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Clinical UPDATE

Risk Stratification in Predicting Esophageal Cancer: A New Paradigm for Managing Barrett's Esophagus

FACULTY

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GOAL

The goal of this activity is to educate health care providers about a novel precision medicine prognostic test that objectively and independently predicts the development of esophageal cancer in patients with Barrett's esophagus (BE).

INTENDED AUDIENCES

The intended audience for this activity comprises gastroenterologists; foregut surgeons; gastroenterology physician assistants, nurse practitioners, and nurses; as well as other clinicians involved in managing patients with BE.

EDUCATIONAL OBJECTIVES

- Summarize the increasing health system burden of esophageal cancer.
- Recognize patients at high risk for developing esophageal cancer.
- Describe diagnostic and prognostic tests that provide actionable information for identifying and managing BE.
- Explain methods to avoid unnecessary surveillance endoscopies.

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Introduction

Esophageal cancer represents a significant global health challenge. This aggressive malignancy has a poor prognosis and low survival rates, even with treatment. Globally, esophageal cancer ranks 11th among cancers in incidence (511,054 new cases) and 7th in mortality (445,391 deaths),[1] and represents 1 in every 18 cancer deaths.[2] Men account for approximately 70% of cases.[2] In the United States and most Western populations, the overall incidence of esophageal cancer has risen since the early 1970s.[3] In 2023, there were 21,560 new cases and 16,120 deaths in the United States.[4] The 5-year relative survival rate, based on data for 2013 to 2019, is 21.7%.[4]

Most esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or esophageal adenocarcinoma (EAC).

SCC arises from small polypoid excrescences, denuded epithelium, and plaques commonly located in the cervical esophagus or upper and middle thoracic esophagus.[5,6] The main risk factors are alcohol consumption and tobacco use; Black race; human papillomavirus infection; and preexisting anatomical conditions such as achalasia, caustic strictures, gastrectomy, and atrophic gastritis.[6] Other factors may also play a role, including hot beverage consumption and exposure to nitrosamines and inhaled or ingested polycyclic aromatic hydrocarbons.[7,8]

EAC starts in the glandular cells, mainly found in the lower thoracic esophagus, and includes adenocarcinoma of the distal esophagus and gastroesophageal junction (GEJ).[6] The only known precursor to EAC is Barrett's esophagus (BE) metaplasia, which has been associated with epidermal growth factor polymorphisms and other conditions that increase exposure to esophageal acid.[6] The primary risk factors are white race, male sex, and gastroesophageal reflux disease (GERD).[6] Obesity and increased abdominal circumference are also implicated, as these conditions can potentiate reflux. EAC is the most prominent subtype of esophageal cancer in the United States and most Western countries.

Progression from BE to cancer is preventable if high-risk patients are treated with endoscopic eradication therapy (EET). This therapy can be highly effective; however, identifying the high-risk patients who will benefit most and the low-risk patients for whom long-interval surveillance may be appropriate remains challenging. Most data suggest that the presence of high-grade dysplasia (HGD) is highly predictive of subsequent malignancy, but reported rates of progression vary. The risks associated with low-grade dysplasia (LGD) are even less clear, especially as reliably distinguishing LGD from regenerative changes or reactive atypia accompanying active inflammation can be difficult for pathologists.[9] Current surveillance strategies are predominantly based on histologic tissue analysis and have limitations, as a meaningful proportion of patients with BE in surveillance can progress to EAC despite having no history of dysplasia.[9,10] This educational activity summarizes current data on esophageal cancer and BE and reviews current guidance on endoscopic screening in patients with BE, risk stratification models, and a new method of precision testing that can help identify a patient's personalized risk for progression to EAC.

Burdens and Challenges in Esophageal Cancer

EAC is the fastest-growing cancer in the United States by incidence.[8] Despite advancements in treatment, it remains highly lethal. Prognosis is strongly related to the stage at diagnosis. Unfortunately, most patients are diagnosed at later stages because they usually do not have obvious symptoms and may remain asymptomatic until the disease has progressed.[11,12] Recent data show that just 18% of esophageal cancers are detected at the localized stage,[6,13] 32% have local organ or lymph node involvement, and 40% have distant metastasis at diagnosis (the remainder were unstaged).[14] Furthermore, most patients with initial locoregional disease will develop distant metastases.[15]

In the United States, 5-year survival for esophageal cancer is less than 20% overall and less than 5% when distant metastasis is present at diagnosis.[16] Earlier disease identification could improve outcomes.

Esophageal cancer is typically aggressive. Tumor growth begins in the inner portion of the esophagus wall. It advances outward through the mucosa, submucosa, muscularis propria, and adventitia[5] via various pathways, including direct extension, lymphatic spread, and hematogenous metastasis.[8] Because the esophagus wall lacks serosa to serve as a barrier between the esophagus and the surrounding structures, a primary tumor can spread rapidly into the thyroid gland, trachea, larynx, lung, pericardium, aorta, and diaphragm. The entire length of the esophagus is also surrounded by an extensive lymphatic drainage system that facilitates lymphatic spread to cervical, mediastinal, and upper abdominal lymph nodes.[8]

Even with endoscopic or surgical resection, the complex anatomy of the mediastinum and GEJ increases the risk for inadequate or incomplete procedures and local tumor recurrence.[15] Other complexities include the highly heterogeneous nature of the malignancy, the lack of reliable biomarkers, and the need for targeted treatments.

Barrett's Esophagus

As noted previously, BE is the only identifiable precursor to EAC. It is recognized as a metaplastic change in the esophageal lining, in which the normal squamous epithelium is replaced by metaplastic columnar cells (**Figure 1**).[17,18] The development of BE is multifactorial, involving chronic exposure of the esophageal mucosa to gastric acid and bile reflux, genetic predisposition, and environmental factors.

The disorder seems to be largely a complication of chronic GERD, a relapsing condition in which stomach content refluxes into the esophagus and beyond.[19] Prolonged exposure of the esophagus to reflux, comprised of gastric acidic substances and bile salts from the duodenum, can erode the esophageal mucosa, promote inflammatory cell infiltration, and eventually cause epithelial necrosis. The prevalence of BE has been increasing in Western countries over recent decades, paralleling the rising rates of obesity and GERD.

An important risk factor for the development of BE is the onset of GERD symptoms before the age of 30 years or frequent (at least weekly) reflux (odds ratio [OR], 15.1).[20] Conversely, an inverse correlation has been found between colonization with *Helicobacter pylori* and BE, with one paper reporting that among individuals with frequent GERD symptoms, the risk for BE was almost 80% lower in those who were *H. pylori*-positive (OR, 2.60) than those who were *H. pylori*-negative (OR, 8.24).[20] Other risk factors for progression from GERD to BE include male sex, white race, cigarette smoking, and central adiposity. A degree of familial clustering has been observed, and genome-wide association studies have identified more than 20 genetic variants associated with BE.[21,22] Overall, most individuals with GERD symptoms do not progress to BE. In a systematic review and meta-analysis of 44 studies, pooled prevalence rates were 7.2% for histologically confirmed BE (range, 3%-14%), and 12% for endoscopically suspected BE among individuals with GERD.[23]

Diagnosis of BE

Barrett's esophagus is often asymptomatic; however, some patients may experience symptoms such as heartburn, regurgitation,

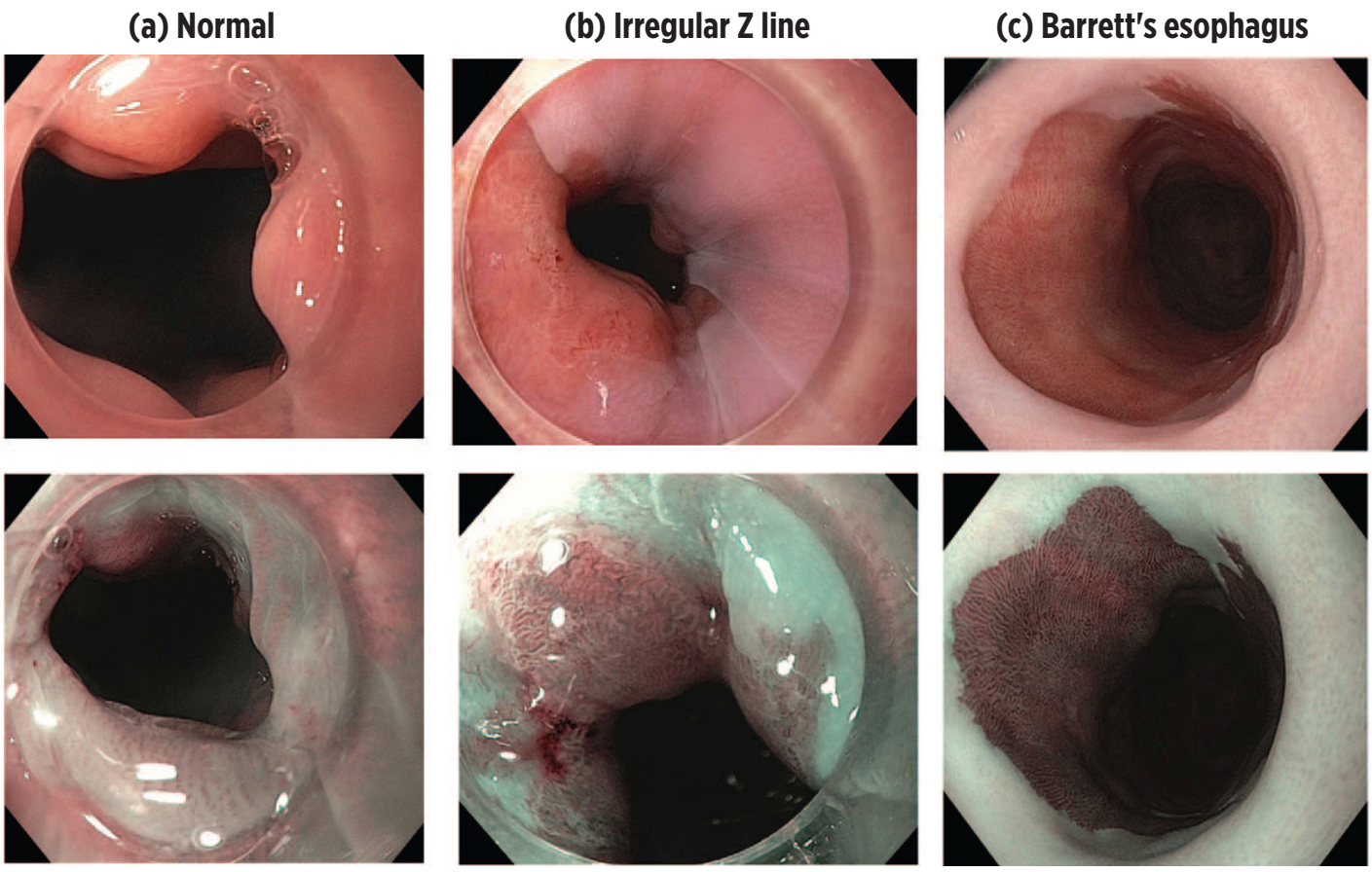

Figure 1. Spectrum of Barrett's esophagus extent under white light endoscopy and narrow band imaging.[18]

Panel A shows a normal squamocolumnar junction that coincides with the gastroesophageal junction (GEJ). Panel B shows an irregular Z line in which the columnar mucosa has variable extensions of short lengths (<1 cm) proximal to the GEJ. Panel C shows long-segment Barrett's metaplasia where the squamocolumnar junction is displaced >3 cm proximal to the GEJ. Short-segment Barrett's metaplasia would appear similar except for lengths <3 cm. Narrow-band imaging enhances the contrast between the squamous and columnar mucosa to allow careful characterization of the squamocolumnar junction in relation to the GEJ.

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dysphagia, or chest pain. Notably, the presence of these symptoms does not reliably predict the presence of BE. Evaluation relies on endoscopic biopsy and histologic evaluation to detect morphologic manifestations of neoplastic transformation. A diagnosis of BE requires the presence of columnar epithelium at least 1 cm above the proximal margin of the gastric folds, according to the universally accepted Prague criteria (**Figure 2**).[24,25] Histologic confirmation shows a combination of intestinalized columnar cells and gastric fundic and gastric cardia-type cells in the mucosa of the tubular esophagus.[26]

In clinical practice, it is common to see biopsies obtained from a normal Z line (the junction of the squamous and columnar epithelia) or a Z line with <1 cm extension into the esophagus, and this has led to misdiagnosis of BE in patients who do not have the condition.[26] Misdiagnosis is common. In the BEER (Barrett's Esophagus Endoscopic Reversal) study, which examined the accuracy of BE diagnosis in 130 patients, BE was improperly identified in 42 patients (32.3%) without visible columnar-lined esophagus proximal to the gastric folds or any goblet cells detected on biopsy.[27]

Screening and Surveillance in BE

Malignant transformation of BE follows a stepwise progression from nondysplastic BE (NDBE) to LGD, HGD, intramucosal carcinoma, and invasive EAC.[9] The current approach to reducing EAC-related mortality relies on upper endoscopy with biopsy to determine the degree of dysplasia present.

Stepwise progression and stage-dependent survival in EAC provide the rationale for screening and surveillance. Despite an overall low risk for progression from GERD or BE to EAC, screening is recommended in individuals with multiple risk factors for BE because treatment options for EAC are limited, and early detection is critical. Screening is not routinely performed in the general GERD population, as evidence has yet to prove conclusively that such screening can reduce mortality.[28]

Current guidelines recommend that screening be considered in those with 3 or more of the following risk factors[26]:

- Age older than 50 years
- Male sex
- Chronic (>5 years) and/or frequent (weekly or more) symptoms of GERD
- White race
- Presence of metabolic syndrome
- Current or history of smoking
- Confirmed family history in a first-degree relative with BE or EAC

The American College of Physicians (ACP) supports screening in patients with GERD and

difficult or painful swallowing, bleeding, anemia, weight loss, or recurrent vomiting.[29] The ACP advises against routine screening in women of any age or men younger than 50 because the incidence of esophageal cancer in these populations is very low.

Once a diagnosis of BE is established, the clinical goal is to prevent progression to EAC, with the current gold standard being regular endoscopic surveillance to detect evidence of neoplastic progression/dysplasia.[30] Current guidelines recommend surveillance of all patients with BE every 3 to 5 years based on the degree of dysplasia.[25,31] Other key recommendations for screening and surveillance are provided in **Table 1**.

Diagnostic and Screening Challenges in BE

Histologic findings of dysplasia are imperfect markers for disease progression in BE, as rates of progression to cancer can vary widely, even within the subclassifications of LGD vs HGD. The annual rate of progression of BE to HGD/EAC ranges from 0.12% to 9.1%, depending on the baseline diagnosis, clinical setting, and the number and specialty of pathologists providing the diagnosis.[32] Patients with HGD typically progress at rates of 6% to 19% per year, and those with LGD can have rates just as low as their nondysplastic counterparts or as high as 13% per year.[33] In confirmed LGD, a 10% annual risk for progression to HGD has been documented, but rates vary widely.[34] There is marked heterogeneity among studies reporting progression rates in patients with indefinite for dysplasia (IND) findings.[35]

More than 2 million upper endoscopies are performed annually in the United States in adults with GERD symptoms, at an estimated cost of more than $1.5 billion. However, BE progression rates are low and variable; most patients do not progress to EAC[36]; consequently, endoscopic surveillance is only modestly effective.[37] Up to 25% of those diagnosed with EAC report having had a surveillance endoscopy within the previous year,[38] and only 5% to 7% of patients diagnosed with EAC even have a prior diagnosis of BE.[30] A large proportion of BE occurs in patients without reflux symptoms; only 5% to 15% of individuals with GERD have BE, and between 20% and 50% of those with EAC have no prior GERD symptoms.[39] Furthermore, some cases progress from BE to EAC despite having no history of dysplasia. Others with an advanced degree of dysplasia never develop cancer. This suggests that frequent endoscopic examinations of all patients may not be necessary and may expose those at low risk for progression to excess risk and cost.[40]

Table 1. AGA Best Practice Advice Statements: Screening and Surveillance for BE[25]

Screening	• Screening with standard upper endoscopy may be considered in individuals with established risk factors for BE and EAC—presence of ≥3 risk factors • Nonendoscopic cell collection devices can be considered as an option to screen for BE
Endoscopic examination	• Screening and surveillance exams should be performed using high-definition white light endoscopy and virtual chromoendoscopy • Screening and surveillance exams should define the extent of BE using a standardized grading system documenting the circumferential and maximal extent of the columnar-lined esophagus (Prague classification) with a clear description of landmarks and the location and characteristics of visible lesions when present • Advanced imaging technologies such as endomicroscopy may be used as adjunctive imaging techniques to identify dysplasia • Sampling during screening and surveillance exams should be performed using the Seattle biopsy protocol • Wide-area transepithelial sampling may be used as an adjunctive technique to sample the suspected or established Barrett's segment (in addition to the Seattle biopsy protocol) • Patients with erosive esophagitis may be biopsied when concern of dysplasia or malignancy exists, with the caveat that a repeat endoscopy after 8 weeks of twice-daily PPIs is performed
Risk stratification	• Tissue systems pathology-based prediction assay may be used for risk stratification of patients with NDBE • Risk stratification models may be used to selectively identify individuals at risk for Barrett's-associated neoplasia
Provider expertise	• Given the significant interobserver variability among pathologists, the diagnosis of BE-related neoplasia should be confirmed by an expert pathology review • Patients with BE-related neoplasia should be referred to endoscopists with expertise in advanced imaging, resection, and ablation
Follow-up and surveillance	• Patients with BE should be placed on at least daily PPI therapy. • Patients with NDBE should undergo surveillance endoscopy in 3 to 5 years • In patients undergoing surveillance after endoscopic eradication therapy, 4-quadrant random biopsies should be taken of the esophagogastric junction, gastric cardia, and the distal 2 cm of the neosquamous epithelium as well as from all visible lesions, independent of the length of the original BE segment

BE, Barrett's esophagus; **NDBE,** nondysplastic Barrett's esophagus; **PPI,** proton-pump inhibitor.

Several aspects of endoscopy with biopsy in BE contribute to this. First, pathologic analysis can be challenging in certain cases, such as background inflammation or IND.[35] Some cases are ambiguous: Reactive atypia, an epithelial response to inflammation, can appear morphologically similar to BE but does not indicate a risk for cancer.[41] It is particularly difficult to deduce inflammation adjacent to ulcers, erosions, and mucosa near the Z line.[41] Detecting subtle lesions can be challenging.[42] Biopsy analysis also cannot detect molecular and cellular changes that precede morphologic alterations or risk-stratify patients without observable dysplasia, who comprise most of the BE population.

LGD is frequently overdiagnosed in the community setting, and substantial inter-/intraobserver variation in the interpretation of dysplasia has also been well documented. This occurs among general and gastrointestinal (GI)

pathologists and even among experts.[43] Up to 85% of LGD diagnoses made by generalist pathologists are downgraded to nondysplastic (ND)/IND on expert review, and 26% to 28% of confirmed LGD cases have no detectable LGD on follow-up.[44] Adherence to screening/surveillance guidelines also varies among settings.[45] Average excess costs associated with the overdiagnosis of LGD have been calculated at $5557 (range, $3115-$8072) per patient in the United States.[46]

Other limitations to using biopsies to detect progression during surveillance include its invasive nature, limited tissue volume,[41] and random sampling during endoscopy, by which the tested sample represents a very small proportion of esophageal tissue.[47] In fact, appropriately performed Seattle protocol biopsies can represent as little as 4% to 6% of the BE area. Biomarkers in the BE segment exhibit spatial and temporal variability, and EAC (and dysplasia) can be multifocal, occurring at multiple levels.[42,48] EAC may also exhibit field cancerization, in which the area around the lesion is undergoing molecular and cellular changes associated with malignant transformation but appears histologically nondysplastic.[42]

One adjunctive technique that can improve upon random biopsy sampling is wide-area transepithelial sampling of the esophagus with computer-assisted 3-dimensional analysis. This system uses brush sampling to obtain transepithelial specimens circumferentially, covering a larger area of the BE segment, allowing for evaluation of deeper glandular epithelium through full-thickness sampling.[49] The specimens, which can contain 100,000 cells, are stained and analyzed by a proprietary imaging and computer network that allows for a 3-dimensional view.

Another potentially useful technique is unsedated transnasal endoscopy, which uses a thin, sheathed endoscope that typically triggers the pharyngeal reflex significantly less than the oral passage of a standard endoscope.[50] It seems to be generally well-tolerated by patients and can be performed in ambulatory and primary care settings. Transnasal endoscopy is expensive and requires specific expertise; furthermore, the optical quality of most available transnasal endoscopes is somewhat inferior to standard high-definition devices. In addition, availability remains limited, and the procedure is not yet widely embraced by patients, primary care providers, or gastroenterologists. Although some scopes can obtain biopsies, for the most part it is a visual examination only, and histology is not obtained.

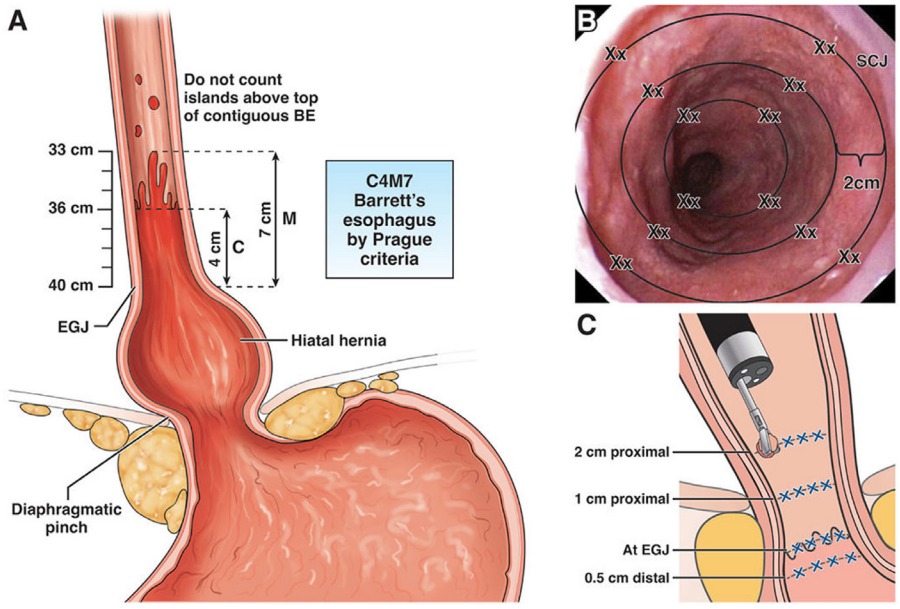

Figure 2. The Prague classification for Barrett's esophagus.[25]

BE, Barrett's esophagus; **EGJ,** esophagogastric junction.

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Endoscopy Alternatives

Traditional upper endoscopy with biopsy remains the gold standard for diagnosing BE; however, a significant need exists for noninvasive screening tools that are easy to administer, patient-friendly, and cost-effective. Current American Gastroenterological Association (AGA) guidance acknowledges this and states that nonendoscopic cell collection methods can be considered as screening options.[25]

Several cell collection methods, listed below, have been developed as nonendoscopic alternatives for screening and have demonstrated tolerability, safety, and sensitivity for the diagnosis of BE. Further data are needed to validate patient selection criteria and identify the optimal settings for their use.[51]

Cytosponge is a novel, minimally invasive cell collection device consisting of a 30-mm polyurethane sponge in a capsule attached to a string. The patient swallows the sponge and when withdrawn, the sponge collects esophageal cells for analysis. The procedure requires minimal training and can be performed by a nurse in a primary care setting. Studies show a sensitivity of 80% and specificity of 92% for detecting BE.

EsophaCap is similar in concept to Cytosponge but smaller in diameter, at 2.5 cm. The patient swallows the capsule with a long string attached to it. Once in the stomach, the gelatin coating on the capsule begins to dissolve. When the sponge is pulled out, it collects cells from which genetic material is obtained. In a study of biomarker methylation, the sensitivity of the 5-marker panel for BE diagnosis was 93%, with 90% specificity in the training set and 93% specificity in the test set. Areas under the curve (AUCs [for which 0.5 indicates *random guessing* and 1 indicates *perfect performance*]) were 0.96 and 0.97 in the training and test sets, respectively.[52]

EsoCheck is designed to collect cells from a targeted region of the esophagus without the need for endoscopy. The sampled cells can then be subjected to any commercially available diagnostic test. A pilot study using a 2-biomarker assay (CCNA1 and VIM) showed 95% sensitivity and 91% specificity.[53]

Risk Prediction

An unmet need remains for a more targeted, patient-centered approach to identify individuals with BE as well as those who are likely to progress to dysplasia and are candidates for EET. Several clinical features and biomarkers have been proposed, and models have been developed and validated for identifying prevalent BE or predicting progression to future EAC.[54]

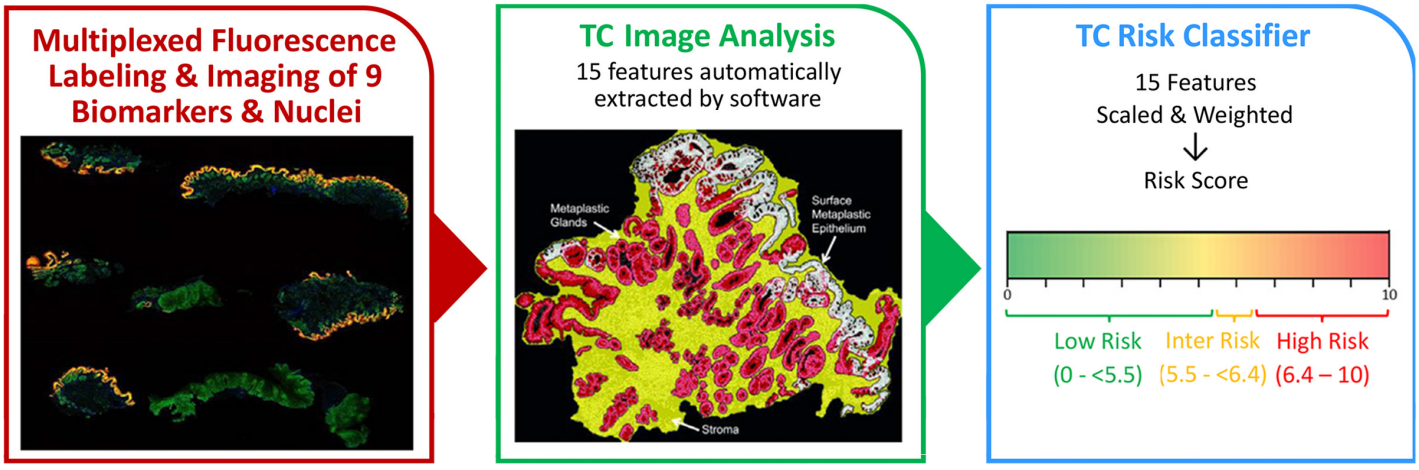


Figure 3. Overview of the TC Barrett's esophagus assay.[69]

TC, TissueCypher.

BE Length

One factor that has emerged as an important predictor of progression to EAC is the length of BE, which is measured using the Prague classification as the distance from the GEJ to the Z line and can be categorized as ultra-short (1-5 mm), short (5 mm-3 cm), or long (>3 cm).[24,55] Recent studies suggest that increasing lengths of BE are significantly associated with greater risk for progression to cancer, and although current guidelines do not recommend surveillance of patients with an irregular Z line only, careful examination of this region is recommended. Several gastroenterology societies, including the British Society of Gastroenterology (BSG),[56] the American College of Gastroenterology,[31] and the Australian Clinical Practice Guidelines,[57] recommend stratifying surveillance intervals according to the extent of BE.

P53

Immunohistochemistry (IHC) detection of the *P53* mutation has been suggested as a biomarker with prognostic and diagnostic significance in BE. It is recommended in some guidelines, such as those from the BSG.[56] However, detectable *p53* abnormalities are absent in some patients with BE and can be present in some individuals who do not develop HGD or EAC. *P53* testing is not recommended in US guidelines or routinely used in the United States.[34] The need for manual scoring and the fact that *P53* is only one among several epithelial and stromal biomarkers for progression represent additional drawbacks.[41]

Other risk-prediction strategies have been developed and are used to varying degrees in clinical practice. These include screening tools such as the Gerson Tool,[58] Locke Tool,[59] Thrift Tool,[60] Michigan Barrett's Esophagus pREdiction Tool,[61] Houston-Barrett's Electronic Screening Tool,[62] Kunzmann Tool,[63] Multi-Biomarker Risk Score,[64] Machine Learning Risk Prediction in Barrett's Esophagus,[65] and Progression in Barrett's Esophagus Score.[40] These tools were developed in various groups of patients, including individuals undergoing endoscopy or colonoscopy, large population-based screening cohorts, and those with BE participating in surveillance for EAC.[54,66] Factors assessed include patient age, sex, body mass index/abdominal obesity, ethnicity, tobacco use, education level, and family history; the presence of GERD and other esophageal symptoms; use of acid-reducing medications; serum biomarkers, including leptin and interleukins; and *H. pylori* status. AUCs for discriminating BE in development studies range from 0.61 to 0.87.[54,66]

Personalizing Risk Stratification With TissueCypher (TC)

Introduction to the Assay

A recent addition to the testing milieu is the TC Barrett's Esophagus Assay, the first FDA-approved artificial intelligence-driven precision medicine test designed to objectively identify patients with NDBE/IND/LGD who are at increased risk for malignant progression. The test takes a systems biology approach to computational anatomic pathology based on spatialomics, which incorporates the spatial context of cell populations and tissue systems while investigating morphology and biomarker expression. By considering the heterogeneity of the tissue microenvironment in deciphering location-dependent protein expression information, this approach quantifies genetic, immunologic, vascular, and morphologic features relevant to patient outcomes.[67] It can potentially improve current diagnostic techniques by capturing key features of the tissue environment and quantifying both genetic and nongenetic heterogeneity.[41]

The TC assay is performed on 5-micron sections of formalin-fixed, paraffin-embedded samples from routine biopsies from the Barrett's segment. The biopsies are labeled by multiplexed immunofluorescence and imaged via whole-slide fluorescence scanning.[47] The resulting images are analyzed using automated analysis software that extracts quantitative data on 9 biomarkers that measure loss of tumor suppressor genes (*p53, p16*), alterations in lipid metabolism (alpha-methylacyl-CoA racemase), amplification of oncogenes (*HER-2*), immune infiltration (CD68, cyclooxygenase 2), angiogenesis (HIF-1α, CD45RO), and apoptotic cells (cytokeratin 20) in addition to morphometric features (nuclear size, shape, and amount of DNA).[42,68] Abnormalities detected/quantified include loss of tumor suppression, loss of cell-cycle control, morphologic changes, increased inflammation, stromal angiogenesis, and altered patterns of infiltrating immune cells.[42] A multivariable classifier integrates the image analysis data into individualized risk scores ranging from 0 to 10 that correspond with low (0-5.5), intermediate (5.5-6.4), or high (6.4-10) risk for progression to HGD/EAC within 5 years (**Figure 3**).[35,67-69]

A low-risk result can allow for the extension of surveillance intervals and reduction in unnecessary medical procedures for selected patients. Conversely, a high-risk result could trigger a change to shorter surveillance intervals or intervention with EET to prevent progression to EAC.

The assay can be used on small tissue samples to extract molecular and spatial information from the tissue system and the preneoplastic field.[42] By providing personalized quantitative/objective measurement, independent of histologic diagnosis or presence of dysplasia or clinical risk factors, TC is an adjunctive tool to improve objectivity and accuracy in risk-stratifying patients, contributing to risk-tailored management. In its Best Practices publication, the AGA noted that the "TissueCypher assay may be of benefit for risk stratification of patients with NDBE."[25]

The clinical body of evidence for TC includes several independent investigations that studied progressors and nonprogressors across the United States and Europe. Key studies are described below.

Technical Feasibility Study

A 2015 technical feasibility study demonstrated that TC detected statistically significant differences between BE biopsies with HGD and ND biopsies with reactive atypia, indicating that assessment of tissue for epithelial cell abnormalities and cellular changes in the lamina propria may serve as an adjunct to conventional pathology in the assessment of BE.[41] This study showed that the same formalin-fixed paraffin-embedded tissue blocks used for routine pathology could be used for multiplexed fluorescence biomarker labeling and quantitative image analysis and that TC consumes less of the biopsy tissue than traditional pathology by imaging multiple biomarkers in separate fluorescence channels on each slide. It also found that the assay revealed molecular and cellular differences that may not be evident with traditional methods and single-marker IHC staining with manual interpretation.[41]

Clinical Validation Studies

Four clinical validation studies were conducted to further clarify the use of TC.

Establishing risk categories

The first clinical validation study compared data for patients with baseline histologic diagnoses of NDBE, IND, or LGD who progressed to HGD or EAC in at least 1 year (n=79) matched with patients who did not progress (n=287).[67] Training and validation sets were used to establish cut points for low-risk (0 to <5.5), intermediate-risk (5.5 to <6.4), and high-risk (6.4 to 10) TC scores. The predicted high-risk group had a 9.4-fold increased risk for developing HGD/EAC compared with the low-risk group. These risk classes provided independent predictive information that outperformed traditional risk factors, including general pathologists and expert GI diagnoses. The authors noted that patients with high-risk BE have "loss of tumor suppression and cell-cycle control, stromal angiogenesis, altered patterns of infiltrating lymphocytes, increased inflammation, and morphology abnormalities, which are early indicators of progression."[67]

Detecting prevalent HGD/EAC

The second clinical validation study showed that TC detected prevalent HGD/EAC missed by standard white-light endoscopy and histology in patients with BE.[42] In this case–control study, the assay was performed on ND, IND, and LGD biopsies from 30 patients with HGD/EAC identified up to 1 year from BE diagnosis and 145 patients without prevalent or incident HGD/EAC. The AUC for the TC test to distinguish those with prevalent HGD/EAC from those without was 0.89. The risk for prevalent HGD/EAC was 46 times higher in the high- vs low-risk groups, and the predictive power of TC was greater than that of expert GI and general pathologist diagnosis in detecting prevalent HGD/EAC in NDBE.[42]

Detecting incident progression

Another trial examined the ability of TC to predict risk for future progression to HGD/EAC within 5 years in BE patients.[47] This study included samples from individuals with BE that were ND (n=227), IND (n=23), or LGD (n=18) who progressed to HGD/EAC with a median time to progression of 2.7 years, and 210 patients showing no progression to HGD/EAC with a median surveillance time of 7 years. Using the cutoffs identified previously, a high-risk TC score predicted a 4.7-fold increased risk for progressing to HGD/EAC compared with a low-risk score (95% CI, 2.5-8.8; $P<0.0001$). The prevalence-adjusted positive predictive value (PPV) at 5 years was 23%, indicating that 23% of patients who scored high-risk would progress to HGD/EAC within 5 years. The prevalence-adjusted negative predictive value (NPV) was 96.4%, indicating that 96.4% of low-risk patients would not progress to HGD/EAC within 5 years.[47]

This study also identified a subset of patients with NDBE who nonetheless scored high risk on TC and progressed at a higher rate (26%) than those with expert-confirmed LGD (21.8%) at 5 years.[47] The authors concluded that "a high-risk score in patients with ND[BE] may support the early use of [EET] or increased surveillance to prevent HGD/EAC. This is a crucial finding because these are the 'at-risk' group who are not identified by the current standard of care."[47]

Finally, the results supported the idea that analysis of multiple spatial levels of the esophagus provides key information for risk stratification. Among progressors with a low-risk class on at least 1 biopsy level, 39.1% were upstaged to intermediate (17.4%) or high risk (21.7%) when another biopsy level from the same endoscopy was assessed.[47]

Confirming incident prediction and the at-risk subset

Adding to this accumulated knowledge, the fourth validation study confirmed the ability of TC to predict incident progression in patients with NDBE and identify those with NDBE who progress at a higher rate than those with expert-confirmed LGD.[69] For this investigation, samples from patients with NDBE and LGD were prospectively analyzed using endoscopy (38 progressors and 38 nonprogressors). A high-risk TC score was associated with a prevalence-adjusted annual progression rate of 6.9% in patients with NDBE. The overall prevalence-adjusted PPV and NPV for prediction of progression within 5 years were 34.6% and 97.7%, respectively. The assay identified 50% of those who progressed from NDBE to HGD/EAC.[69]

When only the most distal biopsy level was evaluated, high-risk scorers were 3.2 times more likely to progress to HGD/EAC than low-risk scorers ($P=0.0032$), and 30.4% of patients who progressed scored high risk (sensitivity, 30.4%), whereas 95% of those who did not progress scored low or intermediate risk (specificity, 95%).[69] When multiple levels were examined, high-risk patients were 5.5 times more likely to progress than low-risk patients ($P\leq0.0001$). This suggested that all available biopsies from an endoscopy should be submitted for testing for the fullest possible assessment and that brushes or sponges that sample large areas may be useful. The authors concluded that TC could identify NDBE progressors before the appearance of morphological changes associated with dysplasia and that patients scoring high risk should be referred to specialists with expertise in BE and managed similarly to those with confirmed LGD, including considering shorter surveillance intervals or EET or preventive endoscopic ablation.[69]

Cost-Effectiveness Study

A 2019 study demonstrated that TC-directed patient management was cost-effective and may be associated with improved health care utilization and patient outcomes vs standard-of-care (SOC)-directed surveillance and treatment.[32] This study used Markov decision

modeling and simulation to compare cost and quality-adjusted life-years in a hypothetical cohort of 10,000 patients with a diagnosis of BE from the perspective of a US health insurer with care delivered by an integrated health system. SOC was based on clinical guidelines and the system's usual practices.[32]

Results showed that targeting endoscopic therapies to patients who scored high risk increased the use of such treatments by 58.4%, which reduced the progression to HGD and EAC by 51.7% and 47.1%, respectively, and reduced EAC-related deaths by 37.6%, over the 5 years.[32] A surveillance interval of 5 years in the low-risk group, independent of the pathologic diagnosis of dysplasia, reduced the use of endoscopy by 16.6%. Sensitivity analyses indicated that although the assay strategy would add cost during the initial 3 years of adoption, it was estimated to lower future costs and improve outcomes over 5 years due to reduced surveillance in low-risk patients and early treatment in high-risk patients.[32]

Retrospective Cohort Studies Using the SURF Cohort

Three studies retrospectively analyzed samples and data from the screening cohort of the SURF (SURveillance vs RadioFrequency ablation) randomized clinical trial, which enrolled BE patients with community-practice diagnoses of LGD at 9 European sites between June 2007 and June 2011.[70] These trials compared the performance of TC with that of generalist and expert pathologists in predicting the progression of BE.

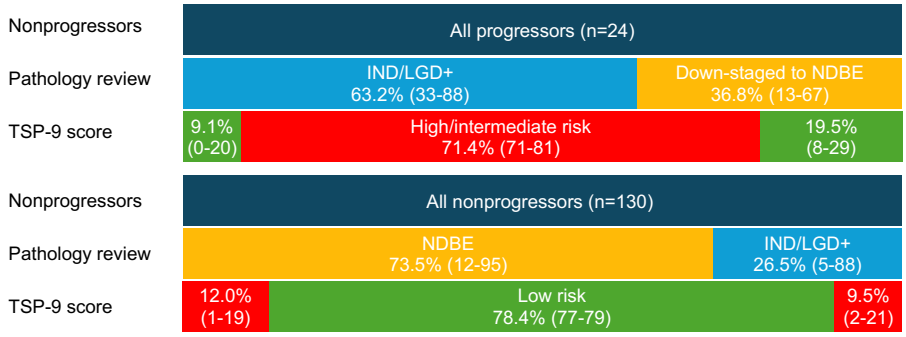


Figure 4. TC performance vs pathologists in detecting progressors.[72]

Comparison of diagnoses and TC test results in subsets of patients who progressed (A; n=24) and did not progress (B; n=130) to HGD/EAC within 5 years. Mean and [range] are shown.

EAC, esophageal adenocarcinoma; **HGD,** high-grade dysplasia; **IND,** indefinite for dysplasia; **LGD,** low-grade dysplasia; **NDBE,** nondysplastic Barrett's esophagus; **TC,** TissueCypher; **TSP,** Tissue Systems Pathology Test.

Focusing on LGD

The first of these examined outcomes for 155 patients.[34] Slides were reviewed; classified as LGD, IND, or NDBE by 3 expert pathologists; and tested by the TC assay. Patients who scored high risk on TC were 6.7 times more likely to progress to HGD/EAC than those who scored low risk. When TC and pathology results were assessed adjunctively, up to 85.3% of progressors were detected. Notably, the assay detected 56% of progressors who had been down-staged to NDBE by the pathologists. This patient cohort may be missed by the current SOC but could benefit from preventive EET. In this study, the 3 pathology experts agreed on only 51.7% of cases, underscoring the significant interobserver variability in standard biopsy analysis.[34]

Another blinded cohort study of the SURF screening population (N=154) compared the accuracy of predicting HGD/EAC from biopsies analyzed by TC and a larger group of 16 generalists and 14 expert pathologists from 5 countries.[71] In this cohort, TC demonstrated higher sensitivity vs pathology review in detecting patients who progressed (71% vs 63%; *P*=0.01186), and when it was used in conjunction with pathology, the sensitivity of the pathologist diagnoses of IND/LGD increased from 63.2% to 80.4% (*P*=0.00000176; **Figure 4**).[71]

There was wide variability in predictive accuracy by generalists and only moderate agreement even among expert pathologists in this study (κ coefficient, 0.43 [with ≤0 indicating *no agreement* and 1.0 indicating *perfect agreement*). For the pathologists in the lowest 10th percentile in terms of sensitivity, the addition of TC increased their sensitivity from ≤46% to ≤79%. However, the combined predictor had lower specificity and PPV than the TC test alone and demonstrated significant variability depending on which pathologist reviewed the slides, indicating that TC alone provided overall higher accuracy and reliability in clinical use.[71]

Notably, pathologists down-staged 36.8% of progressors to NDBE, and TC identified 43% of these individuals. This high-risk subset may be missed by pathology review but detected by the assay. TC also down-staged more nonprogressors than pathology review. Using the 2 methods in conjunction improved sensitivity for the detection of progressors from ≤62.3% to ≤92%.[71]

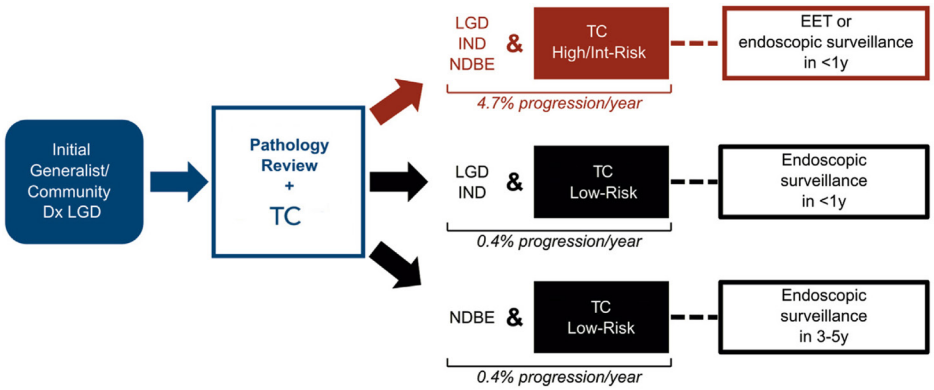


Figure 5. Proposed use of TC to aid the management of patients with BE with a community-based diagnosis of LGD; adjunctive use of the assay results with expert pathology review to guide management decisions.[72]

Dx, diagnosis; **EET,** endoscopic eradication therapy; **IND,** indefinite for dysplasia; **INT,** intermediate; **LGD,** low-grade dysplasia; **NDBE,** nondysplastic Barrett's esophagus; **TC,** TissueCypher.

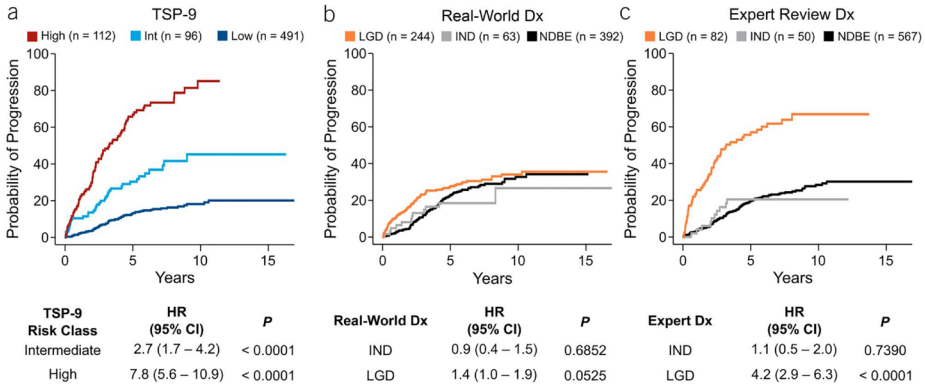
The authors of this study proposed a schematic to Illustrate the incorporation of TC data into the clinical management of patients with community diagnoses of BE (**Figure 5**).[71] For those with low-risk scores, surveillance is recommended in 3 to 5 years for NDBE and less than 1 year for LGD or IND. Those with intermediate- or high-risk scores are recommended to undergo EET or endoscopic surveillance in less than 1 year, regardless of their degree of dysplasia. The authors indicated that in some cases, TC could even be used independently rather than as an adjunct to pathology review.[71]

Standardizing management

The same cohort of SURF patients was analyzed in a study that modeled each patient's journey using diagnoses from 16 generalists and review by 14 expert pathologists.[72] Patient management decisions were randomly simulated 500 times to determine the most likely care plan with or without using TC results to guide management. Each simulation was scored according to whether the resulting management decision was appropriate based on known progression/nonprogression outcomes from the SURF trial.[72] Significantly more patients received appropriate management in the simulations that incorporated assay data vs SOC alone (100% vs 80.8%; *P*=0.0007) In addition, the percentage of patients with all simulations resulting in appropriate management increased significantly from 9.1% for pathology alone to 58.4% when TC was used with pathology, and further to 77.3% when only TC results were used.[72]

Among progressors, use of the assay increased the proportion of patients who received EET from 24.4% to 46.8% (*P*=0.024) and decreased the proportion who received long surveillance (3-5 years) from 33.4% to 0 (*P*=0.012). Among nonprogressors, using TC increased the use rate of long surveillance intervals from 81.7% to 100% (*P*=0.0081).[72]

Incorporating TC data also increased the consistency of decisions made by different pathologists. With SOC management alone, only 7.1% of patients had no deviation in management with review by different pathologists; with TC, this increased to 57.1%.[72] The authors concluded that TC clinically and statistically improved the SOC by increasing the likelihood of appropriate management decisions in all patients and decreasing the variability associated with dysplasia-directed care. Management guided by TC can standardize care plans by increasing the early detection of progressors receiving therapeutic interventions and increasing the percentage of nonprogressors who can avoid unnecessary therapy and be managed by surveillance alone.[72]



TSP-9 Risk Class	HR (95% CI)	P
Intermediate	2.7 (1.7 – 4.2)	< 0.0001
High	7.8 (5.6 – 10.9)	< 0.0001

Real-World Dx	HR (95% CI)	P
IND	0.9 (0.4 – 1.5)	0.6852
LGD	1.4 (1.0 – 1.9)	0.0525

Expert Dx	HR (95% CI)	P
IND	1.1 (0.5 – 2.0)	0.7390
LGD	4.2 (2.9 – 6.3)	< 0.0001

d

Multivariable Analysis Comparing Pathology Diagnosis versus TSP-9

TSP-9 Compared with Real-World Dx

Variable	HR (95% CI)	P
Real world – IND vs NDBE	1.0 (0.5 – 1.9)	0.92
Real world – LGD vs NDBE	1.3 (0.9 – 1.7)	0.16
TSP-9 – Intermediate vs Low	2.7 (1.7 – 4.3)	< 0.0001
TSP-9 – High vs Low	7.7 (5.5 – 11.1)	< 0.0001

TSP-9 Compared with Expert Dx

Variable	HR (95% CI)	P
Expert – IND vs NDBE	1.1 (0.5 – 1.9)	0.83
Expert – LGD vs NDBE	2.2 (1.5 – 3.4)	< 0.0001
TSP-9 – Intermediate vs Low	2.5 (1.6 – 4.0)	< 0.0001
TSP-9 – High vs Low	6.2 (4.4 – 8.9)	< 0.0001

Figure 6. Risk stratification with TC vs pathology diagnosis.[73]

Kaplan-Meier analysis of the probability of progression to HGD/EAC in patients with BE stratified into (a) low-, intermediate-, and high-risk TC classes; (b) NDBE, IND, and LGD subsets by real-world diagnosis abstracted from health records; and (c) NDBE, IND, and LGD by expert review. Multivariable analysis (d) compared prediction of progression by TC vs real-world and expert review. N=699 patients with BE, including 150 incident progressors, 40 patients with prevalent HGD/EAC, and 509 nonprogressors.

BE, Barrett's esophagus; CI, confidence interval; dx, diagnosis; **EAC,** esophageal adenocarcinoma; **HGD,** high-grade dysplasia; **HR,** hazard ratio; **IND,** indefinite for dysplasia; **LGD,** low-grade dysplasia; **NDBE,** nondysplastic Barrett's esophagus; **TC,** TissueCypher; **TSP,** Tissue Systems Pathology Test.

Pooled Analyses

Finally, 2 pooled analyses of TC have been conducted to examine the existing study data en masse. The first reviewed patient-level data from studies[34,47,67,69] predicting incident progression to HGD or EAC.[68] This included data for 552 patients with ND (n=472), IND (n=32), or LGD (n=48) at baseline, 152 of whom experienced incident progression and 400 who did not. A high-risk TC classification and expert-confirmed LGD emerged as independent predictors of increased risk for progression to HGD/EAC (OR, 6.0 and 2.9, respectively). When TC and expert confirmation were combined, the accuracy of the prediction increased significantly, both in the whole cohort (C-statistic, 0.75 vs 0.68; *P*<0.0001) and the NDBE subset (C-statistic, 0.72 vs 0.63; *P*<0.0001). The sensitivity and specificity of the high-risk TC classes were 38% and 94%, respectively. Notably, in patients with NDBE, a TC high-risk score predicted an 18-fold increased risk for progression vs a TC low-risk score and identified 52% of progressors, all of whom were missed by SOC assessment alone.[68]

The second pooled analysis expanded on these results by including 5 published studies in 699 individuals with BE[34,42,47,67,69] and evaluating the predictive performance of TC in clinically relevant patient subsets.[73] Key results included the following (**Figure 6**)[73]:

- The TC assay provided significant risk stratification in patients with NDBE, IND, or LGD (*P*<0.0001); those who scored high risk were 7.8 times more likely to progress than those who scored low risk (hazard ratio [HR], 7.8; *P*<0.0001).
- Overall, the sensitivity for detecting disease progression was 62.3% for TC vs 28.3% for expert pathologist-confirmed LGD. Used in conjunction with expert review, assay results detected 67.9% of progressors.
- TC results had stronger predictive power than clinicopathologic features, including segment

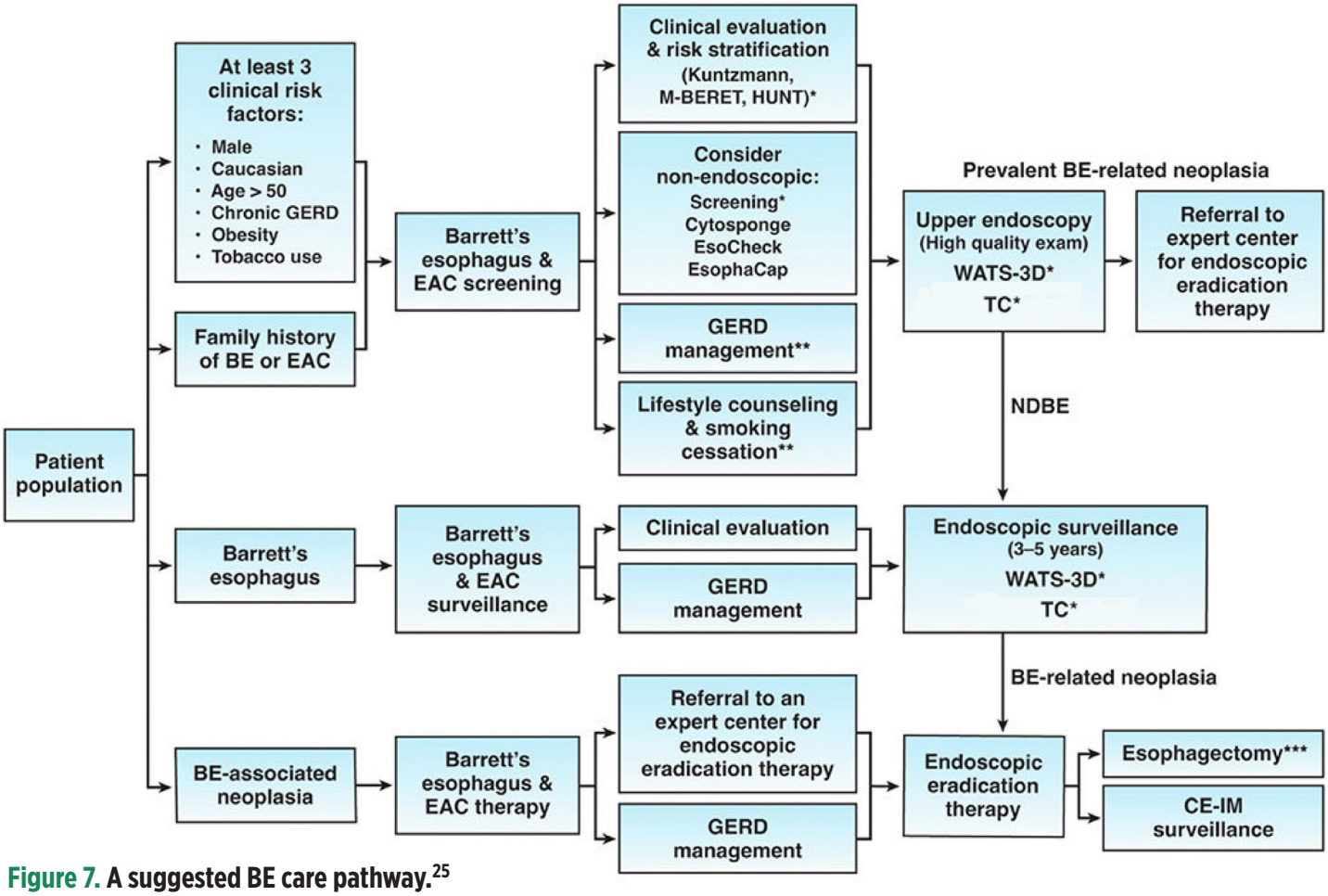


Figure 7. A suggested BE care pathway.[25]

* May be utilized as per best practice advice. ** When clinically appropriate. *** For T1b or higher stage cancers by EMR or neoplastic disease refractory to EET.

BE, Barrett's esophagus; **CE-IM,** complete eradication of intestinal metaplasia; **EAC,** esophageal adenocarcinoma; **GERD,** gastroesophageal reflux disease; **HUNT,** Nord-Trondelag Health Study; **M-BERET,** Michigan BE Prediction Tool; **NDBE,** nondysplastic Barrett's esophagus; **TC,** TissueCypher; **WATS-3D,** wide-area transepithelial sampling with computer-assisted 3D analysis.

length, hiatal hernia, age, sex, and pathology diagnosis.

- Patients with high- or intermediate-risk scores by the assay were 7 times and 2 times more likely to develop incident HGD/EAC than those with low-risk scores ($P<0.0001$ and $P=0.0079$, respectively)
- Those with NDBE who scored high risk progressed at a similar rate (3.2% per year) as those with expert pathologist-confirmed LGD (3.7% per year). This finding indicates that some patients with NDBE will benefit from being managed similarly to those with LGD. Despite having no observable morphologic changes consistent with dysplasia, their Barrett's mucosa may harbor molecular and cellular changes associated with an increased risk for progression.
- The assay demonstrated 77.5% sensitivity in detecting missed cases of prevalent HGD/EAC, compared with 50% for expert diagnosis of LGD. The test also provided significant risk stratification in patients considered to be clinically low-risk (NDBE, female, short-segment BE) and high-risk (IND/LGD, male, long-segment BE; $P<0.0001$ for comparison of high- vs low-risk classes). The findings add to the evidence that the TC assay predicts incident progression as well as the presence of missed prevalent HGD/EAC independent of clinicopathologic variables in a broad array of patients with BE.

Treatments for BE

Intervention strategies for patients with BE and dysplasia/early neoplasia include treatment for GERD and EET, including ablative techniques, endoscopic mucosal resection, and surgery. These should be considered in the context of an overall patient care pathway, as suggested in the recent AGA Clinical Practice Update (**Figure 7**).[25]

EET

The treatment strategy most used in BE with dysplasia is EET. This technique has significantly changed the management of BE-related neoplasia and is the subject of a new clinical practice guideline from the AGA (**Table 2**).[74] A minimally invasive approach, EET combines resection (endoscopic mucosal resection and/or endoscopic submucosal dissection) of visible lesions in the affected segment and ablative techniques, such as radiofrequency ablation and cryotherapy, to eradicate any residual, flat, NDBE. Data suggest that successful ablation of BE reduces the risk for developing cancer by 90%.[31] In one study, EET reduced the risk for progression from NDBE or LGD to EAC by 3.8- to 7.4-fold, leading to improved health outcomes.[75]

EET procedures are relatively safe but are not risk-free. Adverse events (AEs) can include esophageal stenosis (15%), post-procedural

bleeding (4%), and perforation (0.8%).[76,77] The overall risk for AEs with EET has been estimated at 8.8%.[77]

PPIs

Proton pump inhibitors (PPIs) are often prescribed to individuals with GERD, as some preclinical biomarker-based research and observational studies have demonstrated that these agents may prevent neoplastic progression in BE. For example, a systematic review and meta-analysis of observational studies found that PPI therapy was associated with a 71% reduction in the risk for HGD or EAC (adjusted OR, 0.29) in patients with BE.[78]

Epidemiologic studies also suggest that individuals using aspirin (or other nonsteroidal anti-inflammatory drug [NSAID]) in combination with a PPI seem less likely to develop EAC.[25] One mechanism of this effect involves NSAID-induced cyclooxygenase 1 and 2 (COX-1 and COX-2) inhibition, which modulates prostaglandin E2 (PGE2), a hormone associated with resistance to apoptosis, increased angiogenesis, and enhanced invasion in Barrett's mucosa and other GI neoplasias.[79] In a randomized phase 2 trial using downregulation of PGE2 as a surrogate biomarker and primary end point, 114 patients with BE were randomized to receive the PPI esomeprazole (40 mg twice daily) along with either high-dose (325 mg/day) or low-dose (81 mg/day) aspirin or placebo for 28 days.[79] Post-intervention esophageal biopsies demonstrated a statistically significant decrease in levels of PGE2 in the high-dose aspirin cohort, suggesting a benefit with this therapy.

Longer-term outcomes were studied in AspECT (Aspirin and Esomeprazole Chemoprevention in Barrett's metaplasia Trial), in which participants received either high-dose (40 mg twice daily) or low-dose (20 mg once daily) esomeprazole, with or without aspirin (300 or 325 mg/day) for at least 8 years.[80] In this trial, high-dose PPI significantly lengthened the time to reach the primary composite end point of time to all-cause mortality, esophageal adenocarcinoma, or HGD, compared with low-dose PPI (10.2 vs 8 years; P=0.0068). The effects of PPI and aspirin appeared to be additive, with patients taking high-dose PPI as well as aspirin having the strongest effect. With 20,095 participant-years of follow-up in 2557 patients, this large data set supported the conclusion that PPIs and aspirin can be used as chemopreventive therapy. However, several limitations of this trial are acknowledged. It was not double-blinded, the event rate was low, and only a small effect size was noted. The overall benefit was skewed toward all-cause rather than cancer-related mortality, which is more relevant to the BE population.

Table 2. Summary of Recommendations and Implementation Considerations From the 2024 AGA Clinical Practice Guideline on Endoscopic Eradication Therapy of Barrett's Esophagus and Related Neoplasia[74]

Recommendation	Implementation considerations
In individuals with BE with HGD, the AGA recommends EET over surveillance	• After completion of EET, surveillance should be performed at 3, 6, and 12 mo, then annually • Surveillance endoscopies after EET should obtain targeted tissue sampling of visible lesions and random biopsies of the cardia and distal 2 cm of the tubular esophagus
In individuals with BE with LGD, the AGA suggests EET over surveillance. Patients who place a higher value on the well-defined harms and lower value on the benefits (which are uncertain) regarding reduction of esophageal cancer mortality would reasonably select surveillance endoscopy	• After completion of EET, surveillance should be performed at years 1 and 3 after CE-IM, then revert to surveillance intervals used in NDBE • The tissue sampling protocol used should be the same during surveillance and after EET for HGD
In individuals with NDBE, the AGA suggests against the routine use of EET	NA
In patients undergoing EET, the AGA suggests resection of visible lesions followed by ablation of the remaining BE segment over resection of the entire BE segment	• In patients with only a small area of BE beyond the visible lesion, completion of endoscopic resection in the same setting is acceptable and may be preferred over repeated procedures to perform ablation • RFA is the preferred ablative modality
In individuals with BE with visible neoplastic lesions that are undergoing endoscopic resection, the AGA suggests the use of either EMR or ESD based on lesion characteristics	NA

AGA, American Gastroenterological Association; **BE,** Barrett's esophagus; **CE-IM,** complete eradication of intestinal metaplasia; **EET,** endoscopic eradication therapy; **EMR,** endoscopic mucosal resection; **ESD,** endoscopic submucosal dissection; **HGD,** high-grade dysplasia; **LGD,** low-grade dysplasia; **NA,** not applicable; **NDBE,** nondysplastic Barrett's esophagus.

Anti-Reflux Procedures

Anti-reflux procedures may also be an option for certain patients, as they can effectively reduce reflux episodes, heal esophagitis, and decrease associated symptoms.[81] The most relevant surgical option is fundoplication, which aims to create an effective barrier to reflux at the GEJ and thus attempt to improve physiologic and mechanical issues that may be involved in the pathogenesis of GERD. This can be performed as an open or laparoscopic surgery and can be total or partial. Variations include 120-degree anterior, 180-degree, 270-degree, and 360-degree Nissen fundoplication.[81]

However, it should be noted that data have not conclusively demonstrated that patients with BE who undergo anti-reflux procedures have a lower risk for progression to neoplasia than those treated medically. For example, the National Institutes for Health and Care Excellence, which completed a review of RCTs considering this question, concluded that based on current evidence, surgery cannot be recommended for prevention of progression to dysplasia or cancer in the setting of BE (although it can be offered as an alternative to patients who are intolerant to or unwilling to take long-term acid-suppression medication.[82] In addition, fundoplication carries a risk for acute postoperative AEs (including gas bloat, infection, bleeding, and perforation) in approximately 4.1% of cases, dysphagia in approximately 50% of cases, and prolonged structural and functional complications.[83]

Alternatives include transoral incisionless fundoplication, in which a new gastroesophageal valve is formed nonsurgically inside the stomach to enhance barrier function[84] and magnetic sphincter augmentation, which involves the implantation of a series of interlinked magnetic beads, which form a flexible ring that resists opening the lower esophageal sphincter to prevent reflux but expands to nearly twice its original size to allow for swallowing.[85,86]

Conclusion

Endoscopic screening to detect BE in selected patients with multiple risk factors for BE and subsequent endoscopic surveillance is supported by current guidelines, as these efforts can facilitate the early detection of BE, dysplasia, and neoplasia, as well as provide opportunities for treatment with EET. However, many patients with an advanced degree of dysplasia do not progress to EAC, and some patients with NDBE do progress. To improve surveillance efficiency and cost-effectiveness, efforts are needed to identify risk factors for malignant progression that extend beyond histologic dysplasia and to stratify BE patient management based on their individual risk for disease progression. Novel methods of precision testing that can help identify a patient's risk for progression to dysplasia or cancer will be essential in further optimizing and refining the management strategy for this condition.

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