in real time without the need for tissue, and "sniffing out" VOCs via the novel electronic nose. It is conceivable that these risk stratifying biomarkers combined with a family history and risk factors for esophageal adenocarcinoma development will be synthesized into a single model to predict risk for neoplastic progression

were found to have a substantial overlap of SNPs, suggesting a shared genetic susceptibility for the two disorders [17].

Other GWAS studies have analyzed selected SNPs within different inflammatory pathways or the interaction between SNPs and the well-known epidemiologic risk factors for Barrett's esophagus including GERD, cigarette smoking, and body-mass index (BMI) to derive information on the contribution of genetic susceptibility to the risk of developing Barrett's esophagus and esophageal adenocarcinoma. Buas et al. selected five different inflammation-related pathways that have been previous linked with Barrett's esophagus and esophageal adenocarcinoma [18]. Only germline variations in the cyclooxygenase pathway (specifically in the antioxidant microsomal glutathione S-transferase 1 [MGST1] gene) were significantly associated with risk for Barrett's esophagus and the combined outcome of Barrett's esophagus and esophageal adenocarcinoma; none of the five inflammatory pathways were associated with risk of esophageal adenocarcinoma alone [18]. Using GWAS, Dai et al. found that subjects who had a SNP in the FOXP1 gene (which has been shown in earlier GWAS studies

to be significantly associated with the risk of Barrett's esophagus [19–21]), in the absence of reflux symptoms, had an odds ratio (OR) of developing Barrett's esophagus of 1.5; the highest OR of 6.0 was found for patients with reflux symptoms who had no SNP in their FOXP1 gene [22]. The presence of at least weekly reflux symptoms and a SNP in the FOXP1 gene significantly decreased the risk of Barrett's esophagus from an OR of 6.0 to 5.44 [22]. No significant associations were found between any of the other epidemiologic risk factors and Barrett's esophagus or esophageal adenocarcinoma alone [22]. Most recently, the addition of 18 SNPs associated with esophageal adenocarcinoma to a clinical risk score (age, sex, BMI, smoking status, and esophageal conditions) did not change the area under the receiver operating characteristic curve (AUC) to predict the 5-year risk of developing esophageal adenocarcinoma suggesting that germline mutation testing might be better used as an adjunct to screening strategies for Barrett's esophagus rather than that for predicting cancer risk [23•].

Blood-based biomarker testing, also called "liquid biopsy," is performed as a surrogate to tissue-based biomarker testing. Liquid biopsy assesses the molecular profile of circulating cells, cellular DNA, or RNA, exosomes or secretomes captured in a blood sample. Recent studies have demonstrated that this technique for biomarker detection maybe feasible to screen for Barrett's esophagus. The most promising biomarker in liquid biopsy studies has been the detection of circulating microRNAs (miRNAs), which are small (approximately 21–25 nucleotides in length), non-coding RNAs that function primarily to inhibit gene expression. *Bus* et al. found that circulating levels of miRNA-194-5p, miRNA-95-3p, and miRNA-451a were significantly increased and those of miRNA-136-5p were significantly decreased in patients with Barrett's esophagus compared to control subjects [24]. Furthermore, when these four miRNAs were combined, this biomarker panel was found to distinguish controls from those with Barrett's esophagus with AUC of 0.832, a sensitivity of 78.4%, and a specificity of 85.7% [24].

Tissue-Based Biomarkers: Endoscopic Acquired Tissue

Data are lacking regarding the benefit of endoscopic screening for Barrett's esophagus to reduce deaths from esophageal adenocarcinoma. Additionally, there are drawbacks to using an endoscopic approach for screening including the high cost of endoscopy and potential adverse outcomes with an invasive procedure. Therefore, it is unlikely that biomarker-based screening will be performed using endoscopically acquired tissue specimens. In contrast, patients with established Barrett's esophagus enrolled in endoscopic surveillance programs routinely undergo endoscopic tissue acquisition for histologic assessment. In this setting, biomarkers whose use requires endoscopically acquired tissue may provide a diagnostic or predictive yield over that of the traditional histologic evaluation of dysplasia.

p53 Immunostaining

p53 immunostaining performed on paraffin-embedded tissues has been proposed as an adjunct to routine histologic assessment of dysplasia by the British Society for Gastroenterology [5]. Wild-type p53 protein is rapidly degraded, but some p53 mutations render the protein stable so that its levels accumulate (overexpression), whereas other mutations lead to loss of expression, both of which can be easily detected in tissue samples by immunostaining. Aberrant p53 expression (overexpression or loss of expression) was prospectively studied as a predictor of progression to high grade dysplasia (HGD) or esophageal adenocarcinoma in 91 patients with non-dysplastic Barrett's esophagus enrolled in a surveillance program [25]. Over a median follow-up period of 71 months, 11 of the 91 patients (12%) progressed to HGD or cancer [25]. In those patients who progressed to HGD or cancer, aberrant p53 expression was found significantly more often (63.6%) than in those patients who did not progress (7.5%) [25]. Using multivariate analysis, aberrant p53 expression detected by immunostaining was found to be a significant (hazard ratio, HR 17) and independent predictor of neoplastic progression [25]. More recently, a case-control study evaluated the ability of p53 immunostaining to predict progression to HGD or cancer in patients with non-dysplastic Barrett's esophagus. In the patients who progressed to HGD or cancer, p53 had an abnormal expression pattern in 44.4% whereas in patients who did not progress, only 8.5% had abnormal p53 expression detected by immunohistochemistry. In addition, all of these patients had p53 sequencing performed which demonstrated a strong correlation between p53 overexpression detection by immunohistochemistry and sequence mutations ($p < 0.001$) [26••].

DNA Content Abnormalities Detected by Flow Cytometry

As seen from these aforementioned studies, the use of p53 immunostaining alone is imperfect. Not every patient who progressed to HGD or cancer had abnormal p53 expression, and some patients with abnormal p53 expression did not progress to neoplasia. So, the search is still on to find a better predictive biomarker and aneuploidy is one such candidate. Aneuploidy detects gains or losses in parts of chromosomes and reflects genomic instability, a predictor of cancer progression (Reviewed in [27]). Indeed, several earlier reports suggest that flow cytometric evidence of DNA content abnormalities either aneuploidy or elevated 4N [the fraction of cells within a specimen containing 4N (n = sets of chromosomes) exceeds 6%] can predict risk of neoplastic progression in patients with Barrett's esophagus more accurately than histologic grading of dysplasia (Reviewed in [28]). One of the drawbacks of this approach for the clinical practitioner is the need for fresh or frozen esophageal biopsy specimens. Recently, a

case-control study using DNA content abnormalities to risk stratify patients with Barrett's esophagus was assessed on formalin-fixed paraffin-embedded tissues; DNA flow cytometry was performed using published consensus clinical guidelines [29••]. Biopsies of non-dysplastic Barrett's metaplasia rarely demonstrate DNA content abnormalities and thus were used as controls. As expected, 100% of these non-dysplastic biopsies demonstrated normal DNA content [29••]. In contrast, abnormal DNA content was found in 93.8% of Barrett's patients with HGD, and 54% of these patients had concurrent or subsequent cancer diagnosed within 2.4 months [29••]. Patients with low grade-dysplasia and an abnormal DNA content had a risk of progression to HGD or cancer with a HR of 17.9 on multivariate analysis over a 15.5-month follow-up period [29••]. Moreover, in 21 patients whose biopsies were diagnosed as indefinite for dysplasia, 19 patients (90.5%) had normal DNA content, and only one of these patients progressed to HGD over 53 months of follow-up; two patients had an abnormal DNA content and both progressed to HGD or cancer within 2 years [29••]. These promising findings require validation in larger, prospective studies but the ability to use paraffin-embedded tissues and clinical consensus guidelines for operation of the DNA flow cytometer has made this biomarker more feasible than ever for use in clinical practice.

Tissue Systems Pathology Assay

A more recent approach to biomarker detection is that of systems biology, viewing the tissue as a "system" and assessing genetic, immunologic, vascular, and morphologic features relevant to cancer progression [30]. Critchley-Thorne et al. studied a tissue system pathology assay which includes 14 biomarkers of epithelial and stroma cell abnormalities involved in carcinogenesis along with an assessment of nuclear morphology [31]. This 15-feature assay was developed and validated in a nested case-control study of patients with Barrett's esophagus (non-dysplastic, indefinite for dysplasia, or low grade dysplasia) enrolled in surveillance programs at four institutions and followed up to a median time of 5.9 years [31]. During follow-up, some of these patients progressed to HGD or cancer, while others did not. In the training cohort, the investigators developed a risk prediction model based on the performance of the 15 features on the assay. This risk prediction model stratified patients into low-, intermediate-, and high-risk categories. The 5-year probability of progression to HGD or cancer in patients in the low-, intermediate-, and high-risk categories had HRs of 4.19 for intermediate- vs low-risk and 14.73 for high-risk vs low-risk categories [31]. These predicted risk categories provided stronger prognostic power than the use of clinical variables including histologic grading of dysplasia, length of Barrett's metaplasia, age, sex, and percent of cells with p53 overexpression [31]. When this 15 feature assay was applied to a validation cohort, HRs of 2.45 for intermediate- vs low-risk, and 9.42 for high-risk vs low-risk categories were found for 5-year progression to HGD or cancer. In the validation cohort, the prevalence-adjusted negative and positive-predictive values were 0.98 and 0.26, respectively [31]. In a subsequent study, Critchley-Thorne et al. used this same 15 feature assay to predict prevalent HGD or cancer in Barrett's patients diagnosed with non-dysplastic, indefinite, or low-grade dysplasia. Patients in the high-risk category had a 46-fold increased risk for prevalent HGD or cancer (diagnosed with a median time of 140.5 days) compared with the low-risk category [16].

Tissue-Based Biomarkers: Non-Endoscopic Acquired Tissue

If we could acquire cells from the esophagus without the need for sedation or endoscopy, such a tool may potentially be applied for Barrett's screening. Depending on the cost and ease of use, this kind of non-endoscopic screening tool could potentially be used in an office-based setting on the general population. A sponge on a string (SOS) has been developed to non-endoscopically collect cells from the esophagus allowing for biomarker interrogation to be performed on those cells. This technique works by having the patient swallow a capsule with a string attached; that string is held at the mouth allowing for the capsule to dissolve in the stomach and releases the sponge, and the sponge is withdrawn by pulling on the string collecting cells along the way. These cells can then be processed and undergo immunostaining and molecular analysis. One of these platforms, the Cytosponge, has been shown to be safe, feasible, and acceptable to patients in the reported multicenter experience [32••]. Tissue trefoil factor 3 (TFF3), a marker of intestinalization, has been used on cells collected by SOS to screen for Barrett's esophagus [33, 34]. In a case control study with over a thousand patients, the Cytosponge-TFF3 test yielded an overall sensitivity of 79.9% for detecting Barrett's esophagus [34]. Another SOS tool, the Esophacap, has shown excellent safety and tolerability among patients with an AUC to detect Barrett's esophagus ranging from 0.52 to 0.97 when utilized with individual, candidate methylated DNA markers, and an AUC of 1 when using a 2 candidate methylated DNA marker panel [35]. These results are promising and need further validation in a larger population prior to adoption as a wide spread screening tool.

The SOS device can also be utilized to risk stratify those patients with known Barrett's esophagus during surveillance to determine who may be at risk for progression. For example, one study investigated samples obtained via Cytosponge for a biomarker panel (P53, c-Myc, Aurora kinase A, methylation markers MYOD1 and RUNX3, glandular atypia, and TP53 mutation status) in combination with clinical and demographic data to predict the presence of dysplasia, using conventional endoscopy and histologic assessment of dysplasia as the "gold

standard" for comparison [36]. In the discovery cohort, the biomarker panel was narrowed down to glandular atypia, p53 abnormality, and Aurora kinase A positivity in combination with age, waist-to-hip ratio, and length of Barrett's segment to generate low-, intermediate-, or high-risk categories. In the validation cohort of 65 patients, 51 patients had non-dysplastic and 14 had high-grade dysplastic Barrett's esophagus. Of the 65 patients, 25 were in the low-risk category which included 24 patients with non-dysplastic Barrett's mucosa and 1 patient with HGD. Thus, patients categorized as low-risk had a 96% probability of being non-dysplastic. All five of the patients in the high-risk category had HGD whereas 77% of the patients in the moderate-risk group had non-dysplastic Barrett's esophagus and 23% had HGD [36].

In Vivo Imaging for Real-Time Acquisition of Biomarkers

The concept of an optical biopsy has gone from proof-of-concept to commercially available tools in clinical practice which allow for real-time assessment of the lining of the GI tract at micro-architectural detail. Optical biopsies can be used as a real-time surrogate marker for histology that may be utilized for screening. Confocal laser endomicroscopy (CLE) enables visualization of the epithelium to assess both glandular and cellular architecture and can be used to classify metaplastic and dysplastic tissues [37, 38, 39••, 40]. A contrast agent, most commonly fluorescein, must be used with CLE for gastrointestinal imaging. Fluorescence peptides have been developed that preferentially bind to esophageal neoplasia which can be detected by CLE [41]. In a proof-of-concept study, 25 Barrett's patients with a history of HGD or esophageal adenocarcinoma had their esophageal mucosa sprayed with a fluorescein isothiocyanate (FITC)-labeled short peptide (ASYNYDA) followed by CLE imaging. The investigators found an AUC of 0.91 to detect neoplasia using fluorescent peptide imaging [41]. Thus, molecular probes have potential to predict neoplasia in real time during an endoscopic procedure.

Optical coherence tomography (OCT)-based technologies can be used to image a span of the esophagus in a cross-sectional fashion. A commercially available volumetric laser endomicroscopy system allows for a span of imaging of 6 cm of the esophagus. There is excellent inter-observer agreement in differentiating between squamous epithelium, gastric cardia, and Barrett's esophagus [42•]. A tethered capsule OCT device permits similar imaging in a non-endoscopic fashion thus allowing capsule-based imaging to be used as a screening tool for Barrett's esophagus [43]. Different algorithms have been developed and refined that can now distinguish between dysplastic and non-dysplastic Barrett's tissue with OCT-based technologies [44–46]. Another novel platform is optical coherence tomography angiography (OCTA) which enables cross-sectional imaging of the vascularity at the micro-architectural level. OCTA features such as irregular branching and heterogeneous vessel size may allow for a vessel-based characterization of dysplasia in the setting of Barrett's esophagus [47].

Electronic Nose for Sniffing out Biomarkers

An innovative platform being explored is the detection of exhaled volatile organic compounds (VOC) by an "electronic nose" [48]. A pilot study of 122 patients demonstrated an accuracy of 81% by the electronic nose in distinguishing patients with non-dysplastic Barrett's esophagus from those with dysplastic Barrett's esophagus [49]. Essentially, this technology would allow for the performance of a simple, office-based breath test to identify a patient at high risk for harboring esophageal neoplasia.

Biomarker-Guided Clinical Practice: Where the Rubber Meets the Road

Gastrointestinal society guidelines currently recommend that conventional endoscopic screening be considered for individuals with multiple risk factors for Barrett's esophagus, but do not recommend endoscopic screening for Barrett's esophagus in the general population of patients with GERD [3–5]. Among the reasons why endoscopic screening programs have not gained traction for use in the general population are its prohibitively high cost, lack of clear evidence that screening is beneficial to reduce deaths from esophageal adenocarcinoma, and of course, the remaining controversy of whether endoscopic surveillance for those with Barrett's esophagus results in fewer cancer deaths [50•]. For patients with established Barrett's esophagus, endoscopic surveillance for those with non-dysplastic mucosa remains the recommended approach whereas for those with low-grade or high-grade dysplasia, endoscopic eradication therapy combining endoscopic mucosal resection with RFA of the remaining Barrett's esophagus is the preferred treatment modality [3–5]. The computer modeling studies discussed below demonstrate the potential for biomarker-guided screening, surveillance, and treatment strategies to reduce deaths from esophageal cancer at a reasonable cost, thus revealing the potential for biomarkers to change our clinical practice.

Potential for Biomarkers to Guide Screening Strategies to Identify Patients with Barrett's Esophagus

In the past few years, we have seen the development of the SOS technique to non-endoscopically sample cells from the

esophageal lumen and immunostaining of those cells for the biomarker TFF3 has shown promise in screening patients for Barrett's esophagus [33–35]. Recently, Heberle et al. used two independent microsimulation computer models, one from the Massachusetts General Hospital (MGH model) and the other from Erasmus University Medical Center and the University of Washington (Erasmus/UW model), to assess the impact on esophageal adenocarcinoma development and the cost-effectiveness of screening for Barrett's esophagus using this SOS-TFF3 biomarker test compared to conventional endoscopy [51•]. These computer models were previously developed and subsequently validated to replicate the natural history of esophageal adenocarcinoma starting from health and passing through non-dysplastic and dysplastic Barrett's esophagus before culminating in cancer [51•]. Heberle et al. modeled a 1950 birth cohort of US men starting at age 20, and when these men reached age 60, screening was performed on those with GERD symptoms who had not already been diagnosed with cancer [51•]. These men were followed up over their lifetimes or to the age of 100. The screening strategies included the SOS-biomarker first-screening, endoscopic screening, or no screening. In the SOS-biomarker first-screening strategy, patients with positive results underwent endoscopy for confirmation of Barrett's esophagus; patients with negative results on the SOS-biomarker test or negative results on the confirmation endoscopy had no further follow-up. Patients found with Barrett's esophagus underwent surveillance and those subsequently found with HGD were treated with RFA. The no-screening strategy resulted in the development of 13.75 or 16.25 cancers per 1000 GERD patients in the Eramus/UW or MGH models, respectively [51•]. Endoscopic screening reduced the number of cancers that developed per 1000 GERD patients by 51% or 23% whereas the SOS-biomarker test lead to a decrease in cancer development of 41% or 19% in the Eramus/UW or MGH models, respectively [51•]. In both models, endoscopic screening was not cost-effective when the SOS-biomarker first-screening test was available. Moreover, the SOS-biomarker screening arm also included endoscopic surveillance for those patients with confirmed Barrett's esophagus and RFA for those who developed HGD suggesting that this biomarker-based screening-surveillance-therapeutic strategy has the potential not only to decrease deaths from esophageal adenocarcinoma but also the associated costs when using such an approach.

Potential for Biomarkers to Guided Surveillance and Treatment Strategies for Patients with Barrett's Esophagus

Computer modeling has shown that neither surveillance nor RFA for *all* patients with non-dysplastic Barrett's esophagus is cost-effective [52]. Recently, Das et al. used a Markov model to assess cost-effectiveness of RFA in patients with non-dysplastic Barrett's esophagus whose tissues expressed a "high risk for cancer progression" biomarker panel. The investigators modeled four strategies in these patients: (1) biomarker-guided RFA ablation of high-risk patients, (2) no surveillance, (3) the current American College of Gastroenterology recommended surveillance guidelines, and (4) RFA of *all* patients with non-dysplastic Barrett's esophagus [53•]. The patient cohort was a group of 50-year-old white men with non-dysplastic Barrett's esophagus recently diagnosed by endoscopy, who were then followed over their lifetimes. The biomarker panel was commercially available and assessed genomic instability and microsatellite instability across a group of genes implicated in the neoplastic progression of Barrett's esophagus. In the biomarker-guided RFA strategy, patients who were negative for the "high risk" biomarker panel underwent endoscopic surveillance every 10 years rather than every 3 years. The dominate strategy predicted by this model was biomarker-guided RFA, yielding the highest number of quality of life years at the lowest cost and the fewest cancers being diagnosed over the lifetime of the cohort [53•]. Compared with no surveillance, biomarker-guided surveillance had a relative risk (RR) of cancer development of 0.48 with the number needed to treat (NNT) to prevent cancer of 23. Furthermore, biomarker-guided surveillance had a RR of cancer development of 0.49, with a NNT of 24 compared with the ACG guideline-recommended surveillance [53•].

Conclusion

Routine use of biomarkers in the management of Barrett's esophagus is currently not recommended by American gastrointestinal societies, but we anticipate that this recommendation will change in the near future. The promising results of in silico models demonstrating the cost-effectiveness of biomarker-guided screening, surveillance, and therapeutic intervention strategies have increased the incentive to find the elusive "Barrett's biomarker(s)". In recent years, the identification of potential biomarkers has exploded due to incredible advances in genomics techniques, and we are moving away from just using endoscopically acquired tissue biopsies and into serum-, cytology-, and breath-based biomarkers. Such refinements have increased feasibility for the use of biomarkers in busy clinical practices. At the clinical front, non-invasive and minimally invasive screening and surveillance devices and technologic advances in in vivo molecular imaging have moved us closer than ever to eventual implementation. With all these advances in biomarker identification and detection, it is not surprising that biomarker-guided clinical practice can clearly be seen on the horizon.

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Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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