

GUIDELINES

AGA Clinical Practice Guideline on Surveillance of Barrett's Esophagus



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BACKGROUND & AIMS: Barrett's esophagus (BE) is the only identifiable precursor to esophageal adenocarcinoma (EAC). Endoscopic surveillance has been proposed for early detection of BE-related neoplasia and reducing EAC mortality. This clinical practice guideline aims to inform clinicians and patients by providing evidence-based practice recommendations for surveillance in patients with BE. **METHODS:** The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence and make recommendations. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients, conducted an evidence review, and used the Evidence-to-Decision Framework to develop recommendations regarding the role of endoscopic surveillance in patients with BE. The clinical domains addressed included: (1) overall role of endoscopic surveillance, (2) surveillance in patients with columnar-lined esophagus <1 cm, (3) optimal imaging modalities, (4) adjunctive sampling techniques, (5) the utility of biomarkers in risk-stratification, (6) chemopreventive strategies, and (7) antireflux procedures in the prevention of progression in patients with BE. Clinical recommendations were based on the balance between the desirable and undesirable effects, patient values, costs, and health equity considerations. **RESULTS:** The panel agreed on 8 recommendations. Based on the available evidence, the panel provided a conditional recommendation in favor of surveillance for

patients with nondysplastic BE. In patients with columnar-lined esophagus <1 cm, a conditional recommendation was made against endoscopic surveillance. The panel made a strong recommendation in favor of a combination of high-definition white light endoscopy and chromoendoscopy compared with white light endoscopy alone. The panel made no recommendation on the use of enhanced sampling techniques, such as wide-area transepithelial sampling to enhance neoplasia detection and biomarkers such as p53 and TissueCypher to predict progression in BE. The panel provided a conditional recommendation for the use of daily proton pump inhibitor therapy compared with no therapy and compared with antireflux surgery to prevent progression in BE. **CONCLUSIONS:** This document provides a comprehensive outline on the role of surveillance in patients with BE. Key implementation statements included in this document stress the importance of a high-quality endoscopy examination, sampling using a structured biopsy protocol, and confirming the diagnosis of BE-related neoplasia by an expert pathologist. This document also provides guidance on surveillance intervals and management of patients with BE-related low-grade dysplasia and indefinite for dysplasia. Providers should engage in shared decision making based on patient preferences. Limitations and gaps in the evidence are highlighted to guide future research opportunities. **GUIDELINE ENDORSEMENT:** This guideline is endorsed by the Canadian Association of Gastroenterology.

Keywords: Barrett's Esophagus; Esophageal Adenocarcinoma; Surveillance; Chromoendoscopy; Biomarkers; Chemoprevention; Proton Pump Inhibitor; Antireflux Surgery.

Executive Summary

Esophageal adenocarcinoma (EAC) is a lethal cancer with increasing incidence and sobering mortality rates over the past several decades.¹ The incidence of EAC rose 5-fold from the 1970s to the 2010s, and adenocarcinoma now represents the most common form of esophageal cancer in Western populations, with a dismal overall 5-year survival rate of approximately 20%.² Survival from all but the earliest stage of EAC remains poor.³ Barrett's esophagus (BE) is the only identifiable precursor lesion for EAC and characterized by replacement of squamous epithelium in the distal esophagus by metaplastic specialized columnar epithelium in response to chronic gastroesophageal reflux-induced injury and inflammation.^{4,5} Recent evidence suggests that most cases of EAC arise from BE or from intestinalized metaplastic precursor cells in the gastric cardia.^{4,6} BE is believed to progress to EAC in a stepwise and probabilistic fashion through steps of low-grade dysplasia (LGD), then high-grade dysplasia (HGD), before developing into invasive EAC. Given that the prognosis of EAC is strongly related to stage at diagnosis, endoscopic surveillance in patients with BE has been proposed with the goal of early detection of BE-related neoplasia. These patients can then be referred for endoscopic eradication therapy (EET), reducing the morbidity and mortality related to esophagectomy and ultimately preventing EAC mortality.⁷⁻¹⁰

Objective of the Review and Guideline

The American Gastroenterological Association (AGA) developed this clinical practice guideline to provide evidence-based recommendations for endoscopic surveillance in patients with BE. Importantly, the role of EET was addressed in a recent AGA guideline¹⁰ and screening for BE and EAC will be addressed in a future guideline document. This document addresses the overall role and effectiveness of endoscopic surveillance, endoscopic surveillance in patients with columnar-lined esophagus <1 cm, optimal imaging strategies, adjunctive sampling techniques to improve detection, biomarkers and other risk stratification strategies to guide surveillance, chemoprevention and antireflux procedures for prevention of progression in patients with BE.

Target Audience

The target audience for these guidelines includes primary care, internal medicine, family medicine, gastroenterology, oncology, and surgery health care providers; patients; and policy makers. These recommendations are not intended to be used as the standard of care, but as a guide to facilitate management of patients with BE and

related neoplasia.¹⁰ Each recommendation in this guideline is accompanied by implementation considerations or qualifying remarks that should be considered an integral part of the recommendation statement and should not be omitted. Although no single recommendation can encompass every individual circumstance and context, it can be used to address the benefits and harms of treatments and support the processes of shared decision making based on patients' values and preferences.

Methods

Overview

This document represents the official recommendations of the AGA. These recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework for diagnostic tests and strategies and adheres to best practices in guideline development, as outlined by the National Academy of Medicine ([Supplementary Tables 1 and 2](#)).¹¹

Organization and Panel Composition

The guideline panel included 14 members with clinical expertise in BE and methodologic expertise (1 senior and 3 junior guideline methodologists). Members of the AGA guideline committee helped review all the synthesized evidence, contributed to discussion, and helped develop the clinical decision support tool. A librarian assisted with designing and executing the relevant literature searches.

Management of Conflict of Interest and Guideline Funding

Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies, the National Academy of Medicine, and Guidelines International Network standards.¹²⁻¹⁴ Development of this guideline was wholly funded by the AGA Institute with no support from the industry. A full list of conflicts can be accessed at the AGA's National Office in Bethesda, MD.

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Abbreviations used in this paper: AGA, American Gastroenterological Association; AI, artificial intelligence; BE, Barrett's esophagus; CD, crypt dysplasia; CE, chromoendoscopy; DDR, dysplasia detection rate; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; EtD, Evidence to Decision; EET, endoscopic eradication therapy; FN, false negative; FP, false positive; GERD, gastroesophageal reflux disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HGD, high-grade dysplasia; HR, hazard ratio; IHC, immunohistochemistry; IND, indefinite for dysplasia; LGD, low-grade dysplasia; MA, meta-analysis; NBI, narrow-band imaging; NDBE, nondysplastic Barrett's esophagus; NDR, neoplasia detection rate; NPV, negative predictive value; OR, odds ratio; PEEC, post-endoscopy esophageal adenocarcinoma; PEEN, post-endoscopy esophageal neoplasia; PICO, Population, Intervention, Comparison, Outcome; PPI, proton pump inhibitor; PPV, positive predictive value; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse events; SR, systematic review; TN, true negative; TP, true positive; VCE, virtual chromoendoscopy; WATS-3D, wide-area transepithelial sampling; WLE, white light endoscopy.

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0016-5085/\$36.00

<https://doi.org/10.1053/j.gastro.2025.09.012>

Scope

The guideline panel and evidence review team formulated clinically relevant questions on endoscopic surveillance strategies and therapies for BE and related neoplasia. The most recent comprehensive position paper by the AGA on BE was published in 2011, and included guidance on screening, surveillance, biomarkers, and endoscopic therapy.¹⁵ Since then, the AGA has published Clinical Practice Updates on the management of BE with LGD,¹⁶ endoscopic submucosal dissection (including outside the setting of BE),¹⁷ endoscopic treatment of neoplastic BE,¹⁸ screening and surveillance,¹⁹ and most recently, clinical practice guideline on EET of BE and related neoplasia using the GRADE framework.¹⁰

Formulation of Clinical Questions and Determining Outcomes of Interest

Through an iterative process, the guideline panel outlined focused clinical questions related to endoscopic surveillance in patients with BE that were then used to define patients, intervention, comparator, and outcomes (PICO) and used to inform the study inclusion and exclusion criteria and guided the literature search. The AGA Governing Board approved the final set of questions (Table 1).

Search Strategy

Using an *a priori* protocol, an information specialist helped search for recently published systematic reviews and meta-analyses (SR/MA) that used a comprehensive search strategy (PubMed, Embase, and Cochrane Library). We updated the searches to January 2025. When no pre-existing SR/MA meeting our inclusion criteria was identified, a new comprehensive search was conducted on the following databases: Embase, MEDLINE, Cochrane, and PubMed. The search terms used, and the final strategy can be found in the [Supplementary Material \(Supplementary Table 3\)](#). References from published studies and prior guidelines were searched to identify any missing relevant studies. Furthermore, content experts aided in the identification of potentially relevant ongoing studies.

Study Selection, Data Collection, and Analysis

Using Rayyan bibliographic software,²⁰ 2 experts independently screened each title and full-text review of the eligible studies to reach consensus and any conflicts were resolved by the senior methodologist (see [Supplementary Figure 1](#) for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram).²¹ In summary, we prioritized randomized controlled trials (RCTs) and observational studies with control arms (when RCT data were not available or sparse). Data were extracted from each study and MAs were conducted when possible using the generic inverse variance method of weighting and applied the random-effects model (or fixed-effects model when ≤ 3 studies were included) using either STATA software, version 14.2 (StataCorp, College Station, TX, 2015) or Review Manager RevMan software, version 5.3 for comparative studies (Copenhagen, Denmark, The Cochrane Collaboration, 2014), and OpenMeta analyst for statistical analyses of single arm studies (OpenMetaAnalyst, B.

C. Wallace, I. J. Dahabreh, T. A. Trikalinos, J. Lau, P. Trow, and C. H. Schmid). Statistical heterogeneity was assessed using the I^2 index. For risk of bias assessment of diagnostic accuracy studies, we used the revised QUADAS-2 tool²² for diagnostic accuracy studies, the Newcastle Ottawa tool²³ for observational studies and Cochrane risk-of-bias tool for RCTs.

Certainty of the Evidence

We used the GRADE approach to assess the certainty of evidence using the software GradePro Guideline Development Tool (<https://grade.pro.org>). The GRADE approach considers factors, such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias, to rate the certainty of evidence as high, moderate, low, or very low ([Supplementary Tables 1 and 2](#)).²⁴ The results of certainty assessment are reported in evidence profiles available in for all the interventions.

Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence-to-Decision (EtD) framework and consensus was achieved by discussion during virtual meetings of the committee.²⁵ The EtD framework considers the certainty of evidence, balance of benefits and harm, patient values and preferences, feasibility, acceptability, equity, and resource use.²⁵ All EtD tables are presented in the document. The interpretation of strength of recommendations is summarized in [Supplementary Table 2](#). In situations when the recommendation is only supported with very low certainty for the benefits and very low certainty for potential harms, the guideline panel put a higher value on risk avoidance.

Document Review

The guideline underwent external peer review and public comments, and the final document was revised to address pertinent comments.

Recommendations

As outlined, a summary of the recommendations and the accompanying implementation considerations is provided in [Table 2](#). A clinical decision support tool is presented in [Figure 1](#).

Endoscopic Surveillance

In patients with NDBE, endoscopic surveillance may allow for early detection of BE-related neoplasia (early EAC or HGD) and endoscopic eradication with the goal of reducing morbidity and mortality associated with esophagectomy and EAC-related mortality.⁷⁻¹⁰ The panel deemed the following outcomes as critical: EAC-specific mortality, all-cause mortality, detection of early stage EAC and HGD, and complications from diagnostic esophagogastroduodenoscopy (EGD). EAC diagnosis was an important outcome ([Table 1](#)).

Table 1. Population, Intervention, Comparison, Outcome Questions

Focused question	Patients	Intervention	Comparator	Outcomes
1. Should patients with BE without dysplasia undergo endoscopic surveillance?	Adult patients with NDBE	Endoscopic surveillance	No surveillance	Benefits: Reduction in EAC-related mortality (critical) Reduction in all-cause mortality (critical) Earlier stage of EAC detection (critical) Harms: Bleeding Perforation SAEs
2. Should patients with columnar-lined esophagus <1 cm with intestinal metaplasia undergo endoscopic surveillance?	Adult patients with columnar-lined esophagus <1 cm	Endoscopic surveillance	No surveillance	Benefits: Progression to EAC (critical) Progression to HGD/EAC (critical) Reduction in EAC mortality Harms: Bleeding Perforation SAEs
3. What is the optimal imaging strategy for patients with BE undergoing endoscopic surveillance?	Adult patients with BE undergoing surveillance	CE (standard or virtual) plus high-definition WLE	WLE	Benefits: Increased yield of neoplasia (dysplasia and EAC) detection (critical) Reduction in rates of PEEC and PEEN Improved diagnostic characteristics for neoplasia detection (sensitivity and specificity) Reduction in the number of biopsies required Time to complete endoscopy Harms: Bleeding Perforation AEs related to dye-based chromoendoscopy Serious adverse events
4. What is the role of adjunctive sampling techniques in patients undergoing surveillance endoscopy?	Adult patients with BE undergoing surveillance	Structured biopsy protocol plus WATS-3D sampling	Structured biopsy protocol	Benefits: Increased yield of neoplasia (dysplasia and EAC, excluding CD or IND) detection (critical) Reduction in rates of PEEC and PEEN Prediction of development of dysplasia or progression Harms: Bleeding Perforation SAEs

Table 1. Continued

Focused question	Patients	Intervention	Comparator	Outcomes
5 and 6. In patients with BE undergoing surveillance endoscopy, is the use of biomarkers superior to grade of dysplasia in prediction of progression?	Adult patients with BE undergoing surveillance endoscopy (stratified by NDBE, IND/LGD)	Combination of p53 staining with histology Combination of TissueCypher with or without histology	Standard histopathology	Benefits: Diagnostic characteristics (sensitivity, specificity, TP, TN, FP, and FN) (critical outcome) Improved prediction of progression to HGD/EAC (critical outcome) Proportion of cases with change in management (EET, change in frequency of surveillance endoscopy)
7. What is the role of chemopreventive strategies in prevention of progression in patients with BE?	Adult patients with BE	Once-daily PPI PPI plus aspirin Twice-daily PPI therapy	No PPI therapy Daily PPI therapy	Benefits: Reduction in progression to EAC (critical) Reduction in progression to HGD/EAC (critical) Reduction in EAC mortality Harms: AEs related to PPI therapy AEs related to aspirin therapy
8. What is the role of antireflux procedures in the prevention of progression in patients with BE?	Adult patients with BE	Antireflux procedures	PPI therapy	Benefits: Reduction in progression to EAC (critical) Reduction in progression to HGD/EAC (critical) Reduction in EAC mortality Harms: AEs related to PPI therapy AEs related to antireflux surgery

What is the role of endoscopic surveillance in patients with nondysplastic Barrett's esophagus?

Recommendation 1: In patients with NDBE, the AGA suggests performing endoscopic surveillance compared with no surveillance. (Conditional recommendation, low certainty of evidence)

Implementation Considerations

- Data supporting optimal surveillance intervals is limited but most experts on the panel advise a high-quality endoscopy every 3 years. Surveillance intervals may be extended to every 5 years in patients at lower risk of progression, for instance, those with short-segment BE (<3 cm).
- Discontinuation of surveillance endoscopy in patients with NDBE should be considered based on age and medical comorbidities.

Summary of the Evidence

Evidence informing this recommendation is derived from an RCT, comparative cohort studies, and case-control studies. A prior SR/MA of observational studies (1996–2017) evaluated the association of BE surveillance on EAC-related mortality, overall mortality, and stage at diagnosis.²⁶ We updated the search (2017 through January 2025) and identified 832 studies, of which 36 underwent full-text review, but no new relevant comparative cohort studies were identified (Supplementary Table 3). The only available new evidence was a recently published RCT, the Barrett's Esophagus Surveillance vs Endoscopy at Need Study (BOSS trial).²⁷ The SR/MA by Codipilly et al²⁶ included 4 cohort studies with the largest study by El-Serag et al²⁸ comparing 209 patients diagnosed with EAC during surveillance vs 215 patients with EAC with prior BE diagnosed by nonsurveillance endoscopy. The BOSS trial conducted at 109 centers in the United Kingdom, randomized 1733 patients to surveillance endoscopy every 2 years and 1719 patients were offered "at need" endoscopy only for evaluation of symptoms. For the primary outcome of overall survival (including cancers aside from EAC), median follow-up was 12.8 years. Mean age at time of randomization was 63 years, 71% of patients were male, and 56% of patients had long-segment BE.

Harms of surveillance endoscopy were assessed using 2 large national databases and the BOSS trial. Kim et al²⁹ retrospectively evaluated 387,647 patients in Korea who underwent upper endoscopy and reported serious complications within 30 days of procedure including bleeding, perforation, and cardiopulmonary events. Wang et al³⁰ evaluated more than 7 million upper endoscopies in the United States and assessed for infections within 7 days of endoscopy.

Benefits

For EAC-specific mortality, the SR/MA by Codipilly et al²⁶ found a pooled relative risk (RR) of 0.60 (95% CI,

0.50–0.71) corresponding to 231 fewer EAC deaths per 1000 (from 289 fewer to 168 fewer) (Table 3). Overall survival data came from the BOSS trial, which randomized 3453 patients to surveillance every 2 years vs symptom-triggered endoscopy, with a median follow-up of 12.8 years. The primary outcome, overall survival, showed no significant difference between groups (hazard ratio [HR], 0.95; 95% CI, 0.82–1.10), with an absolute difference of 9 fewer deaths per 1000. Supporting evidence from Codipilly et al showed a modest mortality benefit (HR, 0.75; 95% CI, 0.59–0.94), which persisted after adjusting for lead-time bias (HR, 0.85; 95% CI, 0.75–0.95).

Data for the critical outcome of overall survival were derived from the BOSS trial. All-cause mortality in the surveillance group was 19.2% (333 deaths in 1733 patients) vs 20.7% in the "at need" endoscopy group (356 deaths in 1719 patients) (HR, 0.95; 95% CI, 0.82–1.10). The absolute risk reduction in the group undergoing scheduled endoscopic surveillance was 9 fewer per 1000 (from 34 fewer to 18 more) (Table 3). As supportive evidence, for the outcome of all-cause mortality, the SR/MA by Codipilly et al²⁶ examined 3 studies with comparative groups and found an HR of 0.75 (95% CI, 0.59–0.94). The SR/MA also performed sensitivity analyses attempting to adjust for lead-time bias for the outcome of all-cause mortality, which also found an attenuated reduction in mortality in the group undergoing endoscopic surveillance vs no surveillance (HR, 0.85; 95% CI, 0.75–0.95). Data for the important outcome of stage of EAC diagnosis, early-stage EAC and HGD detection was higher in the scheduled surveillance group, 3.3% (58 of 1733 patients) vs 1.2% (20 of 1719 patients) in the at-need surveillance group (RR, 2.82; 95% CI, 1.73–4.56) with 21 more cases of early-stage EAC/HGD detected per 1000 (from 8 more to 41 more). Additional evidence from Codipilly et al also showed cohorts with prior BE diagnosis were significantly more likely to present with earlier stage EAC (stage 0/I) compared with cohorts without a prior diagnosis of BE (RR, 5.52; 95% CI, 3.7–8.24; $I^2 = 96\%$) (Table 3).

Harms

Harms of surveillance endoscopy were assessed using 2 large databases. Assessing for adverse events within 30 days after endoscopy, Kim et al²⁹ reported low rates of serious complications: bleeding (7.9 per 10,000 persons), perforation (0.4 per 10,000 persons), cerebrovascular accidents (2.8 per 10,000 persons), acute myocardial infarction (2.8 per 10,000 persons), and congestive heart failure (1.5 per 10,000 persons). In a US study of more than 7 million endoscopies, Wang et al³⁰ found a 7-day post-endoscopy infection rate after of 30 per 10,000 individuals, with respiratory infections in 0.3% of patients and bacteremia in 0.07% of patients. The BOSS trial reported serious adverse events (SAEs) in 8 patients (0.46%) in scheduled surveillance and 7 patients (0.41%) in the "at need" endoscopy group.²⁷

Certainty of the Evidence

The overall certainty of evidence for benefits and harms was low (Table 3). For EAC-related mortality, evidence

Table 2. Summary of Recommendations and Implementation Considerations

Recommendations	Strength of recommendation	Certainty of evidence
Endoscopic Surveillance		
1. In patients with NDBE, the AGA suggests performing endoscopic surveillance compared to no surveillance. <i>Implementation considerations for recommendation 1:</i> - Data supporting optimal surveillance intervals is limited but most experts on the panel advise a high-quality endoscopy every 3 yr. Surveillance intervals may be extended to every 5 yr in patients at lower risk of progression, for instance those with short-segment BE (<3 cm). - Discontinuation of surveillance endoscopy in patients with NDBE should be considered based on age and comorbidities.	Conditional	Low
2. In patients with columnar-lined esophagus <1 cm with intestinal metaplasia, the AGA suggests against surveillance endoscopy.	Conditional	Very Low
3. In patients undergoing surveillance endoscopy for BE, the AGA recommends using a combination of high-definition WLE plus CE compared WLE alone. <i>Implementation considerations for recommendation 3:</i> - Among the CE modalities that meet optimal performance characteristics, the choice of CE modality (virtual or dye-based CE) should be based on endoscopist and center expertise. - CE-directed biopsies should be used as an adjunct to sampling using a structured biopsy protocol. - A structured biopsy protocol includes targeted biopsies from any visible lesions and random 4-quadrant biopsies every 2 cm if no history of dysplasia and every 1 cm if there is a history of dysplasia.	Strong	Moderate
General Implementation Considerations for Endoscopic Surveillance:		
- Endoscopic evaluation in patients with suspected or confirmed BE should meet the requirements of a high-quality endoscopic examination. - Refer patients with BE-related neoplasia, including patients diagnosed with LGD and IND to high-volume endoscopists with expertise in EET, pathologists with expertise in BE neoplasia and access to multidisciplinary care. - Histologic diagnosis of BE-related dysplasia or early cancer should be confirmed by an expert pathologist. - The diagnosis of BE and IND and LGD should be confirmed by a repeat upper endoscopy by an expert endoscopist within 6 mo on high-dose acid suppressive therapy primarily to rule out prevalent HGD or EAC. - In patients with confirmed LGD choosing surveillance, the panel continues high-dose acid suppressive therapy and performs an upper endoscopy at 6-mo intervals for 1 yr, then annually, until there is a change in histologic grade of dysplasia. - In patients with IND, the panel performs annual endoscopy until there is a change in histologic grade of dysplasia. - In patients with IND confirmed by expert pathology review, the expert panel does not perform EET.		
4. In patients undergoing surveillance endoscopy for BE, the AGA makes no recommendation for or against the use of WATS-3D as an adjunctive sampling technique to a structured biopsy protocol.	Knowledge gap	—
Biomarkers		
5. In patients diagnosed with NDBE, BE with IND or BE with LGD, the AGA makes no recommendation for or against the routine use of p53 assessment as an adjunct test to histopathology to predict progression to HGD or EAC.	Knowledge gap	—
6. In patients diagnosed with NDBE, BE with IND or BE with LGD, the AGA makes no recommendation for or against the routine use of TissueCypher testing as an adjunct test to histopathology.	Knowledge gap	—

Table 2. Continued

Recommendations	Strength of recommendation	Certainty of evidence
Prevention of Progression		
7. In adult patients with BE, the AGA suggests the use of daily PPI therapy compared with no PPI therapy for the prevention of neoplastic progression of BE. <i>Implementation considerations for recommendation 7:</i> In patients with BE, counsel tobacco cessation and weight loss if overweight or obese.	Conditional	Low
8. In patients with BE, the AGA suggests use of PPIs over surgery for the prevention of neoplastic progression to HGD or EAC.	Conditional	Low

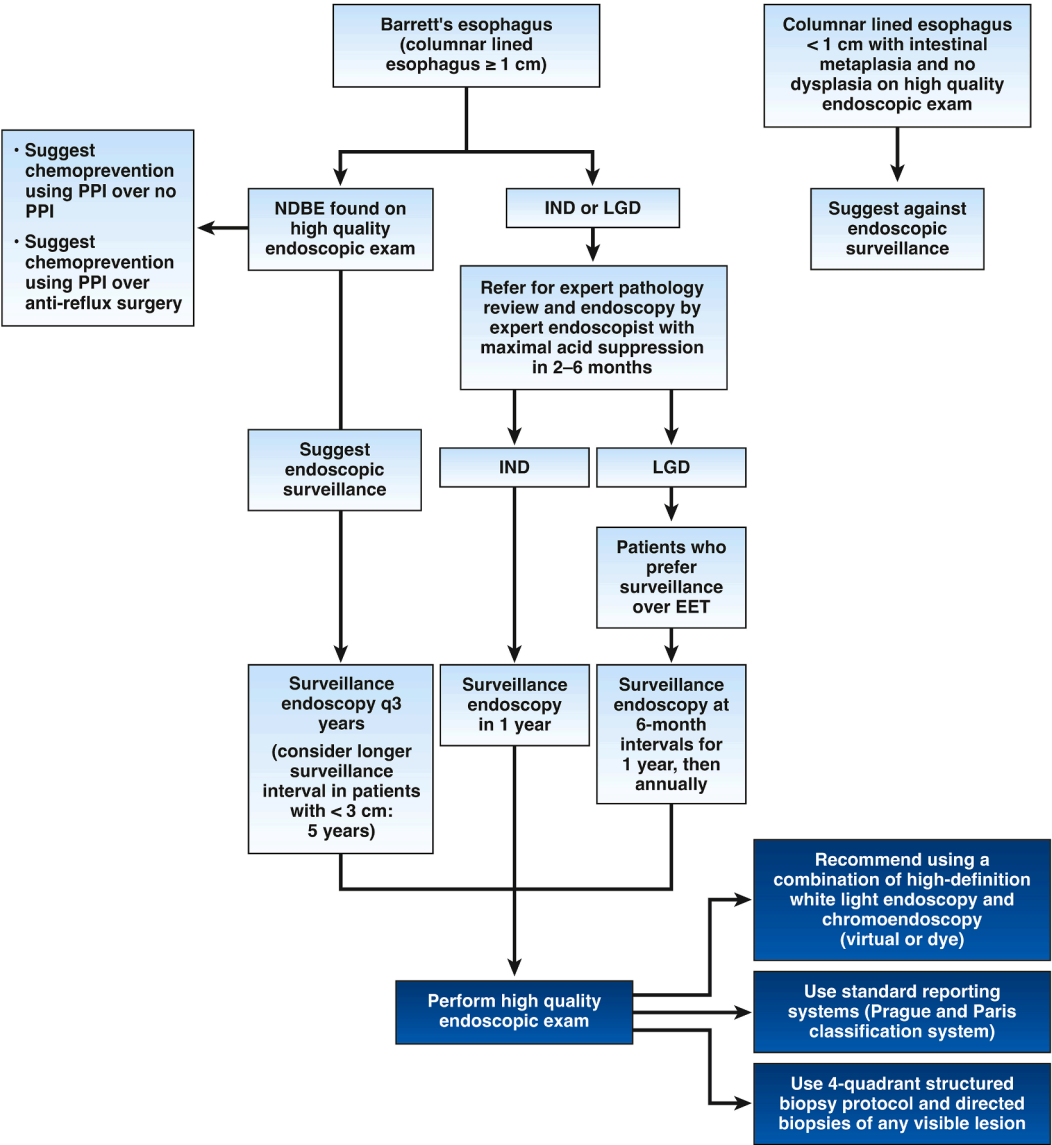


Figure 1. Clinical decision support tool for surveillance in Barrett’s esophagus.

Table 3. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for Population, Intervention, Comparison, Outcome Question: Role of Endoscopic Surveillance in Patients With Nondysplastic Barrett's Esophagus

Study	Study design	Risk of bias	Certainty assessment			Other considerations	Patients, n (%)		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision		Surveillance	No surveillance	Relative (95% CI)	Absolute (95% CI)		
Time to death (from all causes) (median follow-up 12.8 yr) 1 study	Randomized trials	Not serious	Not serious	Not serious	Very serious ^a	None	333/1733 (19.2)	356/1719 (20.7)	HR, 0.95 (0.82–1.10)	9 fewer per 1000 (from 34 fewer to 18 more)	⊕⊕○○ Low ^a	CRITICAL
EAC diagnosis 1 study	Randomized trials	Not serious	Not serious	Not serious	Very serious ^b	None	40/1733 (2.3)	31/1719 (1.8)	RR, 1.28 (0.80–2.04)	5 more per 1000 (from 4 fewer to 19 more)	⊕⊕○○ Low ^b	IMPORTANT
Early-stage EAC and HGD detection rates 1 study	Randomized trials	Not serious	Not serious	Serious ^c	Serious ^b	None	58/1733 (3.3)	20/1719 (1.2)	RR, 2.82 (1.73–4.56)	21 more per 1000 (from 8 more to 41 more)	⊕⊕○○ Low ^{b,c}	CRITICAL
EAC-related mortality from NRS 4 studies	Nonrandomized studies	Serious ^d	Not serious	Not serious	Not serious	None	335/677 (49.5)	3834/13,465 (28.5)	RR, 0.73 (0.57–0.94)	77 fewer per 1000 (from 122 fewer to 17 fewer)	⊕○○○ Very low ^d	CRITICAL

Table 3. Continued

Study	Study design	Risk of bias	Certainty assessment			Other considerations	Patients, n (%)		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision		Surveillance	No surveillance	Relative (95% CI)	Absolute (95% CI)		
EAC-related mortality (NRS cohort studies with well-defined surveillance) 4 studies	Nonrandomized studies	Serious ^e	Not serious	Not serious	Not serious	None	101/282 (35.8)	144/249 (57.8)	RR, 0.60 (0.50–0.71)	231 fewer per 1000 (from 289 fewer to 168 fewer)	⊕○○○ Very low ^e	CRITICAL
Complications from diagnostic EGD, data from large cohort study with 387,647 patients 1 study	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None	Retrospective, observational cohort study with total of 387,647 patients who underwent EGD Bleeding rate was 7.9/10,000 people Perforations 0.4/10,000 people CVA, AMI, and CHF 2.8/10,000, 4.4/10,000, and 1.5/10,000 people, respectively				⊕⊕○○ Low	CRITICAL

AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident; NRS, nonrandomized studies.

^aCI crosses the minimal important difference threshold of 1%–1.4%: from clinically significant mortality reduction to clinically significant increase in mortality.

^bVery small event number and CI crossing from clinically no important cancer diagnosis to clinically important cancer diagnosis.

^cSurrogate outcome, for patient important outcome, such as decrease in EAC mortality.

^dLead and length time biases: 3 studies in this group had data adjusting for lead time bias and no studies adjusted for length time bias. Sensitivity analysis after accounting for lead-time bias resulted in a substantial attenuation in mortality benefit (HR, 0.85; 95% CI, 0.75–0.95).

^eLead and length time biases: adjusting for lead-time with additional adjustment for stage and treatment of cancer eliminated the association between endoscopic surveillance and EAC-related mortality (HR, 1.27; 95% CI, 0.78–2.07).

came from nonrandomized studies with very low certainty due to serious risk of bias and no adjustment for length time bias with only 3 studies adjusting for lead-time bias. For overall mortality and early stage EAC/HGD, evidence from a single RCT and supporting observational data was low certainty due to serious or very serious imprecision. The effect estimates crossed 3 minimal important difference thresholds (minimal important difference, 1%–1.4%) ranging from clinically significant mortality reduction to clinically significant increase in mortality

Discussion

The guideline panel acknowledged several factors that ultimately impacted the evidence to decision process for this recommendation (Supplementary Table 4). Firstly, despite the limitations in the evidence (low certainty), the panel made the judgment that there are likely benefits from surveillance, and those benefits are likely small to moderate. Although the BOSS trial is the first and only RCT of surveillance of BE and contributed important evidence to address the question, it did not report directly on EAC-specific mortality. The study was likely underpowered to detect small differences in all-cause mortality and would have been underpowered for the outcome of EAC-specific mortality if it had been ascertained, as the study planned for a mortality rate of 1.25% per year and HR of 1.3 without surveillance, translating roughly to an absolute expected difference of 0.29% per year. Although 5-year mortality from EAC is 79%,³¹ patients with BE are 10 times as likely to die from non-EAC causes than EAC.³² A recent SR/MA that assessed EAC and non-EAC mortality risk in patients with BE showed all-cause mortality was elevated in patients with BE compared with population controls (pooled standardized mortality ratio, 1.24; 95% CI, 1.01–1.53) driven in part by increased EAC mortality risk (standardized mortality ratio, 8.98; 95% CI, 5.12–15.77). Patients with BE were 10 times more likely to die from noncancer etiologies than EAC (RR, 10.71; 95% CI, 5.98–19.16).³²

Observational studies suggest a progression rate of NDBE to EAC of 0.6% per year and a RR with surveillance for EAC mortality of 0.6,^{26,33–35} which would translate to a substantially smaller expected absolute difference in mortality of 0.19% per year with surveillance compared with no surveillance. The BOSS trial observed 356 deaths in 1719 patients over a median of 12.8 years in the “at need” arm for a mortality rate of roughly 1.6% per year. A difference of 0.19% per year with surveillance as expected based on observational studies would roughly equate to an HR of 0.88 for overall mortality, which is within the CIs of the effect observed in the BOSS trial. Furthermore, in the BOSS trial, 59% of subjects in the control arm underwent upper endoscopies “at need,” including for subjectively worsening symptoms of gastroesophageal reflux disease (GERD); the median intervals between endoscopies were only slightly longer than those assigned to surveillance (25.7 months vs 24.8 months), limiting the ability to detect differences between surveillance and no surveillance. In addition, nearly 25% of patients at study inception did not

have intestinal metaplasia and more than one-half of the EACs were diagnosed in the surveillance arm with T stage >1, which is far greater than observed in prospective high-quality surveillance programs,³⁶ limiting the generalizability of these results. It is unclear how many surveillance endoscopies adhered to the basic tenets of a high-quality endoscopic examination.³⁶ For these reasons, the panel relied heavily on observational studies acknowledging the limitations (ie, potential for selection effects for whom endoscopy was performed, lead-time and length-time bias, and potential unmeasured confounders).

Overall, surveillance likely provides small to moderate benefit, the harms were judged to be trivial, and surveillance was expected to be acceptable to patients and feasible to implement. Costs of surveillance were judged to be moderate. Although the BOSS trial suggested surveillance was not cost-effective, it did not account for the contamination described above and in the Markov analysis modeling extension of the trial beyond the observed period, it assumed there was no mortality benefit from shifting stages with earlier diagnosis.³⁷ A prior SR of cost-effectiveness analyses regarding surveillance strategies that included EET for dysplasia, found that each of the identified studies concluded that surveillance was cost-effective.^{38–40} The panel concluded that the evidence supports a conditional recommendation for surveillance in patients with NDBE, recognizing variability in patient values and preferences.

Implementation Considerations for Recommendation 1

Endoscopic surveillance intervals. Although the evidence likely supports endoscopic surveillance for NDBE, data guiding optimal surveillance intervals are limited. Early recommendations (every 2–3 years) were based on expert opinion and small case series of patients undergoing surveillance.⁴¹ No RCTs and few empirical studies have evaluated interval timing. Some early cohort studies (predating the availability of high-definition endoscopes and virtual chromoendoscopy, and unknown quality of biopsy sampling) suggested dysplasia detection declined with longer intervals between endoscopies. In studies totaling 21 patients who progressed to cancer, dysplasia was detected in 54% at endoscopies performed 2 years before cancer detection, but only in 18%, 20%, and 25% at 3, 4, and 5 years, respectively.^{42–44} One case-control study comparing patients with GERD who died from EAC or gastric cardia adenocarcinoma compared with controls with GERD found a protective effect only with a prior endoscopy performed at 2 or 3 years; however, none of the controls spared from cancer death had undergone esophagectomy, raising concerns about the biological mechanism explaining the observed association.⁴⁵ A cohort study of patients undergoing close surveillance with Seattle protocol biopsies demonstrated that somatic chromosomal alterations increased dramatically between 24 and 48 months before progression to cancer, along with co-selection of large regions of gains or losses in chromosomes and chromosome instability, which occur with or before evidence of histologic dysplasia.^{46,47}

The risk of neoplastic progression from NDBE has since been evaluated by numerous studies, and the observed incidence of progression to cancer depends on study design (population-based vs active surveillance cohort), duration of follow-up, definition of BE, and whether patients with neoplasia diagnosed within the first year are excluded.^{33,34} A modeling study indicated that the study designs would converge to an incidence of 6.4 per 1000 patient-years with long enough follow-up.³⁵ Guidelines have primarily relied on cost-effectiveness analyses, which are calibrated to these observed progression rates for suggesting surveillance intervals. Cost-effectiveness analyses that have included strategies of endoscopic therapy of dysplastic BE have identified optimal surveillance intervals of every 2–5 years in NDBE, depending on the setting (United States with shorter intervals than United Kingdom, where the willingness-to-pay threshold is lower) and sex (shorter intervals in men than women).^{38–40} Based on the modeling of male individuals with BE in the United States and the cohort studies above, the expert panel endorses endoscopic surveillance intervals of every 3 years in patients with NDBE.⁴⁰

The effectiveness of surveillance is dependent on a high-quality endoscopic examination. Studies have shown a high prevalence of missed dysplasia and cancer particularly on index examination, with pooled data showing a 17% rate of postendoscopy esophageal adenocarcinoma (PEEC) and postendoscopy esophageal neoplasia (PEEN) in patients with BE undergoing surveillance.^{1,48} Prior guidelines and these recent observations have fueled the discussion on repeating an upper endoscopy in patients with NDBE within the first year of index endoscopy to reduce the rates of PEEC and PEEN. However, early repeat examinations may lead to overuse of resources and associated costs. Thus, the preferred approach is to ensure high-quality index examination with appropriate sampling (biopsy protocols) as detailed in subsequent sections. However, if clinical circumstances preclude this optimal endoscopic assessment of BE, repeat endoscopy within the first year of diagnosis of NDBE may be considered.

Risk stratification. Although experts generally endorse a 3-year surveillance interval in NDBE, there are several clinical variables that might be used to stratify risk of progression and guide surveillance intervals. The risk factor with the greatest evidence is length of BE,⁴⁹ and other guidelines have also recommended surveillance every 5 years in patients with short segment BE (<3 cm).^{50–52} One SR/MA reported that increasing BE length per centimeter was associated with an increased risk of progression to HGD/EAC (odds ratio [OR], 1.25; 95% CI, 1.16–1.36).⁵³ Another MA of 1979 patients with BE length <3 cm and 2118 patients with BE length of ≥3 cm demonstrated that the annual risk of progression to EAC was significantly lower for shorter segments than for long-segment BE (0.06% vs 0.31%; OR, 0.25; 95% CI, 0.11–0.56).⁴⁹ The risk of progression to HGD or EAC doubles for every 4 cm increase in length.⁵³ However, there is no direct evidence indicating short-segment BE is associated with a longer dwell time in the dysplastic or intramucosal cancer state and extending surveillance intervals may reduce surveillance effectiveness, despite lower progression risk.

Smoking is associated with approximately 1.5 times higher odds of progression.⁵³ Male sex also confers higher

risk, with the 2 MAs^{53,54} reporting a 2-fold increase, although a third MA with individual-level data found a weaker association (HR, 1.44).⁵⁵ The Progression in Barrett's Esophagus score was developed by combining known risk factors: male sex (9 points), smoking (5 points), and BE length (1 point/cm), plus including confirmed LGD (11 points).⁵⁶ A score <11 predicted low risk of progression to HGD or EAC of 0.13% per year over mean follow-up of 6 years in the development cohort, and 0.2% per year over a median follow-up of 7.5 years in a validation study.⁵⁷ It should be noted that the point estimates used in Progression in Barrett's Esophagus for the effects of male sex and smoking (HR, 3.0 and 1.8, respectively) were stronger than identified in the MA above, and weaker for length (doubling every 6 cm). Additional studies are needed to understand the role of age (advancing age is associated with increased risk of progression, but with uncertain effect size) and body mass index (increased risk of progression; OR, 1.06 per increments of 5 kg/m²).⁵⁸ Although family history has been associated with BE and with EAC,⁵⁹ there are very limited data regarding the risk of family history on progression from NDBE.⁶⁰

The panel acknowledged recent studies evaluating the capsule-sponge test as a nonendoscopic tool to address the current limitations of endoscopic surveillance.^{61–63} In a recent prospective study of 910 BEs, 489 (54%) were classified as low risk (clinical and capsule-sponge biomarkers were negative), 283 (31%) as moderate risk (negative for capsule-sponge biomarkers, positive for clinical biomarkers, ie, age, sex, and BE length) and 138 (15%) as high risk (p53 abnormality or glandular atypia regardless of clinical biomarkers, or both).⁶¹ Patients with both atypia and aberrant p53 had the highest risk of HGD/EAC (RR, 135.8; 95% CI, 32.7–564), whereas the prevalence of HGD/EAC in the low-risk group was 0.4% (95% CI, 0.1–1.6) with a negative predictive value (NPV) for any dysplasia or EAC of 97.8% (95% CI, 95.9–98.8). This strategy has the potential to decrease the endoscopic burden and improve risk stratification, although further research is needed to define its role in BE surveillance.

Discontinuation of surveillance. As patients age and develop comorbidities, the benefits of surveillance decline due to increase procedural risks and competing mortality, particularly from cardiovascular disease.^{64,65} Based on a survey of gastroenterologists, most support discontinuing surveillance of NDBE based on age and comorbidities.⁶⁶ Although no RCTs or prospective studies have been performed to guide the timing of discontinuation, cost-effectiveness analysis using 3 models suggested optimal discontinuation ages ranging from 65 to 83 years, depending on sex and comorbidities.⁶⁷ Optimal discontinuation was at younger ages in women compared with men due to the lower risk of progression, despite the longer life expectancy. The European Society of Gastrointestinal Endoscopy recommended cessation of endoscopic surveillance in individuals at age 75 years in the absence of a history of dysplasia.⁵⁰ We propose initiating the conversation about discontinuation of surveillance at the earliest potential penultimate EGD (eg, age 75 years in a man without comorbidities), introducing the concept of diminishing benefit and rising risk with continued surveillance with advancing age. The age at which to discontinue should be based on patient life expectancy

(due to comorbidities) and might also be influenced by risk of progression (length of BE); fitness to undergo repeat endoscopy; and ability to tolerate endoscopic, surgical, or oncologic therapies for esophageal neoplasia.

What is the role of endoscopic surveillance in patients with columnar-lined esophagus <1 cm with intestinal metaplasia without neoplasia?

Recommendation 2: In patients with columnar-lined esophagus <1 cm with intestinal metaplasia without neoplasia, the AGA suggests against endoscopic surveillance. (Conditional recommendation, very low certainty of evidence)

Columnar-lined esophagus <1 cm is a finding that has been reported in approximately 15% of the population undergoing upper endoscopy.⁶⁸ Observational studies have reported an up to 44% prevalence rate of intestinal metaplasia in patients with columnar-lined esophagus <1 cm.^{69,70} To address surveillance in this population, the panel identified the following critical outcomes: progression to HGD/EAC, progression to EAC, and endoscopic complications.

Summary of the Evidence

Evidence informing the recommendation was derived from 6 single-arm observational cohort studies. No existing SR/MA evaluating this question was identified, so a de novo literature search (through March 1, 2025) was conducted (Supplementary Table 3). This search identified 1014 studies, of which 74 underwent full-text screening and 6 relevant studies were included in the final analysis. We could not address the critical outcome of progression to EAC alone, as not all studies reported disaggregate outcomes for HGD and EAC. No study addressed the patient-important outcome of EAC-related mortality. The largest study was by Anaparthi et al⁷¹ (408 patients, 5 US tertiary care centers) included patients with <1 cm BE without dysplasia (excluding patients who developed HGD or EAC within 1 year of BE diagnosis to exclude prevalent neoplasia) who were followed for a mean of 5.2 years. The BE cohort was 88% men, mean age was 59.2 years, and 93% of the cohort were White. Incident HGD/EAC

developed in 5 patients with an annual risk of HGD/EAC of 0.23% per year. Data regarding the harms of surveillance endoscopy were derived largely from 2 large national database studies, as previously summarized in PICO question 1.^{29,30}

Benefits and Harms

For the critical outcome of progression to HGD/EAC, we performed an MA and found a pooled incidence of 0.1 per 100 patient-years (Figure 2). There were no data on progression to EAC or EAC-specific mortality. Data on SAEs associated with endoscopy, were previously summarized in PICO question 1 on the use of surveillance endoscopy in NDBE (Table 3).

Certainty of the Evidence

The overall certainty across the critical outcomes was low (Table 4). For the outcome of progression to HGD/EAC, the evidence was very low, as we relied on data from single-arm, nonrandomized studies with serious risk of bias and indirectness, as these studies consisted only of studies without a comparator arm. It is also unclear whether patients underwent endoscopic surveillance under a structured protocol or whether outcomes were based on endoscopy performed as needed. AEs associated with surveillance endoscopy were assessed from observational cohort studies with low certainty of evidence due to serious risk of bias. One cost-effectiveness study was used in the evidence to decision making.⁷² No study addressing patient values and preferences were identified.

Discussion

The guideline panel made a recommendation against routine endoscopic surveillance in patients with columnar-lined esophagus <1 cm with intestinal metaplasia without neoplasia. The panel considered several factors, including the low risk of progression to HGD/EAC and minimal benefit from surveillance (Supplementary Table 5).^{73–75} Although intestinal metaplasia is common in patients with columnar-lined esophagus <1 cm (reported an up to 44% of patients), the panel weighed the minimal benefit against the burden of lifelong surveillance, including costs, procedural risks, strain on endoscopy resources, and patient anxiety.^{69,70} In addition, the inconsistent terminology and description of this finding at

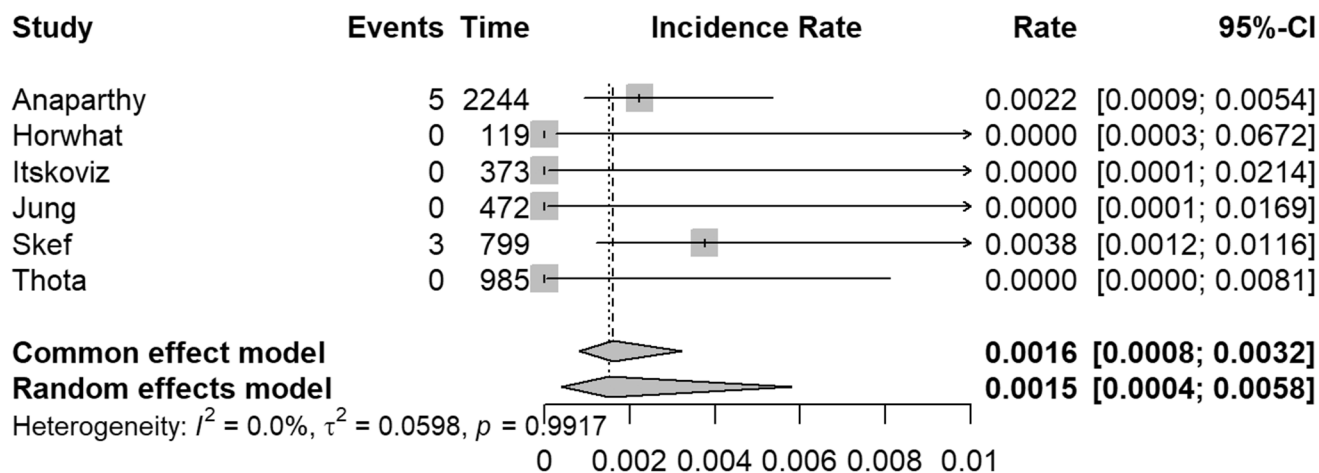


Figure 2. Forest plots for progression to HGD or EAC in patients with columnar-lined esophagus <1 cm with intestinal metaplasia.

Table 4. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for Population, Intervention, Comparison, Outcome Question: Role of Endoscopic Surveillance in Patients With Columnar-Lined Esophagus <1 cm

Study	Study design	Risk of bias	Certainty assessment				Impact	Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations			
Progression to HGD/EAC 6 studies	Nonrandomized studies	Serious ^a	Not serious	Serious ^b	Not serious	None	No comparative data from RCT or nonrandomized studies were found that informs of the benefits or harms of surveillance vs no surveillance in patients with CLE IM <1 cm. We identified only single-arm studies reporting on natural progression of CLE IM <1 cm to HGD/EAC in patients who underwent follow-up EGDs. The pooled incidence was 0.1 per 100 patient-years.	⊕○○○ Very Low ^{a,b}	CRITICAL
Complications from diagnostic EGD, data from large cohort study with 387,647 patients 1 study	Nonrandomized studies	Not serious	Not serious	Not serious	Not serious	None	Retrospective, observational cohort study with total of 387,647 patients who underwent EGD Bleeding rate was 7.9/10,000 people Perforations 0.4/10,000 people CVA, AMI, and CHF 2.8/10,000, 4.4/10,000, and 1.5/10,000 people, respectively	⊕⊕○○ Low	CRITICAL

AMI, acute myocardial infarction; CHF, congestive heart failure; CLE, columnar-lined esophagus; CVA, cerebrovascular accident; IM, intestinal metaplasia.

^aSuspected selection bias, given small studies and limited follow-up time.

^bAll the studies are single-arm studies on natural progression of the patients with IM in CLE <1 cm and no real intervention.

endoscopy (such as esophagogastric junction intestinal metaplasia or irregular Z-line) and the substantial interobserver variability in endoscopic diagnosis, add to the uncertainty of defining this population.⁷⁶ A recent decision modeling analysis evaluated the cost-effectiveness of endoscopic surveillance (no surveillance, 1-time endoscopy at 3 years, endoscopy every 3 years and endoscopy every 5 years) in patients with a diagnosis of esophagogastric junction intestinal metaplasia.⁷² Surveillance strategies were assessed based on annual cancer progression incidence rates (0.01%, 0.05%, 0.12%, and 0.22%). At the lowest progression rates, either no surveillance (annual incidence rate of 0.01%) or 1-time endoscopy (annual incidence rate of 0.05% or 0.12%) can be considered; however, more data are required on progression rates to identify the optimal strategy. The guideline panel acknowledged the very low certainty evidence outlining potential for missed prevalent neoplasia in patients with columnar-lined esophagus <1 cm.⁶⁹ Therefore, a critical component in the decision making regarding endoscopic surveillance in these patients is whether a high-quality endoscopic examination was performed. If the quality of the index examination is in question, a repeat 1-time high-quality examination can be performed to rule out prevalent neoplasia. Based on the above uncertainties, patients who place a higher value on the potential benefit of endoscopic surveillance in preventing EAC progression, especially in patients who did not undergo a high-quality index endoscopic examination and place a lower value on the risks of endoscopy, can reasonably choose to undergo a 1-time repeat surveillance endoscopy. Future studies addressing the role of risk stratification and identification of patients with columnar-lined esophagus <1 cm at high risk of progression to HGD/EAC are needed.

What is the optimal imaging strategy for Barrett's esophagus patients undergoing endoscopic surveillance? Should adult patients with Barrett's esophagus undergo surveillance endoscopy using high-definition white-light endoscopy plus chromoendoscopy vs white-light endoscopy alone?

Recommendation 3: In patients undergoing surveillance endoscopy for BE, the AGA recommends using a combination of high-definition WLE plus CE compared with WLE alone. (Strong recommendation, moderate certainty of evidence)

Implementation Considerations

- Among the CE modalities that meet optimal performance characteristics, the choice of CE modality (virtual or dye-based CE) should be based on endoscopist and center expertise.
- CE-directed biopsies should be used as an adjunct to sampling using a structured biopsy protocol.
- A structured biopsy protocol includes targeted biopsies from any visible lesions and random 4-quadrant biopsies every 2 cm if no history of dysplasia and every 1 cm if there is a history of dysplasia.

Several advanced imaging techniques, such as dye-based chromoendoscopy (CE), for example, using acetic acid, or virtual chromoendoscopy (VCE), have been developed to increase detection of dysplasia and early EAC and to identify lesions that may be missed by high-definition white light endoscopy (WLE) and sampling using a structured biopsy protocol. Narrow-band imaging (NBI), the most widely used VCE, enhances mucosal and vascular patterns using filtered blue light without dye. Acetic acid CE highlights neoplastic areas through differential whitening. For this question, the critical outcome was incremental HGD/cancer detection during surveillance (Table 1).

Summary of the Evidence

Evidence comparing CE (including dye-based and VCE) plus WLE vs WLE alone was informed by RCTs. We identified a 2019 SR/MA published by the American Society for Gastrointestinal Endoscopy Standards of Practice Committee⁷⁷ that included 12 RCTs and 1 study was removed because it was an unpublished conference abstract before the year 2020. An updated search identified 1033 studies, yielding 1 additional RCT⁷⁸ (Supplementary Table 3). The final MA included 12 RCTs (crossover or tandem design): 6 studies used dye-based CE,^{78–83} 5 studies used VCE,^{84–88} and 1 study used both.⁸⁹ All studies were from Western countries. Baseline pathology varied among studies, including HGD/EAC (3 studies)^{80,84,89}; all degrees of dysplasia, including NDBE (6 studies)^{78,81–83,85,88}; all degrees of dysplasia, including NDBE, except EAC (1 study),⁷⁹ BE with dysplasia (1 study),⁸⁷ and LGD only (1 study).⁸⁶

Benefits

An MA of 11 RCTs (including 795 patients in the CE plus WLE group and 795 patients in the WLE alone group) demonstrated a higher detection rate of HGD/EAC compared with WLE alone (RR, 1.2; 95% CI, 1.03–1.4; $I^2 = 0\%$) (Supplementary Figure 2) with an absolute increase of 33 more cases per 1000 patients (from 5 more to 67 more). For all dysplasia (LGD/HGD/EAC), based on 10 RCTs including 817 participants in each arm, CE plus WLE detected 368 of 817 dysplasia cases compared with 311 of 817 with WLE alone (RR, 1.16; 95% CI, 1.07–1.27; $I^2 = 0\%$) detecting 61 more cases per 1000 patients (27 more to 103 more) (Supplementary Figure 2, Supplementary Tables 6 and 7).

Subgroup analyses were also performed of studies examining dye-based CE or VCE plus WLE. An MA of 5 RCTs (323 patients in each arm) comparing dye-based CE plus WLE with WLE alone demonstrated a similar point estimate for the detection of HGD/EAC as in the overall analysis (RR, 1.19; 95% CI, 0.96–1.46; $I^2 = 0\%$) detecting 12 more cases per 1000 patient (3 fewer to 30 more). For all dysplasia (LGD/HGD/EAC), dye-based CE plus WLE compared with WLE alone (6 RCTs including 443 participants in each arm) detected 53 more cases per 1000 patients (6 more to 108 more) (RR, 1.19; 95% CI, 1.02–1.39;

$I^2 = 28.4\%$). Comparing VCE plus WLE with WLE alone, an MA of 6 RCTs (472 patients in each arm demonstrated a similar point estimate (RR, 1.22; 95% CI, 0.97–1.52; $I^2 = 0\%$) to the overall estimate, detecting 52 more cases per 1000 patient (7 fewer to 123 more). For all dysplasia detection (4 RCTs including 374 participants in each arm) 80 more cases per 1000 patient were detected (95% CI, 5 fewer to 186 more) with an RR of 1.16 (95% CI, 0.99–1.37; $I^2 = 0\%$) (Supplementary Figures 2 and 3, Supplementary Table 6).

Given the potential for selection bias by including studies with enriched populations (patients with an established diagnosis of HGD/EAC), a subgroup analysis of 7 RCTs (564 patients in each arm) was performed^{78,79,81–83,85,88} that included patients undergoing endoscopy for NDBE and BE-related neoplasia and reflects the general BE surveillance population more accurately. CE plus WLE improved detection of HGD/EAC compared with WLE alone (RR, 1.55; 95% CI, 1.05–2.29; $I^2 = 0\%$) and overall dysplasia detection (RR, 1.17; 95% CI, 0.95–1.46; $I^2 = 0\%$). For the outcome of number of biopsies required to diagnose dysplasia, 1 crossover RCT (123 patients with BE) compared NBI-targeted biopsies of abnormal mucosa with high-definition WLE using the Seattle biopsy protocol.⁸⁸ Both WLE and NBI detected 92% of patients with intestinal metaplasia (similar rates of detection), but NBI required fewer biopsies per patient (3.6 vs 7.6; $P < .0001$). NBI detected a higher proportion of areas with dysplasia (30% vs 21%; $P = .01$), and all 100% (all 14) of HGD/EAC cases but only 29% of LGD cases. All areas that harbored HGD and EAC had an irregular mucosal or vascular pattern. We found no studies specifically addressing the role of CE in reducing rates of PEEC and PEEN.

Harms

CE is generally safe and well-tolerated, with no significant adverse events reported. Risks include allergic reactions to dyes, although this is rare, and theoretical concerns about methylene blue, getting photosensitized by white light, potentially leading to oxidative DNA damage, particularly in Barrett's mucosa.⁹⁰ Finally, CE may slightly increase biopsy numbers and procedure time, but the overall risk of harm is considered very low, particularly with VCE. VCE adds no extra cost as it is integrated into most endoscopes. A single cost-effectiveness study showed that dye-based CE using acetic acid in high-risk patients with BE was more cost effective than random biopsy sampling.⁹¹

Certainty in Evidence of Effects

The overall certainty of evidence was moderate (Supplementary Tables 6 and 7). For the outcome of detection of HGD/EAC, there was no risk of bias or inconsistency, but we considered the indirectness of the outcome due to lack of longitudinal follow-up (to determine long-term impact of CE) and lack of a true gold standard.

However, these limitations are likely to apply equally to both CE and WLE. Certainty was rated down for imprecision, as CIs crossed the minimal important difference threshold, thus the overall certainty was moderate. The panel also discussed potential selection bias due to inclusion of enriched populations with BE-related neoplasia referred for EET. This was mitigated by performing a sensitivity analysis. Finally, the panel also acknowledged that all studies were conducted at expert centers largely by expert endoscopists and the assessment of diagnostic and incremental yields of dysplasia among nonexpert centers may lead to different estimates.

Discussion

Several advanced imaging techniques have been developed to improve dysplasia and early EAC detection, beyond high-definition-WLE and structured biopsy protocol. CE-directed examination may be conducted using dye-based approaches that requires the application of various topical dyes or solutions to the BE mucosa or VCE that uses light filters within the endoscope to achieve enhancement of the mucosal surface abnormalities. Among the VCE platforms, NBI is the most widely used in clinical practice. It uses blue light with narrow-band filters that enables detailed imaging of the mucosal and vascular surface patterns with a high level of resolution and contrast.⁹² Other VCE platforms use proprietary post-image acquisition processing technology to modify the white-light image to enhance the superficial mucosal and vascular patterns.⁷⁷ Among the various dye-based CE approaches, acetic acid CE is the most widely studied and used in clinical practice. Acetic acid CE enhances mucosal surface patterns by contrast staining—initial application results in an initial whitening of the BE segment and areas of neoplasia lose this whitening more rapidly than NDBE epithelium.⁵⁰

The performance characteristics of CE in BE surveillance patients have been reported on a per-lesion analysis and not per-patient analysis. The American Society for Gastrointestinal Endoscopy Preservation and Incorporation of Valuable Endoscopic Innovations document has provided acceptable performance thresholds for advanced imaging techniques in BE surveillance.⁹³ NBI (sensitivity, 94.2%; NPV, 97.5%; specificity, 94.4%) and acetic acid CE (sensitivity, 96.6%; NPV, 98.3%; specificity, 84.6%) have been shown to meet acceptable performance thresholds.^{93,94} An international group of experts has developed and validated an NBI classification system for detection of dysplasia and EAC in patients with BE using NBI images of NDBE, HGD, and EAC to characterize regular and irregular mucosal and vascular patterns visible by NBI.⁹⁵ The overall sensitivity and specificity for these criteria to detect HGD/EAC in selected still images was 80% and 88% and improved to 91% and 93%, respectively, when the assessment of images was made with high confidence. The panel suggests the use of this classification system in routine clinical practice acknowledging the learning curves associated with these advanced imaging techniques. Training tools, such as the

Barrett's Oesophagus-Related Neoplasia web-based training course, which is an available validated training course focused on improving early neoplasia detection⁹⁶ and can be accessed at www.iwgco.net, www.ueg.eu, or www.best-academia.eu.

Implementation Considerations for Recommendation 3

Choice of chromoendoscopy. Given the similar (incremental) yield of dysplasia detection using VCE and dye-based CE,⁷⁷ the guideline makes no recommendation on CE

modality (VCE over dye-based CE, type of VCE platform or type of dye) (Supplementary Figures 2 and 3). The choice should depend on endoscopist and institutional expertise. All contemporary endoscopy systems include VCE platforms and circumvent several issues related to dye-based CE, such as the need for additional equipment (dye and catheters) and time, difficulty achieving complete and uniform coating of the mucosal surface, and inability to detect superficial vascular patterns. This question was designed to address the adjunctive role of CE to high-definition WLE and not as a substitute for a structured sampling protocol, as areas that do not appear suspicious

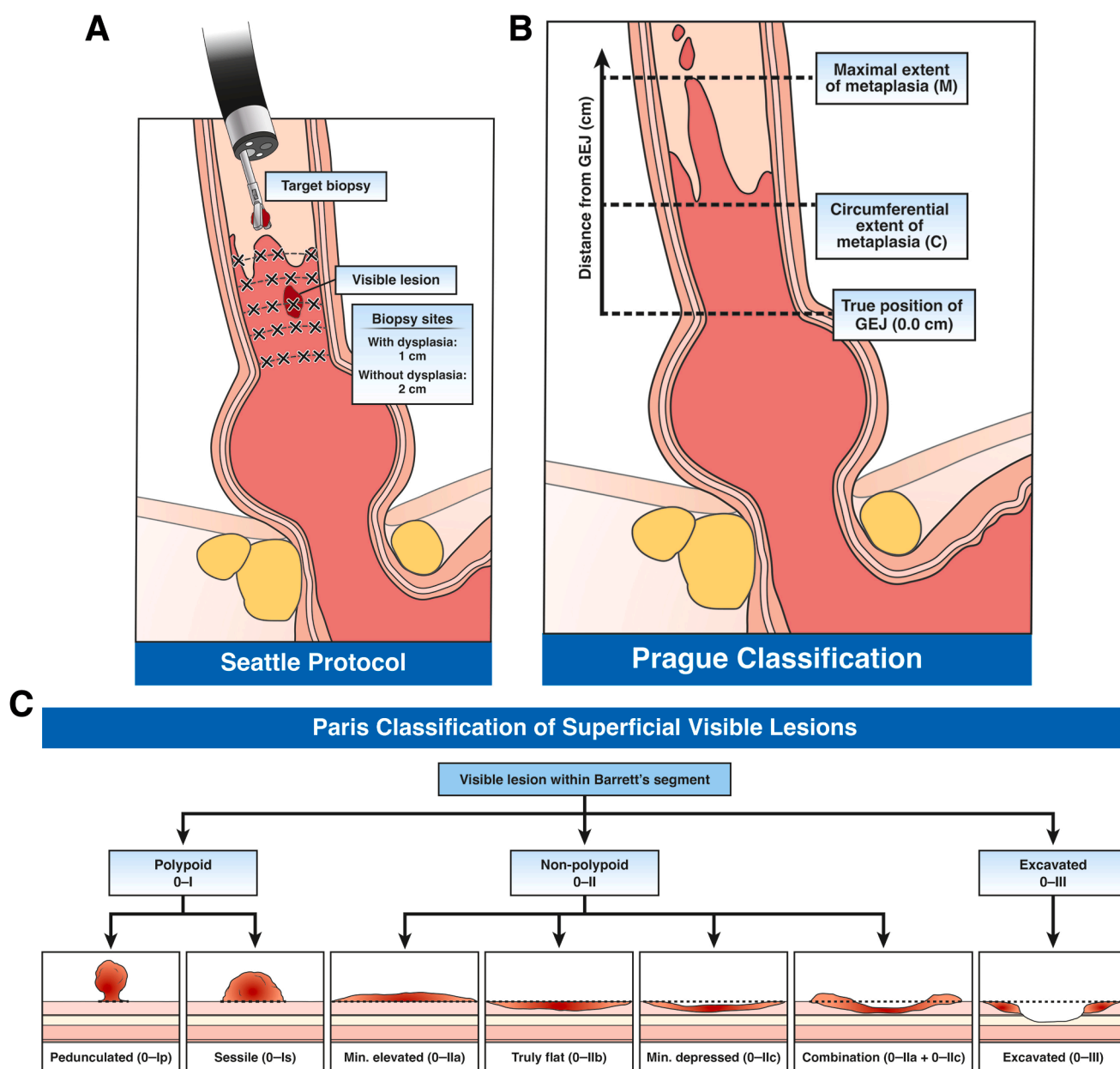


Figure 3. (A) Sampling of BE using a structured biopsy protocol. (B) Prague classification system to define the length of the Barrett's segment. (C) Paris classification system to define any visible lesion within the Barrett's segment.

on CE may still harbor dysplasia.⁸⁸ A meta-regression analysis in an SR/MA showed that the overall number of biopsies strongly correlated with the diagnostic yield of dysplasia.⁹⁷ Thus, CE-directed biopsies should not be used as a substitute for sampling using a structured biopsy protocol.

The role of artificial intelligence (AI) in improving detection of dysplasia and early EAC detection is evolving. AI platforms using computer-aided detection and computer-aided diagnosis systems have shown promise in identifying neoplastic areas, and potentially quantitating the comprehensiveness of endoscopic examinations.^{98–104} Preliminary studies have also demonstrated that these platforms can outperform endoscopist in both BE images and videos¹⁰⁵ and be used during live endoscopic procedures.^{99,100} Using a benchmarking test set, the computer-aided detection system was superior to endoscopists in detecting neoplasia (90% vs 74%; OR, 3.75) for images and 91% vs 67% (OR, 11.68) for videos and non-inferior to BE experts. A recent pilot study also showed that computer-aided diagnosis assistance increased characterization performance of BE-related neoplasia by general endoscopists to the level of expert endoscopists.¹⁰⁶ Although it is anticipated that these AI platforms will impact the current approach to BE surveillance, the clinical utility of AI in routine practice requires validation in RCTs.¹⁰⁷

Structured biopsy protocol. After careful initial examination, patients with BE undergoing surveillance endoscopy should be sampled using a structured biopsy protocol, such as the Seattle biopsy protocol, to minimize sampling bias. The Seattle biopsy protocol includes targeted biopsies of all visible or suspected lesions plus 4-quadrant random biopsies every 1–2 cm throughout the Barrett's segment extending from the squamocolumnar junction to the lower esophageal sphincter (Figure 3A).¹⁰⁸ Specimens should be placed in separate jars labeled by distance from the incisors. The goal of sampling with the Seattle protocol, although potentially time intensive, is to help increase the accuracy and yield of detection of dysplasia and EAC in patients with BE undergoing surveillance endoscopy.^{97,109,110} Multiple observational studies support the routine use of a structured biopsy protocol. Pooled data from 2 studies (506 patients) showed a higher rate (19.1%) of dysplasia detection with Seattle protocol compared with those undergoing nonprotocolized biopsies (2.6%; RR, 6.27; 95% CI, 2.75–14.33) in patients with BE undergoing surveillance.¹¹¹ In a UK study (222 patients) a systematic 4-quadrant biopsy protocol was associated with a higher proportion of dysplasia detection (LGD/HGD/EAC) (73% vs 27%) compared with solely targeted biopsy with WLE.¹⁰⁹ A retrospective study found that systematic 4-quadrant biopsies outperformed NBI-targeted biopsies with 57.1% of HGD and 86.3% of LGD events diagnosed using biopsies from protocolized 4-quadrant biopsies.¹¹²

Limitations of the Seattle biopsy protocol include suboptimal adherence rates (49%).^{110,113,114} An important factor associated with low adherence is longer BE segment length with the likelihood of nonadherence increasing by 31% for every 1 cm of BE in the GIQuIC (Gastrointestinal Quality Improvement Consortium) national quality benchmarking registry.^{115,116} Also, this approach samples a fraction of the entire Barrett's segment, is time-consuming, and is associated with considerable costs. Despite these limitations, the Seattle biopsy protocol currently remains the best-studied biopsy protocol for BE and a cornerstone of a high-quality BE examination. In sum, in the context of existing observational data, patients with BE undergoing screening or surveillance endoscopy should be sampled using a structured biopsy protocol (ie, the Seattle biopsy protocol).

General Implementation Considerations for Endoscopic Surveillance

- Endoscopic evaluation in patients with suspected or confirmed BE should meet the requirements of a high-quality endoscopic examination.
- Refer patients with BE-related neoplasia, including patients diagnosed with LGD and indefinite for dysplasia (IND) to high-volume endoscopists with expertise in EET, pathologists with expertise in BE neoplasia and access to multidisciplinary care.
- Histologic diagnosis of BE-related dysplasia or early cancer should be confirmed by an expert pathologist.
- The diagnosis of BE and IND and LGD should be confirmed by a repeat upper endoscopy by an expert endoscopist within 6 months on high-dose acid suppressive therapy primarily to rule out prevalent HGD or EAC.
- In patients with confirmed LGD choosing surveillance, the panel continues high-dose acid suppressive therapy and performs an upper endoscopy at 6-month intervals for 1 year, then annually, until there is a change in histologic grade of dysplasia.
- In patients with IND, the panel performs annual endoscopy until there is a change in histologic grade of dysplasia.
- In patients with IND confirmed by expert pathology review, the expert panel does not perform EET.

High-Quality Endoscopic Examination

In patients with known or suspected BE, it is important to perform a meticulous high-quality endoscopic examination with appropriate sampling for accurate disease staging and minimize the risk of missed dysplasia or neoplasia. The

AGA Clinical Practice Update for a high-quality upper endoscopy examination¹¹⁷ suggests preprocedure, intra-procedure, and postprocedure best clinical practices. These best clinical practices as they relates to patients with BE are highlighted below and in Table 5.

Preprocedure. Indications, benefits, and risks should be discussed in detail as part of informed consent. Optimization of acid suppressive therapy before endoscopic surveillance can help improve interpretability of results and antithrombotic management should follow published guidelines.¹¹⁸

Intraprocedure. Prior guidelines⁵⁰ have endorsed a 10-step approach to a high-quality endoscopic examination in BE.¹¹⁹ The first steps rely on achieving and documenting adequate mucosal visualization, followed by identifying the esophageal landmarks. A critical step is careful and systematic examination of the Barrett's segment using high-definition WLE and CE (virtual or dye-based) to enhance identification of subtle mucosal lesions and vascular pattern abnormalities. Although data are limited, a single study showed that average inspection time of more than 1 minute for every 1 cm of Barrett's mucosa was associated with higher detection of suspicious lesions (54% vs 13.3%).¹²⁰ A European society guidelines recommend a procedure time of ≥ 7 minutes for upper endoscopy and inspection time of ≥ 1 min/cm of the circumferential extent of the BE mucosa.¹²¹

For documentation, use of a standardized reporting system is recommended. Prague classification is optimal to describe the circumferential and maximal extent of the columnar mucosa and location of the proximal gastric folds and diaphragmatic hiatus. Size and location of any islands proximal to the maximal extent of the BE

segment should be documented. The Prague classification system (Figure 3B) has been studied in endoscopists with varying degrees of experience¹²² and in different settings¹²³ with excellent reliability (coefficient of 0.94–0.95 in videos BE segments of ≥ 1 cm).¹²⁴ Size, location, and macroscopic appearance of any visible lesion using the Paris classification (Figure 3C) is best to describe superficial neoplasia.¹²⁵ Representative images of visible lesions in patients with BE are highlighted in Figure 4. In addition to photo documentation of routine landmarks, any suspicious lesions or findings would benefit from more rigorous photo documentation with annotation and inclusion of descriptive details to help inform future management. Finally, any presence or absence of erosive esophagitis should be graded and reported using the Los Angeles classification system. In the presence of active Los Angeles classification grade C or D esophagitis, BE surveillance endoscopy should be repeated at least 6 weeks after optimizing antireflux therapy with random biopsies obtained on the follow-up examination after healing of active esophagitis. However, a detailed inspection and targeted biopsies of any suspicious lesions are recommended, even in the presence of severe reflux esophagitis, to prevent delays in diagnosing dysplasia and malignancy. Although the potential for overcalling dysplasia (especially LGD) in the setting of active inflammation exists, this should not preclude obtaining biopsies, as expert pathologists have been shown to be able to distinguish inflammation from true LGD.¹²⁶ When such samples are obtained, documentation should include the presence and severity of the esophagitis visualized. Treatment for 8 weeks was

Table 5. Key Considerations for a High-Quality Endoscopic Examination in Barrett's Esophagus

Key consideration	Description
Preprocedure	Informed consent: Discuss indications, benefits, and potential risks of the procedure in detail. Acid suppressive therapy: Optimize therapy before BE surveillance to minimize interpretation challenges due to active esophagitis. Antithrombotic management: Follow published guidelines for periprocedural management of antithrombotic agents.
Intraprocedure	Visualization techniques: Use a distal attachment cap, appropriate insufflation/desufflation, and mucosal cleansing agents and washing to enhance mucosal visibility. Landmark identification: Accurately document the top of the squamocolumnar junction (both maximal and circumferential extent), gastroesophageal junction, and diaphragmatic hiatus. Systematic inspection: Conduct multiple pull-throughs using high-definition WLE and CE (virtual or dye-based) including retroflexion and inspection of the distal esophagus, gastroesophageal junction and gastric cardia, spend adequate time inspecting the Barrett's mucosa to improve detection of Barrett's-related neoplasia. Standardized reporting: Use the Prague classification to describe BE segment extent and length; Paris classification for any visible lesions; Los Angeles classification to describe presence of esophagitis. Photodocumentation: Capture routine landmarks and mark suspicious lesions with annotations and descriptive details. Biopsy protocol: Use the Seattle protocol for systematic sampling.
Postprocedure	Provide follow-up recommendations and timing to resume antithrombotics. Document pending pathology review for further guidance. Ensure surveillance intervals align with guidelines.

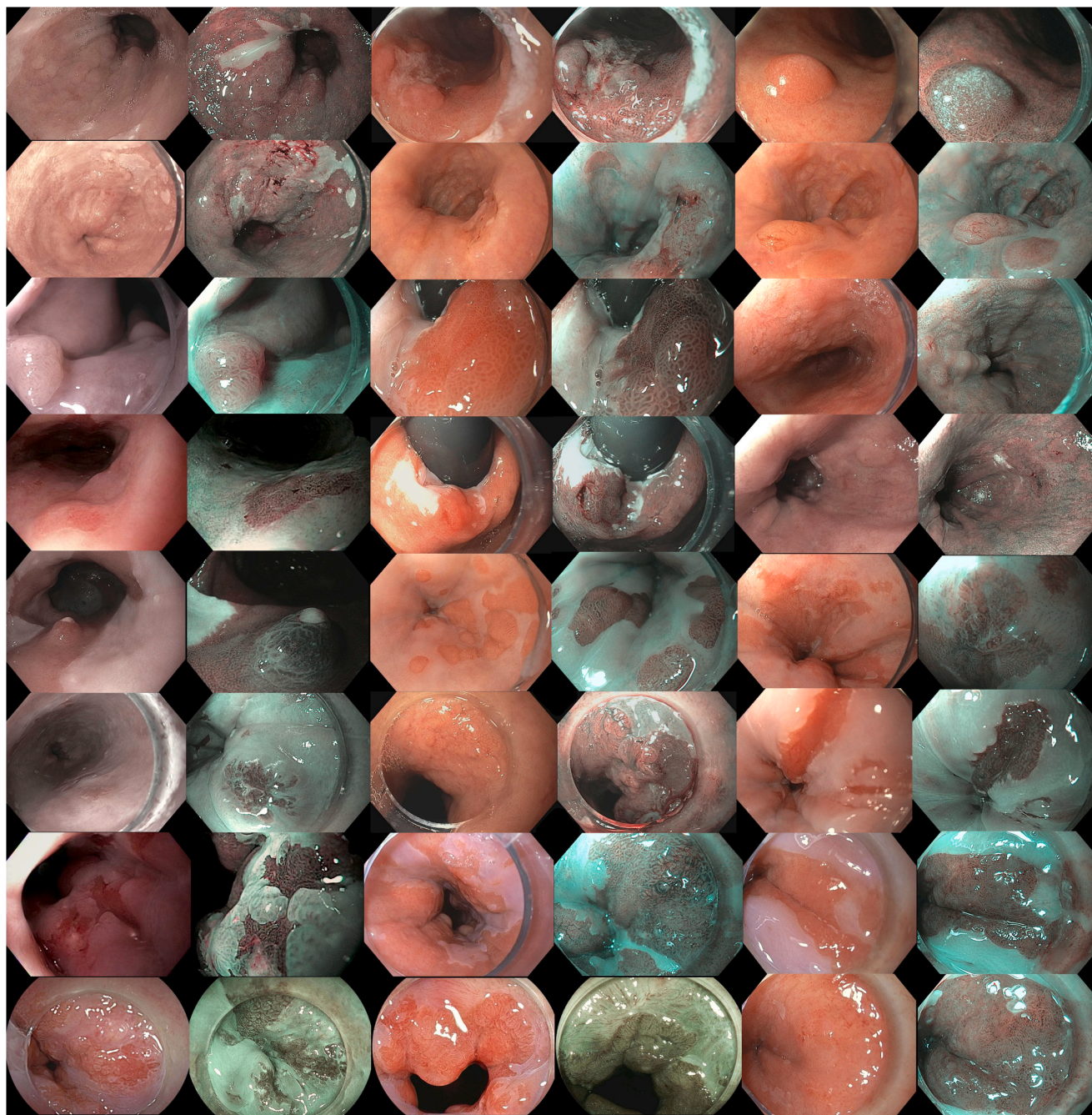


Figure 4. Representative images of visible lesions in patients with BE.

recommended, as this has been the typical duration of most trials of proton pump inhibitors (PPIs) for the healing of esophagitis and has been recommended in prior guidelines.^{127–129} The panel noted that a relook endoscopy (to document healing of significant esophagitis and to assess for any persistent features of malignancy) is likely only needed for those with Los Angeles Classification grades C and D esophagitis (which means a significant portion of mucosal surface is destroyed).¹³⁰ Follow-up EGD may reveal underlying BE in up to 10%–12% of patients.^{131–133} Only after completion of all the above described steps, Seattle

protocol biopsy should be used for sampling of the BE segment.

Postprocedure. Instructions should be provided regarding any follow-up based on endoscopic findings, as well as the timing to resume antithrombotic agents, if applicable. Most patients suspected of harboring BE on index endoscopy are not confirmed as such on histology.¹³⁴ Therefore, endoscopists should refrain from recommending surveillance endoscopy in the report of the index endoscopy until pathology results are available. It is advisable to have a recall system in place for patients with BE undergoing surveillance.

Surveillance in Patients With Barrett's Esophagus and Low-Grade Dysplasia

As outlined in the AGA Guideline on EET for BE, patients with dysplastic BE and EAC should be referred to high-volume endoscopists with expertise in endoscopic examination and resection, and expert pathologists.¹⁰ Up to 27% of patients with BE with LGD and no documented visible lesion referred from community settings to expert endoscopists are found to have a visible lesion that requires endoscopic resection.¹³⁵ In addition, systematic sampling and expert pathology review led to an upgrade from LGD to HGD in up to 26% of patients and even to EAC in 7%–11% of patients, including some cases with advanced EAC not amenable to EET.^{135–138} Regenerative changes from uncontrolled reflux can mimic dysplasia, leading to possible overdiagnoses of LGD or IND.¹³⁹ Studies showed LGD may regress with effective reflux control.^{140,141} Therefore, patients should undergo repeat EGD by an expert endoscopist while on maximum acid suppression (PPI twice daily, 30–45 minutes before meals for at least 2 months) with resection of any visible lesion to rule out prevalent HGD or EAC.

As per the AGA Guideline on EET, patients with BE with confirmed LGD should engage in shared decision making regarding EET vs continued surveillance.¹⁰ Expert pathology review shows that LGD progresses to HGD/EAC at 5.7% annually, warranting closer surveillance than in NDBE.¹⁴² If EET is not pursued, cost-effectiveness models support surveillance every 6 months for 1 year, then annually.⁴⁰ Those surveillance EGDs should ideally be performed by expert endoscopists with targeted tissue sampling of any visible lesions or endoscopic resection and random 4-quadrant biopsies every 1 cm. If findings revert to NDBE, 3-year intervals can be resumed.

Management of Indefinite for Dysplasia

BE and IND is found in up to 8.4% of patients with BE.¹⁴³ A 2020 SR/MA (8 studies, 1441 patients) found a pooled incidents of HGD/EAC of 1.5 per 100 person-years (95% CI, 1.0–2.0) with modest between study heterogeneity ($I^2 = 56.5\%$). The pooled incidence of EAC alone was 0.6 per 100 person-years (95% CI, 0.1–1.1) with considerable between study heterogeneity ($I^2 = 89\%$).¹⁴³ A recent UK cohort study (88 patients) from 2 identified 102 biopsies with BE and IND: endoscopic follow-up was performed in 88% ($n = 78$) patients and 12 of 78 progressed to LGD (15%, 2.6 per 100 person-years), 6 of 78 progressed to HGD (7.7%, 1.3 per 100 person-years), and 6 of 78 progressed to EAC (7.7%, 1.3 per 100 person-years).¹⁴⁴ Predictors of progression included longer BE segment, multifocal and persistent IND. Another multicenter cohort study (242 patients) found that after a median follow-up of 1.5 years, 184 patients (76%) had no evidence of dysplasia, prevalent neoplasia was identified in 23 patients (9.5%; 20 LGD, 2 HGD, 1 EAC) and 35 patients (14.5%) developed incident neoplasia (27 LGD, 5 HGD, 3 EAC).¹⁴⁵

Management of BE and IND poses similar challenges to those with LGD, including variable progression rates, and interobserver variability among pathologists in differentiating

between true dysplasia and inflammatory changes or reactive atypia.¹⁴⁶ In addition, a high proportion of patients with BE and IND do not demonstrate any dysplasia on subsequent endoscopy especially when performed on high-dose PPI therapy.¹⁴⁴ Given the uncertainties in the true risk of neoplastic progression and the reduction in risk of progression to HGD/EAC using EET, EET is not recommended in patients with confirmed BE and IND. However, these patients should also be evaluated at expert centers and undergo repeat endoscopy on twice-daily PPI therapy within at least 6 months with repeat sampling using the Seattle biopsy protocol and resection of any visible lesions to confirm the diagnosis of IND and rule out prevalent HGD or EAC.¹⁴⁴ Patients with confirmed BE and IND should undergo surveillance in 1 year and annually thereafter until there is a change in histologic grade of dysplasia. The role of risk-stratification tools, including the use of biomarkers to more accurately prognosticate the finding of BE and IND, is discussed in another section of this guideline.

What is the role of adjunctive sampling techniques in patients with Barrett's esophagus undergoing surveillance endoscopy? Should adult patients with Barrett's esophagus undergoing surveillance endoscopy be sampled using structured biopsy protocol plus wide-area transepithelial sampling vs sampling using a structured biopsy protocol alone?

Recommendation 4: In patients undergoing surveillance endoscopy for BE, the AGA makes no recommendation for or against the use of WATS-3D as an adjunctive sampling technique to a structured biopsy protocol. (Knowledge gap)

Given the limitations of current endoscopic surveillance strategies, as highlighted above, the use of techniques to improve detection of BE-related neoplasia in patients undergoing surveillance endoscopy has received much attention in recent years. Although advanced imaging techniques focus on increasing detection of dysplasia and early EAC by improving visualization of neoplastic areas, wide-area transepithelial sampling (WATS-3D) attempts to improve detection of intestinal metaplasia and dysplasia by increasing the surface area sampled.⁷⁷ We evaluated the role of WATS-3D as an adjunct to the Seattle biopsy protocol. The critical outcomes that informed the benefits for this PICO question were: (1) yield of HGD/EAC and (2) yield of neoplasia (defined as LGD, HGD, or EAC) (Table 1). Other patient-important outcomes were reduction in rates of PEEC and PEEN, prediction of disease progression (to HGD and/or EAC), and adverse events related to WATS-3D sampling.

Summary of the Evidence

Evidence for the use of WATS-3D as an adjunct to the Seattle biopsy protocol comes from RCTs, cross-sectional studies, and observational studies. No direct comparative evidence with longitudinal follow-up was found. A prior

SR/MA included 7 studies (5 cross-sectional studies, 1 retrospective cohort study, and 1 RCT) and evaluated the incremental yield of dysplasia detected by WATS-3D in conjunction with forceps biopsy compared with forceps biopsy alone.¹⁴⁷ The composite outcome of dysplasia in this prior SR/MA included IND, LGD, HGD, and EAC. An updated search (January 2021–2025) identified 4 additional studies to include in our analysis (2 cross-sectional studies, 1 RCT, and 1 retrospective cohort study) (Supplementary Table 3).^{148–151} We excluded studies examining use of WATS-3D for the purpose of surveillance after EET. Another SR/MA, also published in 2022, did not yield additional data.¹⁵²

Adjunctive yield of neoplasia (LGD, HGD, or EAC) was defined as the proportion of cases of neoplasia identified by WATS-3D plus Seattle biopsy protocol divided by the proportion of cases identified by Seattle biopsy protocol alone (Table 1). In contrast to the previously published SR/MA, we excluded crypt dysplasia (CD) or IND in our outcome due to their low risk of progression and diagnostic variability.⁵⁰ Thus, we excluded the following 2 studies: (1) Johanson et al,¹⁵³ because the dysplasia outcome included CD, and (2) Agha et al,¹⁵⁴ because this study reported dysplasia only for the WATS-3D/Seattle protocol biopsy-discordant cases and we could not obtain adjunctive yield rates. For assessing progression to HGD/EAC among cases of BE with NDBE or LGD, we used data from Shaheen et al,¹⁵⁵ which described progression rates based on WATS-3D diagnosis and compared this with natural history data available in the literature. Historical progression rates published in a prior SR for natural progression of LGD was used as a comparator for the outcome of progression.¹⁴²

We included 9 studies in our final analysis—4 studies including screening and/or surveillance populations and 5 studies including populations enriched for patients with a history of BE-related neoplasia or who were potentially referred for EET. Subgroup analyses were conducted for each. Demographic characteristics among the screening/surveillance cohorts were similar: 39%–78% were male and mean age was 56–61 years. In the enriched cohorts, 53%–82% were male and mean age was 63–68 years. The largest enriched population study (Trindade et al¹⁵¹) included 8471 patients; 1.1% had LGD, 0.13% had HGD, and 0.26% had EAC. In this study, 74% of patients had short-segment BE.¹⁵¹ Demeester et al¹⁴⁹ performed an RCT of 1002 patients (786 for BE screening and 118 for BE surveillance) comparing WATS-3D as stand-alone sampling method vs Seattle biopsy protocol with most endoscopies performed for screening. Demographic characteristics included: 66% were female, mean age was 57 years, 89% of patients were White, and 21% had short-segment BE.¹⁴⁹ Progression to HGD/EAC data came from a retrospective cohort study of 4545 patients with NDBE, CD, or LGD who had both WATS-3D and forceps biopsy and had at least 1 follow-up upper endoscopy with WATS-3D at least 12 months later. Their primary outcome was progression to HGD/EAC on subsequent forceps biopsy.¹⁵⁵ The mean follow-up was 2 years, included 50% of patients were female, mean age of 62 years, and 51% had short-segment BE.

Benefits

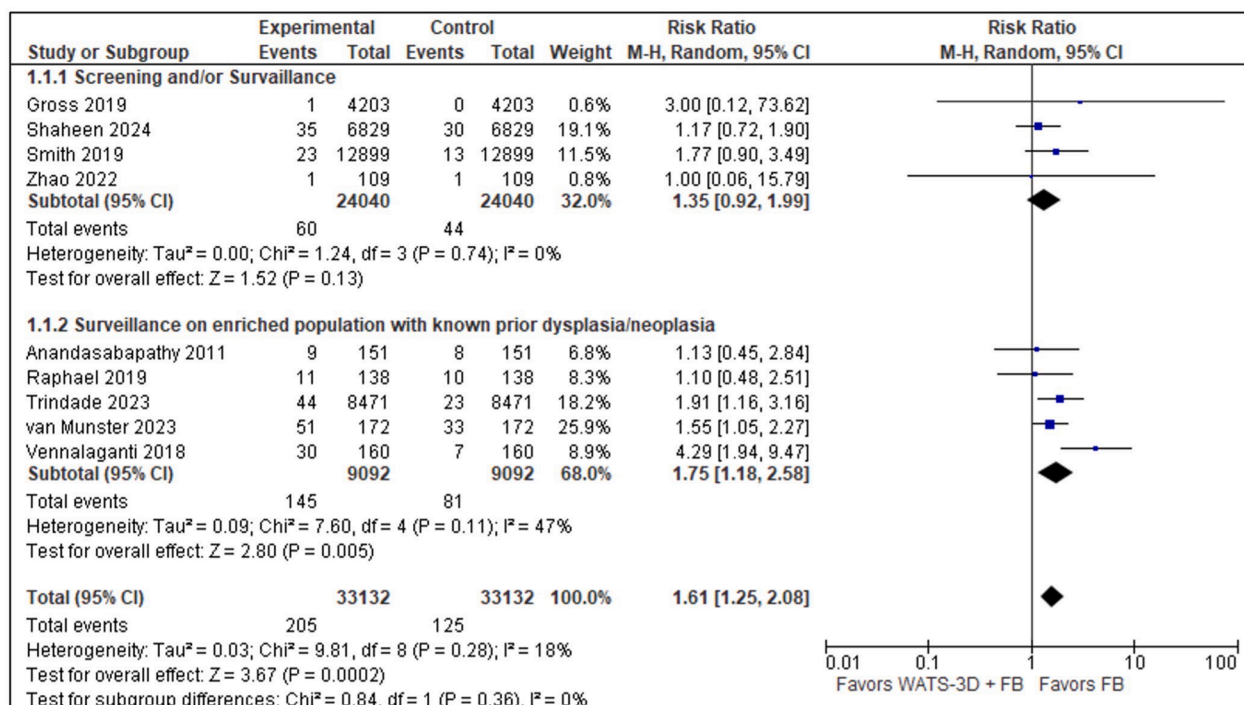
A pooled analysis of 9 studies (33,132 patients) showed that WATS-3D plus Seattle biopsy protocol detected 2 more cases of HGD/EAC per 1000 persons (1 more to 4 more) compared with Seattle protocol biopsy alone (RR, 1.61; 95% CI, 1.25–2.08; $I^2 = 18\%$) (Figure 5). In the subgroup analysis for only the screening/surveillance populations (4 studies), incremental detection of HGD/EAC with WATS-3D plus Seattle protocol biopsy was 1 more per 1000 patients (0–2 more), RR of 1.35 (95% CI, 0.92–1.99). For the enriched population, the RR was 1.75 (95% CI, 1.18–2.58). We also did a sensitivity analysis for the surveillance population only, but including the studies with enriched population (total of 3 studies) and there the RR was 1.68 (95% CI, 1.17–2.42). For the outcome, detection of any neoplasia (LGD/HGD/EAC), MA of 6 studies (19,901 patients), WATS-3D plus Seattle biopsy protocol detected 2 more per 1000 persons (0 more to 4 more) compared with Seattle protocol biopsy alone (RR, 1.36; 95% CI, 1.14–1.64; $I^2 = 0\%$) (Figure 5, Table 6, Supplementary Table 8). In the subgroup analysis for screening or surveillance populations (3 studies), the incremental yield of any neoplasia using WATS-3D plus Seattle protocol biopsies was 3 more per 1000 patients (0–7 more) with an RR of 1.42 (95% CI, 1.00–2.00), and in the 3 studies in the subgroup analysis of the enriched population the RR was 1.33 (95% CI, 1.06–1.68).

We then used data from the retrospective cohort study by Shaheen et al¹⁵⁵ of 4545 patients and compared this indirectly with previously described natural history data on progression of LGD to HGD/EAC. In this study, 5 of 43 patients (11.6%) with LGD diagnosed by WATS-3D progressed to HGD/EAC identified on forceps biopsy in the 2-year follow-up period (5.79 per 100 person-years). In comparison, prior MAs have reported the following progression rates to HGD/EAC: 1.7 per 100 person-years¹⁴² (LGD diagnosed on forceps biopsy) and 0.8 to 13.4 per 100 person-years¹⁶ (LGD with expert pathology confirmation). In addition, in the Shaheen et al study, 28 of 43 patients with LGD diagnosed by WATS-3D (65.1%) had regression to NDBE on subsequent endoscopy. A recent abstract using data from WATS-3D BE registry showed that progression rates to HGD/EAC in patients who were WATS-3D–positive and forceps biopsy–negative were similar to patients who were WATS-3D–negative and forceps biopsy–positive (NDBE: 0.09% vs 0.08%, IND/crypt dysplasia: 1.46% vs 1.59%, and LGD: 5.97% vs 4.8%).¹⁵⁶ These data suggest that clinical management decisions can be based on WATS-3D results even when forceps biopsies fail to confirm the diagnosis. We found no studies specifically addressing the role of WATS-3D in reducing rates of PEEC and PEEN.

Harms

Among the 9 included studies, no SAEs were reported. One perforation occurred in the WATS-3D group (Demeester et al¹⁴⁹) in a patient on chronic steroids post-hiatal hernia repair/fundoplication for GERD. There were no details whether the perforation was related to the

A Detection of HGD/EAC



B Detection of LGD/HGD/EAC

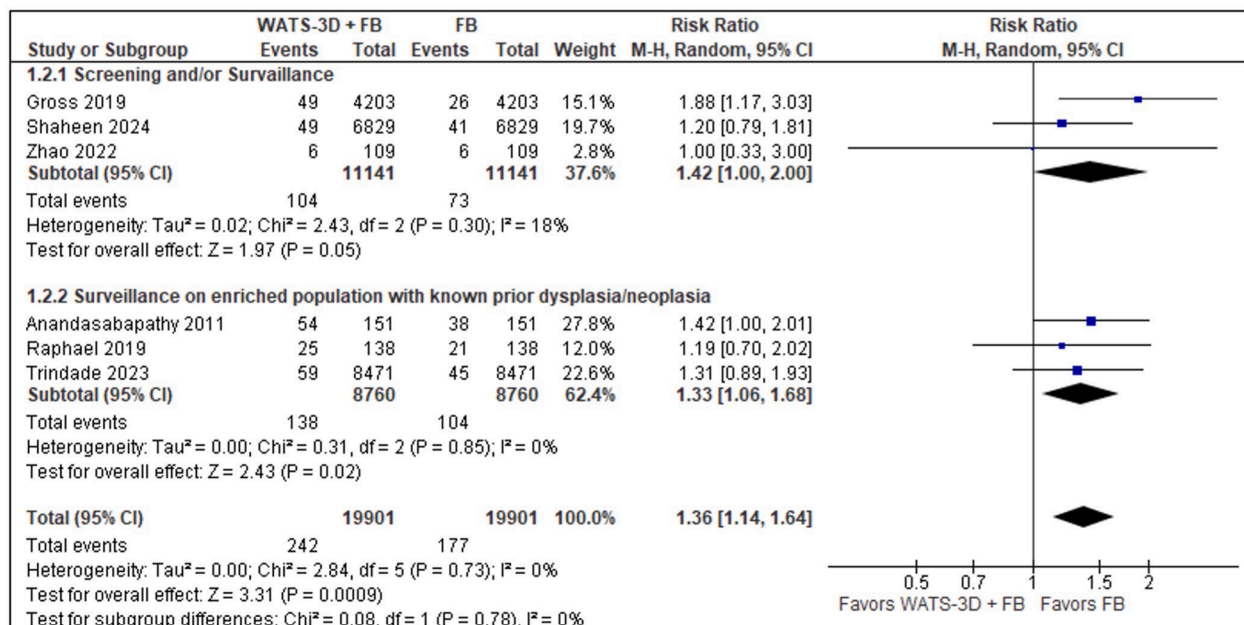


Figure 5. Forest plot of incremental neoplasia detection using WATS-3D plus structured biopsy protocol compared with structured biopsy protocol alone. (A) Detection of HGD/EAC. (B) Detection of LGD/HGD/EAC.

surgery or upper endoscopy. WATS-3D added a mean of 4.5–4.8 minutes to procedure time in addition to Seattle biopsy protocol.^{148,157} The panel acknowledged that this was not relevant if this was associated with an incremental yield in neoplasia detection. The cost-effectiveness of WATS-3D sampling as an adjunct to the Seattle biopsy protocol in patients with BE undergoing surveillance has

not been assessed. Other potential harms include the downstream effects of potential false-positive (FP) results for dysplasia (where the diagnosis of dysplasia is not confirmed on follow-up endoscopy). Prior studies on cancer screening have suggested psychosocial harms or negative impacts on screening adherence associated with FP test results.^{158,159} Additional potential harms could include

Table 6. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for Population, Intervention, Comparison, Outcome Question: Role of Adjunctive Sampling Techniques (Wide-Area Transepithelial Sampling) in Patients With BE Undergoing Surveillance: Neoplasia Detection Rates Between Wide-Area Transepithelial Sampling Plus Structured Biopsy Protocol vs Structured Biopsy Protocol Alone

Study	Study design	Risk of bias	Certainty assessment			Other considerations	Patients, n (%)		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision		WATS-3D+FB	FB	Relative (95% CI)	Absolute (95% CI)		
HGD/EAC detection (diagnostic yield; additional cases detected using WATS-3D as add-on test) 8 studies	Nonrandomized studies	Serious ^a	Not serious	Not serious	Not serious	None	138/22,548 (0.6)	82/22,548 (0.4)	RR, 1.61 (1.25–2.08)	2 more per 1000 (from 1 more to 4 more)	⊕○○○ Very Low ^a	CRITICAL
LGD/HGD/EAC detection (diagnostic yield; additional cases detected using WATS-3D as add-on test) 6 studies	Nonrandomized studies	Serious ^a	Not serious	Not serious	Not serious	None	214/19,901 (1.1)	177/19,901 (0.9)	RR, 1.18 (0.96–1.45)	2 more per 1000 (from 0 fewer to 4 more)	⊕○○○ Very Low ^a	CRITICAL
Harms 1 study	Randomized trials	Not serious	Not serious	Not serious	Extremely serious ^b	None	In the RCT there was only 1 SAE in the WATS-3D group (perforation). Cross-sectional studies with adjunctive diagnostic yield without referent standard test were used. Thus, no downstream harms from FP testing are available. Less concern for FN, given the adjunctive role of the test.				⊕○○○ Very Low ^a	CRITICAL

FB, forceps biopsy.

^aLimited follow-up to assess outcomes related to increased dysplasia detection on WATS and lack of confirmation.^bIn the RCT, there was just 1 event and very wide CI.

unnecessary use of endoscopy for closer surveillance or adverse events after EET for treatment of FP dysplasia (including bleeding, stricture, or perforation).¹⁰

Certainty of the Evidence

The overall certainty in the evidence for critical outcomes was very low (Table 6, Supplementary Table 8). For detection of HGD/EAC or neoplasia (LGD/HGD/EAC), we rated down for risk of bias and imprecision because the included cross-sectional studies reported adjunctive diagnostic yield without reference standard tests (eg, confirmatory endoscopic biopsy), there was limited follow-up, and 5 of the 9 studies included study populations enriched for patients with dysplasia. The risk of false-negative (FN) results was considered less concerning due to the test's adjunctive role. Certainty for adverse events was very low due to imprecision and lack of data on potential harms from FP results.

Discussion

Given the limitations of current endoscopic surveillance strategies, techniques like WATS-3D have gained attention to improve detection of BE-related neoplasia. WATS-3D attempts to improve detection by sampling a broader surface area with an abrasive brush is passed through the channel of the endoscope to sample deeper layers of the glandular Barrett's epithelium across areas with columnar-lined mucosa. The sample acquired by this brush contains disaggregated clumps of structurally intact tissue, the sample is then smeared on a slide, yielding a tissue specimen that is up to 150 μ m in thickness, unlike a typical forceps biopsy slide in which tissue sectioning produces samples that are only 3- to 5- μ m thick.⁷⁷ This is followed by analysis using a neural network algorithm and computer analysis that results in generation of 3D images of the sampled BE. These images are scanned and high-risk features are flagged for pathologists trained in interpretation of WATS-3D samples to review and provide a final diagnosis.^{50,160}

The guideline authors considered several factors when providing a recommendation for this PICO question. Several included studies were conducted using an enriched population of patients with BE (patients with an established diagnosis of BE-related neoplasia referred for EET). However, the real clinical relevance of these adjunctive sampling techniques is best addressed in patients with BE undergoing surveillance endoscopy without known dysplasia. Both the absolute and adjunctive effects were attenuated when the impact of WATS-3D was restricted to a surveillance population. Another limitation is that the incremental benefit in dysplasia detection was not confirmed in subsequent sampling in most studies and the longitudinal follow-up is limited. The increase in dysplasia detection reported on WATS-3D is also largely driven by higher detection rates of LGD. It is not clear that the very small absolute increase in LGD detection is worth the substantial cost. There are no studies assessing the cost-effectiveness of WATS-3D as an adjunctive sampling technique and patient preferences and values have not been

addressed. Future studies need to validate results reporting the natural history of dysplasia detected on WATS-3D sampling alone and demonstrate that these results can be reproduced by nonindustry pathologists, as well as reproducible in community settings with nonexpert endoscopists, improving the generalizability in routine clinical practice. A recent pilot study showed that gastrointestinal pathologists without any prior experience can interpret WATS-3D specimens with a high level of accuracy and reproducibility after a short training session.¹⁶¹ The role of WATS-3D sampling in patients undergoing screening for BE will be addressed in a separate document. Finally, it should be noted that the guideline panel does not recommend against the use of WATS-3D and recognizes the importance of incremental dysplasia and EAC detection in select cases over histopathologic assessment using Seattle biopsy protocol alone. Ongoing prospective trials will address the knowledge gaps discussed above, which will impact the recommendation provided for the use of WATS-3D in routine endoscopic surveillance in patients with BE.

Based on the available literature and as recommended by CDx Diagnostics, WATS-3D sampling should not be used as a substitutive sampling technique to a structured biopsy protocol (Seattle biopsy protocol). The use of WATS-3D sampling technique alone vs the Seattle biopsy protocol in patients with BE undergoing surveillance has not been assessed and is currently being assessed in an ongoing multicenter RCT that will compare the diagnostic yield of LGD/HGD/EAC in patients with BE undergoing surveillance (ClinicalTrials.gov, Number: NCT05530343). This study will also provide the evidence needed to assess the role of WATS-3D as an adjunct to the Seattle biopsy protocol in a nonenriched surveillance population.

Due to the lack of confirmed outcomes, most experts agree that patients diagnosed with dysplasia only by WATS-3D should undergo repeat endoscopy with surveillance within 3–6 months using a structured biopsy protocol and endoscopic resection of any visible lesions. The management of patients diagnosed with HGD/EAC based solely on WATS-3D sampling (without confirmation on repeat endoscopic sampling) should be individualized with consideration for EET and the risks and benefits of EET should be adequately discussed with patients. With WATS-3D,^{160,162} pathologists report CD on WATS-3D samples when dysplasia is detected only in crypts and not in the surface epithelium.¹⁵⁵ Although previous studies suggest that the biologic and molecular properties of CD may be similar to LGD, clinical outcomes data associated with this diagnosis of CD are limited but appear to have intermediate risk between NDBE and LGD.¹⁵⁵ Based on these diagnostic uncertainties, the experts on the panel advise that patients diagnosed with CD, IND, and LGD based solely on WATS-3D should undergo endoscopy by an expert endoscopist on a high-dose acid suppressive regimen within 6 months.

Biomarkers

A biomarker, as defined by the World Health Organization, is any substance, structure, or process that can be

measured in the body or its products and influence or predict the incidence of outcome or disease.¹⁶³ Histologic grading of dysplasia during endoscopy is currently the primary biomarker used for risk stratification and management of BE based on its stepwise progression from LGD to HGD to mucosal EAC and finally, invasive EAC. This process is driven by a series of genetic and epigenetic alterations,¹⁶⁴ leading to chromosomal instability and eventually carcinogenesis. However, dysplasia as a biomarker has significant limitations. These include the existence of patchy and focal distribution of neoplasia within the BE segment and that a structured biopsy protocol samples only a fraction of the entire BE segment. This coupled with the lack of adherence to biopsy protocols adds to the risk of sampling errors.¹¹⁶ In addition, the high degree of inter-observer variability among pathologists for detecting dysplasia decreases the impact and the efficiency of relying on a histologic diagnosis of dysplasia.^{50,165–167} Finally, recent data suggests that a substantial proportion of EACs develop more rapidly through an alternate pathway of genetic and epigenetic alterations, followed by genome doubling and then catastrophically acquiring genomic instability, oncogene amplification, and EAC. This pathway may explain, in part, EACs not detected through endoscopic surveillance programs.^{164,168,169}

In this guideline, the panel evaluated the role of commercially available biomarkers for the neoplastic progression of BE in the United States. The outcomes of interest were the overall performance characteristics (sensitivity, specificity, true positive [TP], FP, true negative [TN] and FN, positive predictive value (PPV), and NPV) and biomarkers as predictors for progression among patients with BE. Similar to previous AGA guidelines on the role of biomarkers in inflammatory bowel disease,^{170,171} the guidelines panel considered the downstream consequences on important patient outcomes corresponding to each possible outcome of the diagnostic test. Patients with TP results are identified as patients at increased risk of progression and would be considered for endoscopic surveillance at shorter intervals or undergo EET. Patients with TN results are at lower risk of progression and might undergo endoscopic surveillance at longer intervals. However, patients with FN results may be falsely reassured and may undergo endoscopic surveillance at longer intervals or no surveillance increasing the risk of undetected progression to EAC that is not amenable to EET. Patients with FP results may undergo unnecessary endoscopies and EET, increasing patient anxiety and resource utilization.

What is the role of p53 assessment in patients with Barrett's esophagus undergoing endoscopic surveillance? Is p53 assessment superior to the grade of dysplasia in predicting progression in patients with Barrett's esophagus?

Recommendation 5: In patients diagnosed with NDBE, BE with IND, or BE with LGD, the AGA makes no recommendation for or against the routine use of p53 assessment as an adjunct test to histopathology to predict progression to HGD or EAC. (Knowledge gap)

p53 is an important tumor suppressor gene and alteration in function is a key event during progression of BE to EAC. The detection of p53 abnormalities in BE by immunostaining is the most widely investigated biomarker that can be used as an adjunct to aid in the diagnosis of dysplasia and as a biomarker for risk stratification in BE. Aberrant expression of p53 protein is evidence of alteration in p53 function (either overexpression or absent expression).⁵⁰ Abnormalities in p53 expression can be detected by p53 immunostaining of formalin-fixed, paraffin-embedded BE tissue or sequencing. Although sequencing provides an objective evaluation of p53 status and can be combined with other genomic biomarkers, this approach is time-consuming, expensive, and requires special instruments and DNA isolation. However, p53 immunohistochemistry (IHC) staining has the largest body of evidence, is faster, relatively inexpensive and can be performed at any pathology laboratory that has the technical capability of performing it.

Summary of the Evidence

Evidence informing the recommendation for the use of p53 as an adjunct test to standard dysplasia assessment of dysplasia in BE surveillance comes from both observational cohort and case-control studies. We identified a 2017 SR/MA (14 studies, 7 cohort, 7 case-control) by Snyder et al¹⁷² that evaluated the risk of progression to HGD/EAC associated with aberrant p53 expression. An updated search (August 2017 to January 2025) identified a total of 581 studies, of which 29 were eligible for inclusion (Supplementary Table 3). We selected studies that assessed p53 IHC as an adjunct test to histopathology assessment of dysplasia/EAC on surveillance esophageal biopsies and reported subsequent progression to HGD/EAC, in patients with baseline NDBE, IND, or LGD and excluded those studies with follow-up of <1 year. The 29 studies included 15 case-control studies, 13 cohort studies, and 1 study with a case-control cohort and a prospective validation cohort. All studies were from Western countries. Baseline pathology with respect to IND, LGD, and NDBE varied and the mean duration of follow-up was 4.4 years (range, 2.3–6.2 years). There was considerable variability between studies in how aberrant p53 expression was assessed and scored strictly overexpression of the p53 protein on IHC (13 studies) or as absent or overexpression of the p53 protein (13 studies) and the definition of aberrant p53 expression was not available for the remaining 3 studies. The threshold for overexpression varied, with some studies using a percentage of positive cells in the epithelium or the glands, and others relied on qualitative assessments by pathologists. In addition, there was inconsistency in antibody selection and staining protocols. All of these differences may have contributed to the significant variation in diagnostic performance of aberrant p53 expression between studies.

Benefits

The critical outcomes that informed the benefits for this PICO question were predicting progression to HGD/EAC

(based on cohort studies) and diagnostic test characteristics (Table 1). The pooled proportion of patients with aberrant p53 expression based on the combined baseline pathology of NDBE, IND, and LGD was 20% (95% CI, 14%–27%; $I^2 = 90\%$). The pooled rate of progression among patients with BE undergoing endoscopic surveillance with aberrant p53 expression to HGD/EAC was 8 per 100 person-years (95% CI, 6–11; $I^2 = 26.5\%$). In contrast, the pooled rate of progression to HGD/EAC among patients without aberrant p53 expression was 0.3 per 100 person-years (95% CI, 0.1–0.6; $I^2 = 26.6\%$). Compared with patients without aberrant p53 expression, patients with aberrant p53 had significantly higher risk for progression to HGD/EAC (RR, 10.17; 95% CI, 6.89–15; $I^2 = 12\%$) (Figure 6, Table 7).

The pooled proportion of aberrant p53 expression in patients with NDBE was 5% (95% CI, 1%–11%; $I^2 = 83\%$). The pooled rate of progression to HGD/EAC among patients with NDBE with aberrant p53 was 7 per 100 person-years (95% CI, 4–11 per 100 person-years; $I^2 = 0\%$) compared with 0.5 per 100 person-years (95% CI, 0–2.2 per 100 person-years; $I^2 = 90\%$) without aberrant p53 expression. Compared with NDBE without aberrant p53, patients with NDBE with aberrant p53 had significantly higher risk for progression to HGD/EAC (RR, 4.8; 95% CI, 3.12–7.38; $I^2 = 92\%$). Using standard annual risk of progression of 0.6% among patients with NDBE,¹⁷³ p53 testing resulted in an absolute increase of 23 additional cases of HGD/EAC per 1000 individuals tested-years (95% CI, 13–38 more cases).

The pooled proportion of aberrant p53 expression in patients BE with LGD was 52% (95% CI, 34%–70%; $I^2 = 79.4\%$). The pooled rate of progression into HGD/EAC among patients with BE and LGD with aberrant p53 expression undergoing endoscopic surveillance was 11 per 100 person-years (95% CI, 4–20 per 100 person-years; $I^2 = 61.9\%$) compared with 1 per 100 person-years (95% CI, 0–5 per 100 person-years; $I^2 = 55.9\%$) without aberrant p53 expression. Compared with patients with BE and LGD without aberrant p53, patients with LGD with aberrant p53 had significantly higher risk for progression to HGD/EAC (RR, 2.53; 95% CI, 1.56–4.1; $I^2 = 0\%$). Using standard annual risk of progression of 1.7% among patients with LGD,¹⁴² p53 testing resulted in an absolute increase of 6 additional cases of HGD/EAC per 1000 individuals tested (95% CI, 1–13 more cases) (Figure 6 and Table 7).

The pooled proportion of aberrant p53 expression in patients with BE and IND was 28% (95% CI, 16%–42%; $I^2 = 81.6\%$). The pooled rate of progression to HGD/EAC among patients with BE and IND with aberrant p53 expression undergoing endoscopic surveillance was 6 per 100 person-years (95% CI, 0–15 per 100 person-years; $I^2 = 73\%$) compared with 1 per 100 person-years (95% CI, 0–2 per 100 person-years; $I^2 = 0\%$) without aberrant p53 expression. Compared with patients with BE and IND without aberrant p53 expression, patients with BE and IND with aberrant p53 expression had a significantly higher risk for progression to HGD/EAC (RR, 4.99; 95% CI, 2.98–8.35; $I^2 = 0\%$). Using standard annual risk of progression of

1.5% among patients with IND,¹⁴³ p53 testing resulted in an absolute increase of 20 additional cases of HGD/EAC detected per 1000 individuals tested (95% CI, 10–36 more cases) (Figure 6 and Table 7).

Harms

No studies specifically addressing harms associated with p53 testing were identified but potential concerns were: unnecessary surveillance endoscopies at shorter intervals or EET for FP results and extending surveillance intervals for FN results. In an MA of 10 studies, the pooled sensitivity was 0.42 (95% CI, 0.30–0.54) and the pooled specificity was 0.96 (95% CI, 0.90–0.99) (Table 7 and Figure 7). Assuming a 0.6% risk for progression in patients with NDBE, for 1 year of follow-up, for every 3 per 1000 TP test results there were 40 FP results and for every 954 TN results there were 3 FN test results. The calculated PPV was 5.96%, and NPV was 99.96% for 1 year of follow-up (Table 7). Furthermore, a subgroup analysis among patients with BE and IND and LGD was performed (IND only [6 studies], LGD and IND together [1 study] and LGD only [5 studies]). The pooled sensitivity for BE and IND/LGD was 0.77 (95% CI, 0.62–0.87) and specificity was 0.76 (95% CI, 0.66–0.85). For patients with BE and IND, the pooled sensitivity was 0.72 (95% CI, 0.47–0.88), and the pooled specificity was 0.79 (95% CI 0.60–0.91). Using a risk for progression of 1.5%, the test accuracy per 1000 individuals was: TP 11, FP 207, TN 778, and FN 4 for calculated PPV of 4.2% and NPV of 99.5%. Similarly, for LGD only, the pooled sensitivity was 0.85 (95% CI, 0.66–0.94), and the pooled specificity was 0.64 (95% CI, 0.55–0.73). Using a 1.73% progression rate, the test accuracy per 1000 individuals was: TP 15, FP 315, TN 668, and FN 2 for calculated PPV of 4.5%, and NPV of 99.7% (Table 7 and Figure 7). The author panel had extensive discussions regarding the downstream consequences of FP results: unnecessary endoscopies and possible EET and potential adverse without any added benefit, potential financial and psychological burden, and unnecessary health care costs and resource overutilization. The FN results could have the potential for false reassurance, leading to extending surveillance intervals, and placing patients at risk for disease progression and poor overall outcomes. The author panel also recognized the significant variability among pathologists in the interpretation of these results, the lack of standardized criteria that may contribute to inconsistent reporting adding to the diagnostic uncertainty complicating clinical decision making.

Certainty in Evidence of Effects

The overall certainty in the evidence was very low (Table 7, Supplementary Table 9). Using the QUADAS-2 tool, there were issues in multiple domains leading to very serious risk of bias: (1) patient selection: case-control study design was used in more than a one-half of the studies and not all the studies stratified results based on baseline histology; (2) index diagnostic test (p53): there

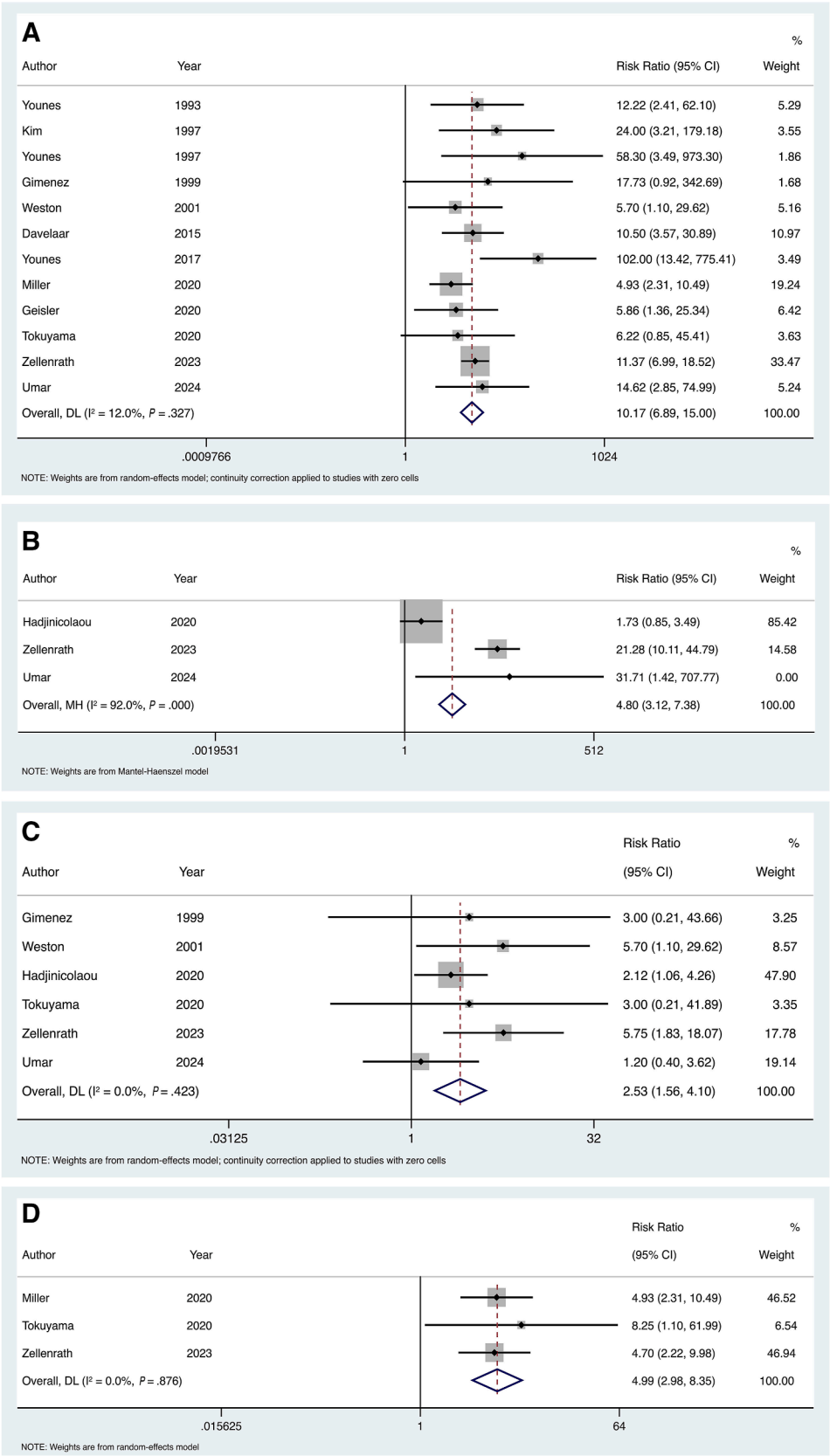


Figure 6. Forest plots for pooled outcome of progression to HGD/EAC in patients with BE with aberrant p53 expression compared with those without. (A) BE with NDBE, IND, and LGD. (B) Nondysplastic BE. (C) BE with LGD. (D) BE with IND.

Table 7. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for Population, Intervention, Comparison, Outcome Question: Role of Biomarkers (p53 Staining) in Predicting Progression in Patients With Barrett's Esophagus Undergoing Surveillance Endoscopy

Sample site	NDBE	IND	LGD
Sensitivity (95% CI) ^a	0.42 (0.30–0.54)	0.72 (0.47–0.88)	0.85 (0.66–0.94)
Specificity (95% CI)	0.96 (0.90–0.99)	0.79 (0.60–0.91)	0.64 (0.55–0.73)
Assumed risk of progression to EAC over 1 yr, %	0.6	1.5	1.73
Outcome, effect per 1000 patients tested			
TPs (patients with aberrant P53 who progress to EAC)	3 (2–3)	11 (7–13)	15 (12–16)
FNs (patients with normal p53, but progress to EAC)	3 (3–4)	4 (2–8)	2 (1–5)
No. of studies	9	7	7
No. of patients	686	271	271
Certainty of evidence	⊕○○○ Very LOW ^{b,c}	⊕○○○ Very LOW ^{b,c}	⊕○○○ Very LOW ^{b,c}
TNs (patients normal p53 and did not progress to EAC)	954 (895–984)	778 (581–887)	668 (609–708)
FPs (patients with aberrant p53, but did not progress to EAC)	40 (10–99)	207 (98–404)	315 (275–374)
No. of studies	9	7	7
No. of patients	2170	706	707
Certainty of evidence	⊕○○○ Very LOW ^{b,c}	⊕○○○ Very LOW ^{b,c,d}	⊕○○○ Very LOW ^{b,c}

NOTE. This table is based on applying the sensitivity and specificity estimates to calculate TPs, FPs, TNs, and FNs in a hypothetical population of 1000 individuals.

^aSensitivity and specificity were pooled from studies that report on combine HGD/EAC outcome.

^bQUADUS 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) patient selection: case-control study design was used in more than one-half of the studies, not all of the studies stratify for baseline pathology; (2) index test: there were concerns regarding applicability if the index test because there was significant variability in interpretation of the test results; (3) reference test was standard biopsy and progression to EAC, but the follow-up period and therefore interpretation varies between the studies.

^cSerious inconsistency, high I^2 .

^dThe FP range crosses the clinical threshold of 20% (200/1000).

were concerns regarding applicability of the index test; and (3) reference test was standard biopsy and progression to HGD/EAC with variable follow-up. Furthermore, there was significant heterogeneity largely driven by significant variability in performing and interpreting p53 testing, imprecision (FP results crossed the clinical threshold of 20% and low event rate for number of patients progressing to HGD/EAC) and finally, indirectness. There was a lack of studies reporting on how p53 results impacts decision making in clinical practice. Studies addressing the cost-effectiveness of p53 assessment are limited and with methodological issues.^{174,175}

Discussion

The guideline panel makes no recommendation in favor of or against the use of p53 testing and the role of p53 for risk stratification among patients with BE as a knowledge gap. There are several issues with the routine use of p53 IHC in clinical practice, including the subjective nature in the interpretation of p53, the need for interpretive skill, and no consistent scoring system. Different criteria have been reported. Redston et al¹⁷⁶ have reported criteria that have undergone internal validation with a large longitudinal cohort and have been validated by sequencing. These criteria and others have

suggested that abnormal p53 IHC stain in a single-positive crypt is a sensitive and specific marker of dysplasia, however, the reproducibility of this system by other pathologists is uncertain.^{176,177} In arriving at this recommendation, the guideline panel heavily weighed the following factors: limited prospective validation data, suboptimal diagnostic characteristics, and the subjective nature of this test. In particular, the panel was uncertain how the results of routine p53 IHC in NDBE should be used to guide management. Patients with aberrant p53 may not have a great enough risk of progression to warrant EET, and patients with normal p53 may not have low enough risk to warrant infrequent surveillance or cessation of surveillance.

Multiple studies have suggested that p53 IHC can be used in confirming the diagnosis of dysplasia and enhancing the interobserver agreement among pathologists, a major issue in the evaluation of patients with BE related neoplasia.^{178–181} Studies have shown that the use of p53 IHC significantly improved diagnostic concordance for dysplasia among pathologists.^{167,181} A study that included 51 pathologists from more than 20 countries investigated BE concordance rates and pathologist features predictive of diagnostic concordance using 55 digitized biopsies across the diagnostic spectrum, before and after viewing matched p53 labeling. Addition of matched p53-labeled slides

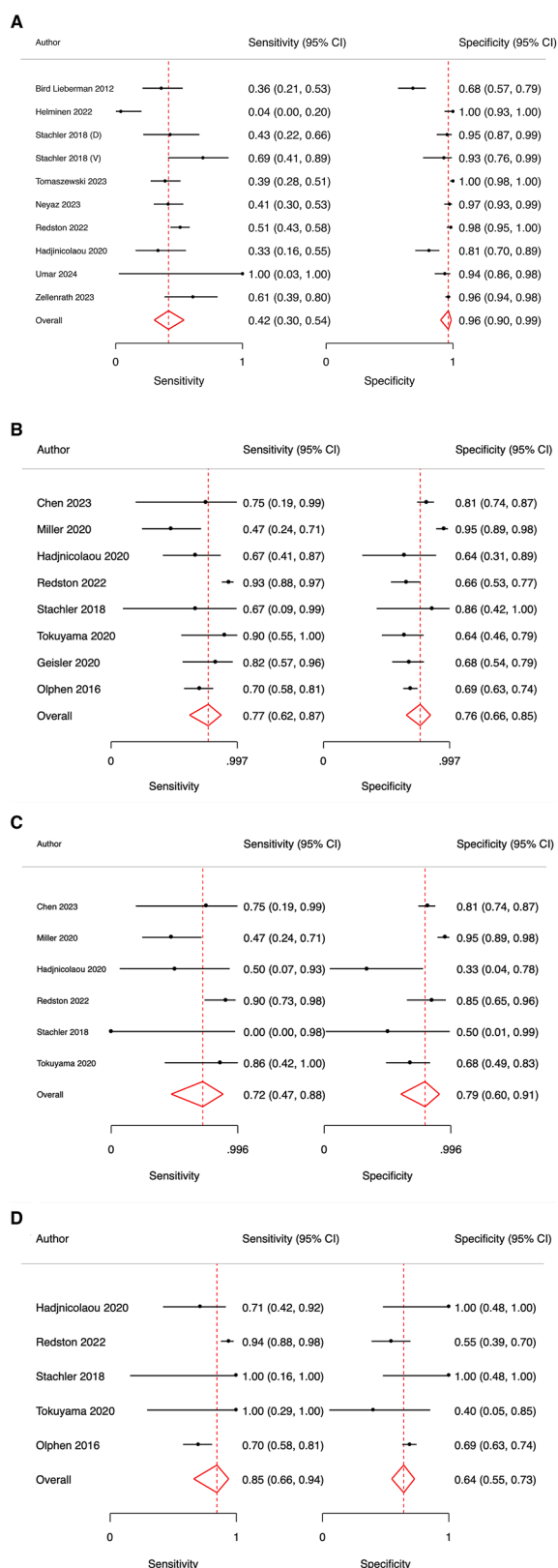


Figure 7. Forest plots for pooled sensitivity and specificity of p53 assessment among patients with BE undergoing surveillance endoscopy. (A) NDBE, sensitivity and specificity. (B) BE with IND/LGD combined, sensitivity and specificity. (C) BE with IND, sensitivity and specificity. (D) BE with LGD, sensitivity and specificity.

improved diagnostic concordance (NDBE: 78.8% vs 83.8%, IND: 22.9% vs 23.5%, LGD: 41.6% vs 46%, HGD: 71.1% vs 70.7%, and LGD/HGD: 77.5% vs 79.3%) and reduced the number of major overinterpretations and underinterpretations.¹⁶⁷ In addition, p53 IHC may also help clarify the presence or absence of dysplasia in cases initially diagnosed as IND by reducing the number of patients diagnosed with IND (>50% reclassified as NDBE).^{146,181} However, progressors to HGD/EAC include patients with histologic LGD but normal p53, so it is not clear that p53 should be used to alter the histologic interpretation of LGD, which still carries independent information.

What is the role of TissueCypher testing in patients with Barrett's esophagus undergoing endoscopic surveillance? Is the TissueCypher test superior to the grade of dysplasia in predicting progression in patients with Barrett's esophagus?

Recommendation 6: In patients diagnosed with NDBE, BE with IND or BE with LGD, the AGA makes no recommendation for or against the routine use of TissueCypher testing as an adjunct test to histopathology. (*Knowledge gap*)

TissueCypher, a tissue systems pathology assay, is an innovative approach that uses systems biology, viewing tissue as a system comprising multiple compartments that can be analyzed quantitatively for genetic, immunologic, vascular, and morphologic features relevant to progression from BE to EAC.¹⁶⁴

Summary of the Evidence

Evidence informing the recommendation for the use of TissueCypher (also known as Tissue Systems Pathology-9 test, Castle Biosciences, Friendswood, TX) as an adjunct test during BE surveillance comes from 5 studies (1 cohort and 4 case-control studies). We identified 2 individual-level data SR/MAs by Iyer et al¹⁸² and Davison et al¹⁸³ that evaluated the risk of progression to HGD/EAC based on TissueCypher risk class (high, intermediate, and low). Both MAs included the same 4 case-control and 1 cohort study by Frei et al¹⁸⁴ (the latter included patients from the screening cohort for the Surveillance vs Radiofrequency Ablation [SURF] trial). An updated literature search (August 2017 to January 2025) (Supplementary Table 3) found no additional studies. Baseline pathology in these studies were the following: NDBE (1 study),¹⁸⁵ LGD (1 study),¹⁸⁴ and a combination of NDBE/IND/LGD (3 studies).^{186–188} The training set cases and controls used to train the algorithm were excluded from both MAs. Four studies assessed the utility of TissueCypher in predicting incident HGD/EAC (≥ 1 year after a BE diagnosis) and 1 study assessed the utility of TissueCypher in predicting prevalent HGD/EAC (within 1 year of BE diagnosis). TissueCypher risk class was divided into high, intermediate, and low.

Benefits

The critical outcomes were: (1) predicting progression to HGD/EAC and (2) test performance (Tables 1 and 8, Supplementary Table 9). The MA by Iyer et al¹⁸² analyzed individual-level data from 552 patients with BE who were tested with TissueCypher (152 progressed to incident HGD/EAC and 400 nonprogressors). Baseline pathology included NDBE (n = 472), IND (n = 32), and LGD (n = 48). In the overall cohort, (1) comparing high-risk vs intermediate/low-risk, TissueCypher had a sensitivity of 38% and specificity of 94% (OR, 6; 95% CI, 2.99–12) for progression to HGD/EAC and (2) comparing high/intermediate risk vs low risk, TissueCypher had a sensitivity of 55% and specificity of 82% (OR, 1.58; 95% CI, 0.8–3.12) for progression to HGD/EAC. In the NDBE subgroup of 472 patients (112 progressors, 360 nonprogressors) (1) high-risk TissueCypher had a sensitivity of 37% and specificity of 96% (OR, 13.55; 95% CI, 4.90–37.43) for progression to HGD/EAC and (2) high/intermediate-risk compared with low-risk category, TissueCypher had a sensitivity of 52% and specificity of 85% (OR, 95% CI, 3.73–9.52) for progression to HGD/EAC. In the LGD subgroup of 48 patients (31 progressors, 17 nonprogressors), high/intermediate risk, TissueCypher had a sensitivity of 71% and a specificity of 35% (OR, 1.33; 95% CI, 0.38–4.71; *P* = .65) for progression to HGD/EAC. In the IND subgroup of 32 patients (9 progressors, 23 nonprogressors), high/intermediate risk, TissueCypher had a sensitivity of 33% and a specificity of 74%, (OR, 1.42; 95% CI, 0.27–7.52; *P* = .68) for progression

to HGD/EAC (Table 8). Data were not available for high risk only among the subgroup of patients with LGD and IND. In a separate study from Davison et al¹⁸³ (40 prevalent progressors, and 509 nonprogressors), TissueCypher had a sensitivity of 77.5% in detecting missed prevalent cases of HGD/EAC. Patients who scored high or intermediate risk were more likely to harbor prevalent HGD/EAC (HR, 30.9; 95% CI, 13.4–87.6 and HR, 7.6; 95% CI, 2.9–20.8, respectively).

Harms

No studies directly addressed harms associated with the use of TissueCypher testing. As described above for high/intermediate risk TissueCypher, results compared with the low-risk category in patients with NDBE yielded a sensitivity of 52% and specificity of 85%. Using the 0.6% HGD/EAC progression rate per year, among 1000 NDBE there were 3 TP results, 3 FN results, 845 TN results, and 149 FP results (Table 8). Calculated PPV and NPV over 5 years was 9.8% and 98.3%, respectively. Lastly, for IND (n = 48) and LGD (n = 32), the numbers of participants in the studies were very low, making the pooled sensitivity and specificity estimates very imprecise. Similar to the discussion regarding the use of p53 testing, the author panel discussed the following downstream consequences of FP results: unnecessary endoscopies and possible EET and potential AEs without any added benefit, potential financial and psychological burden, and unnecessary health care costs and resource overutilization. The FNs could result in

Table 8. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for Population, Intervention, Comparison, Outcome Question: Role of Biomarkers (TissueCypher) in Predicting Progression in Patients With Barrett's Esophagus Undergoing Surveillance Endoscopy

Sample site	NDBE	IND	LGD
Sensitivity of intermediate or high-risk score (95% CI)	0.52 (0.43–0.61)	0.66 (0.58–0.74)	
Specificity of low-risk score (95% CI)	0.85 (0.78–0.92)	0.76 (0.69–0.83)	
Assumed risk of progression to EAC over 1 yr, %	0.6	1.5	1.73
Outcome, effect per 1000 patients tested			
TPs (patients with int/high TC score who progress to EAC)	3 (3–4)	10 (9–11)	11 (10–13)
FNs (patients with low TC score, but progress to EAC)	3 (2–3)	5 (4–6)	6 (4–7)
No. of studies	5		5
No. of patients	112		40
Certainty of evidence	⊕⊕○○ LOW ^a	⊕○○○ Very LOW ^{a,b}	
TNs (patients low TC score and did not progress to EAC)	845 (775–914)	749 (680–818)	747 (678–816)
FPs (patients with int/high TC score, but did not progress to EAC)	149 (80–219)	240 (170–310)	236 (167–305)
No. of studies	5		5
No. of patients	360		40
Certainty of evidence	⊕○○○ Very LOW ^{a,b}	⊕○○○ Very LOW ^{a,b}	

NOTE. This table is based on applying the sensitivity and specificity estimates to calculate TPs, FPs, TNs, and FNs in a hypothetical population of 1000 individuals.

^aQUADUS 2 tool was used for assessing risk of bias and there were issues in multiple domains: (1) patient selection: case-control study design was used in more than one-half of the studies, not all of the studies stratify for baseline pathology; (2) index test: there were concerns regarding applicability if the index test because there was significant variability in interpretation of the test results; (3) reference test was standard biopsy and progression to EAC, but the follow-up period and therefore interpretation varies between the studies.

^bThe FP range crosses the clinical threshold of 20% (200/1000).

the potential for false reassurance, leading to extending surveillance intervals, placing patients at risk for disease progression and poor overall outcomes.

Certainty in Evidence of Effects

The overall certainty in the evidence for TissueCypher was very low (Table 8, Supplementary Table 9). Using the QUADAS-2 tool, there were issues in multiple domains leading to very serious risk of bias and very serious imprecision (the number of patients with IND and LGD was very small). Many of the same limitations to the use of p53 staining were identified with the use of TissueCypher testing (Table 8). The author panel also acknowledged the lack of robust studies on patient preferences, cost-effectiveness, and how TissueCypher results should impact decision making in clinical practice.^{175,189}

Discussion

The guideline panel made no recommendation for or against the use of TissueCypher testing and identified the role of TissueCypher testing for risk stratification among patients with BE as a knowledge gap. TissueCypher is a tissue systems pathology assay that can be analyzed quantitatively for genetic, immunologic, vascular, and morphologic features relevant to progression from BE to EAC.¹⁶⁴ This test is performed on formalin-fixed, paraffin-embedded biopsy specimens that demonstrate BE and uses a spatialomics-based, multiplexed fluorescent imaging platform to automatically and objectively quantify 9 protein-based biomarkers, nuclear morphology, and tissue architecture. The quantitative image analysis is linked to a risk-prediction algorithm that integrates 15 quantitative image analysis features to produce a risk score ranging from 0 to 10, which then classifies patients into high, intermediate, and low risk for progression to HGD/EAC within 5 years.^{186,187,190,191} TissueCypher has the advantage of being an objective test using a locked, automated assay algorithm, but the panel could not recommend its routine use due to suboptimal diagnostic performance, high cost, and lack of prospective validation data. Its test characteristics are similar to p53 when combining high and intermediate risk score, as suggested by the company (albeit without direct comparison with p53 within the same cohorts). Ongoing studies, including a multicenter RCT, will help determine whether TissueCypher can accurately predict progression in patients with BE and LGD and in turn benefit from EET.¹⁹²

Although the panel could not make a recommendation for routine use of these biomarkers for risk stratification in patients with BE undergoing surveillance, it should be noted that the panel does not recommend against the use of these biomarkers, given that these tests may be better in some instances than histopathologic diagnosis and may provide benefit in a subset of patients with BE. Future research needs to focus on validation of biomarkers in prospective trials (ideally RCTs); cost-effectiveness analysis of routine use; automated assessment of p53 expression to reduce subjectivity; and patient values and preferences,

and assess critical end points of EAC incidence and mortality and ultimately define the cohort likely to benefit the most from these tests. Several of these knowledge gaps are currently being assessed in prospective trials, results of which will impact the recommendations provided in this document. In addition, there are several other novel biomarkers (single or panel) that are being investigated currently using biopsy specimens or brushings to improve risk stratification.^{193,194} Studies performing a careful comparison between the available risk-stratification strategies will be needed. Finally, a judgment must be made for acceptance of an FN biomarker test (if at all) that could increase the risk of missed cancer.

What Do Other Guidelines Say?

These recommendations are consistent with the 2022 American College of Gastroenterology guidelines on diagnosis and management of BE.⁵⁰ The British Society of Gastroenterology guidelines state that biomarker panels cannot yet be recommended as routine care until evidence from RCTs is available. However, these guidelines suggest that p53 immunostain may improve the diagnostic reproducibility of a diagnosis of dysplasia in BE and should be considered as an adjunct to routine clinical diagnosis.⁵¹ Similarly, the European Society of Gastrointestinal Endoscopy guidelines do not recommend the routine use of molecular biomarkers in patients with no evidence of dysplasia. Those guidelines recommend the use of p53 IHC to support reproducibility of dysplasia diagnosis and aid the assessment of atypia of uncertain significance.⁵²

Prevention of Progression: Chemoprevention and Antireflux Surgery

What is the role of chemopreventive strategies in the prevention of neoplastic progression in patients with Barrett's esophagus?

Recommendation 7: In adult patients with BE, the AGA suggests the use of daily PPI therapy compared with no PPI therapy for the prevention of neoplastic progression of BE. (Conditional recommendation, low certainty)

Implementation Consideration

- In patients with BE, counsel tobacco cessation and weight loss if overweight or obese.

Summary of the Evidence

Evidence informing the recommendation for the use of PPI therapy vs no PPI to prevent progression to HGD/EAC in patients with BE is derived from RCTs, observational cohort, and case-control studies. A 2020 SR/MA (12 studies, 6 cohort, 6 case-control) evaluated the risk of progression to HGD/EAC in patients on vs off PPI.¹⁹⁵

An updated search (October 1, 2020 to January 2025) (Supplementary Table 3) identified 355 studies, but no relevant studies were identified for further analysis. The prior SR/MA extracted ORs from individual studies, which used multivariate analyses to control for various confounders including age, sex, race, smoking, and BE length. There was significant heterogeneity among the studies ($I^2 = 78\%$).

The 2 largest cohort studies included in the prior SR/MA were by Krishnamoorthi et al¹⁹⁶ and Gaddam et al.¹⁹⁷ Krishnamoorthi et al (12,373 patients in a UK research database) analyzed the incidence of EAC among patients on vs off PPIs, adjusting for age, gender, smoking, body mass index, hiatal hernia, type 2 diabetes, and use of various medications. The mean age was 63 years and 63% were male. Absence of dysplasia at study inception was not identified definitively in this study; however, inclusion of patients who had not had an upper endoscopy within 3 years before study date was used as an indicator of absence of dysplasia. Gaddam et al (3635 patients with BE) followed patients undergoing screening/surveillance to assess risk of HGD/EAC adjusting for sex, age, race, BE length, histamine-2 receptor antagonist use, smoking history, and aspirin or nonsteroidal anti-inflammatory drug use. Mean age was 61 years, 88% were male, and mean BE length was 3.5 cm.

Indirect evidence as supportive data informing the recommendations for the use of PPI was derived from the AsPECT trial, a multicenter (United Kingdom and Canada) RCT examining twice-daily PPI vs once-daily PPI to prevent progression to HGD/EAC, and PPI with aspirin vs PPI alone¹⁹⁸ using a 2×2 factorial design to randomize patients with BE into high-dose (esomeprazole 40 mg twice daily) or low-dose PPI (esomeprazole 20 mg once daily) with or without aspirin (300 mg/325 mg daily) for at least 8 years. Mean age was 59 years, 80% were male, and mean BE length was 4 cm. Median follow-up was 8.9 years (interquartile range, 8.2–9.8 years), making up 20,095 patient-years of follow-up. The primary composite end point was time to HGD, EAC, or all-cause mortality. In total, 2557 patients were recruited between 2005 and 2009, including 1281 in the high-dose PPI group (704 without aspirin, 577 with aspirin) and 1,276 in the low-dose PPI group (705 without aspirin, 571 with aspirin).

Evidence on harms associated with PPI use are derived from 2 RCTs: AsPECT trial, COMPASS, and MANAGE.^{199,200} In the COMPASS trial, 17,598 participants with stable atherosclerotic disease were enrolled in a double-blind, placebo-controlled trial with a 3×2 factorial design and randomized to receive low-dose rivaroxaban with aspirin, high-dose rivaroxaban alone, or aspirin alone. Among participants not already taking a PPI (64% of study cohort), individuals were randomized to receive pantoprazole 40 mg or placebo once daily. Although the study's primary outcome was rate of cardiovascular disease, it also assessed safety outcomes, including PPI adverse effects (pneumonia, *Clostridioides difficile* infection, non-*C difficile* enteric infections, fracture, gastric atrophy, chronic kidney disease,

and dementia). The mean age was 67.6 years, 78% were male, and 60% were White European. The median follow-up was 3 years (interquartile range 2.5–3.6 years).

The MANAGE trial,²⁰⁰ which used a similar factorial design randomized 556 of 1754 patients to receive dabigatran vs placebo, and all patients not taking PPI were also randomized to omeprazole 20 mg once daily vs placebo. Although study results regarding PPI outcomes have not yet been published in a peer-reviewed journal, preliminary findings were made available through communication with the study authors. Patients were followed for a mean of 17 months to assess major upper gastrointestinal events and PPI adverse events, including *C difficile*-associated diarrhea, diarrhea, community-acquired pneumonia, and fracture.

Benefits

The critical outcomes were: (1) progression to HGD/EAC and (2) progression to EAC (Tables 1 and Supplementary Tables 10 and 11). Other patient-important outcomes were EAC mortality. In the SR/MA by Chen et al¹⁹⁵ daily PPI use reduced the risk of progression to HGD/EAC compared with no PPI use, with 84 fewer per 1000 (from 44 fewer to 112 fewer) and a pooled OR of 0.47 (95% CI, 0.32–0.71).

Indirect data from the AsPECT trial comparing high-dose (twice daily) PPI vs low-dose (daily) PPI found 13 fewer HGD/EAC per 1000 (ranging from 9 more to 29 fewer); HGD/EAC occurred in 84 (6.6%) of the twice-daily PPI group vs 100 (7.9%) of the once-daily PPI group (RR, 0.84; 95% CI, 0.63–1.11). For progression to EAC alone, the absolute risk reduction was 1 fewer per 1000 (from 16 more to 12 fewer), but only indirect evidence was available because the comparison was twice-daily PPI with once-daily rather than PPI with no PPI (AsPECT). Comparing twice-daily PPI vs daily PPI, EAC occurred in 40 patients (3.1%) in the high-dose PPI group vs 41 patients (3.2%) in the low-dose PPI group (HR, 0.97; 95% CI, 0.63–1.50) (Supplementary Table 10).

For EAC-related mortality also using the AsPECT trial, high-dose PPI vs low-dose PPI was associated with fewer deaths: 8 events (0.6%) vs 12 events (0.9%), respectively (HR, 0.65; 95% CI, 0.27–1.57). Lastly, the AsPECT trial also evaluated aspirin plus PPI vs PPI alone: HGD/EAC occurred in 65 of 1138 patients (5.7%) who received aspirin vs 93 of 1142 patients (8.1%) who did not receive aspirin. EAC occurred in 31 patients (2.7%) who received aspirin vs 30 patients (2.6%) who did not receive aspirin (HR, 1.0; 95% CI, 0.62–1.58). EAC-related mortality was not analyzed for this comparison due to too few events.

Harms

The patient-important outcome included SAEs related to PPI use. In the AsPECT trial, SAEs attributed to esomeprazole were reported using the Common Terminology Criteria for Adverse Events. Thirteen events across both low-dose (4 SAE) and high-dose (9 SAE) PPI groups were attributed to

the drug, corresponding to a low annual SAE rate of 0.06%. We also evaluated SAEs potentially associated with PPI use in several observational studies.^{199,201–207} We restricted our evaluation to select SAEs based on the perceived frequency with which patients may raise related concerns, such as in the case of dementia, and on availability of evidence (Supplementary Figure 4).

Pooled data from the COMPASS and MANAGE trials for PPI compared with placebo showed minimal risks: an increase of 1 case of *C difficile* infection per 1000 (from 0 fewer to 3 more), 1 more pneumonia per 1000 (from 4 fewer to 7 more), and 5 fewer to 4 more fractures per 1000. Comparing the PPI vs placebo groups, the RRs of *C difficile* infection, fracture, and pneumonia were 2.48 (95% CI, 0.8–7.44), 0.98 (95% CI, 0.81–1.18), and 1.03 (95% CI, 0.88–1.20), respectively (Supplementary Figure 4). The panel acknowledged that both the COMPASS and MANAGE trials had relatively short follow-up (3 years in COMPASS and 1.4 years in MANAGE) limiting conclusions about long-term AEs, which are particularly relevant, given the prolonged use required in patients with BE. A recent meta-analysis of RCTs found no association of cardiovascular events with PPI therapy.²⁰⁸

Certainty of the Evidence

The overall certainty in the evidence across the critical outcomes was low (Supplementary Tables 10 and 11). Despite having higher certainty in harms, given the low certainty in the benefits of PPI, the overall certainty in the evidence was low. For progression to HGD/EAC, the evidence was very low due to inconsistency, as there were studies demonstrating significant benefit with PPIs, whereas some studies did not show any benefit ($I^2 = 78\%$). Although most of the studies were case-control in design with concern for residual confounding, the pooled OR in the prior SR/MA used multivariable-adjusted estimates, and thus, we did not further rate down for risk of bias. As there was direct high-quality evidence for PPI vs no PPI, we largely relied on data evaluating the question of twice-daily PPI vs once-daily PPI and rated down for indirectness on the level of comparison. For adverse events associated with PPI use, we used data from high-quality RCTs that had limited follow-up time, with overall moderate certainty of evidence. Studies addressing the cost-effectiveness of chemopreventive strategies and patient values or preferences using PPI therapy were not identified.

Discussion

PPIs are commonly prescribed in patients with BE to control GERD symptoms, heal erosive esophagitis, and as a chemopreventive agent to reduce progression to dysplasia and EAC.⁵⁰ High-dose twice-daily PPI therapy is standardly prescribed in BE-related neoplasia patients undergoing EET, details are highlighted in the AGA EET Guideline document.¹⁰ Current available evidence from observational studies suggests that PPIs may reduce the risk of neoplastic

progression to HGD/EAC. In addition, histamine receptor antagonists have shown no significant benefit.²⁰⁹

The panel recognized the potential adverse effects of PPIs that have been reported, but many of these studies are low-quality, retrospective, observational studies limited by confounding and other biases and, most importantly, do not establish causality.^{210,211} In most studies, biases can account for the small but statistically significant associations and these associations have no plausible biologic mechanism of action. Given the rarity of adverse events, the absolute risk to patients is small.²¹¹ It is recommended that patients with BE are prescribed at least once-daily PPI therapy to reduce the risk of neoplastic progression. Control of reflux symptoms along with healing/prevention of erosive esophagitis should also be accounted for in the dose of prescribed PPI therapy. The AGA published a recent Clinical Practice Update on long-term PPI therapy use that focuses on ensuring that the patient has a strong indication for long-term use; when indicated, counseling the patient regarding the rationale, the issues related to published literature on adverse events, and that benefits outweigh the potential risks; using the lowest effective dose; and for patients concerned about a specific adverse event, consider describing the absolute excess risk of the adverse event per patient-year and personalizing the discussion of risk.²¹¹

Epidemiologic evidence from observational studies and biomarker-based preclinical studies have shown that aspirin and nonsteroidal anti-inflammatory drugs may reduce the risk of EAC by inhibiting the cyclooxygenase pathway.^{212–217} The AspECT chemoprevention study demonstrated that high-dose PPI was superior to low-dose PPI for lengthening the time to reach the combined end point of death from any cause, HGD, or EAC (time ratio, 1.27; 95% CI, 1.01–1.58; $P = .038$). Censoring those with the use of concurrent nonsteroidal anti-inflammatory drugs, aspirin was superior to no aspirin (time ratio, 1.29; 95% CI, 1.01–1.66; $P = .04$). Finally, combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (time ratio, 1.59; 95% CI, 1.14–2.23; $P = .006$). Because of the small effect size, low event rates, and unclear impact on EAC incidence (the benefit was largely driven from a reduction in all-cause mortality), the panel made no recommendation regarding the use of aspirin or high-dose PPI therapy to prevent neoplastic progression in patients with BE. Long-term data on adverse events related to high-dose PPI are limited. Thus, a decision to prescribe high-dose PPI therapy to prevent neoplastic progression needs to account for the above factors (net benefit vs harms) along with patient values and preferences. The guideline authors acknowledge that the clinical profile of several patients with BE may require daily aspirin for cardio-protection. Evidence from the AspECT trial showed that participants taking aspirin were more likely to have adverse events than those who were not (RR, 1.17; 95% CI, 1.02–1.35) and may have been attenuated by the use of high-dose PPI therapy.^{198,218}

The guideline panel also acknowledged the growing body of literature describing the efficacy of potassium-competitive acid blockers in the management of patients with GERD and discussed in a recent AGA Clinical Practice Update.²¹⁹ The benefits of potassium-competitive acid blockers over PPIs include more rapid onset with initial dosing, no premeal dosing requirement, less variability in pharmacodynamic effects related to CYP2C19 metabolism, higher potency, and longer duration of effects; however, long-term safety data are lacking, and their role in BE for reflux symptoms, healing of erosive esophagitis and reduction in neoplastic progression in patients undergoing EET, is not known, and finally these medications are costly. Extrapolating the available data from patients with GERD, potassium-competitive acid blockers may be considered in patients with BE who continue to have symptoms or erosive esophagitis on twice-daily PPI therapy.

Implementation Consideration for Recommendation 7

In addition to acid suppression with PPIs, preventing neoplastic progression also includes behavioral modification. Tobacco use is both reflux-inducing as well as mutagenic,²²⁰ increasing the odds of developing BE by 67%. Many risk-prediction models, therefore, include smoking history as a factor when evaluating eligibility for screening for BE.⁵⁰ Furthermore, tobacco use also has been identified as a risk factor in BE progression to HGD as well as EAC,²²¹ with an HR of progression that is nearly double among tobacco users compared with nonusers. Likewise, tobacco cessation may reduce BE-associated risks. Previous data demonstrated that among smokers who had quit for >20 years, there was no increased risk of BE.²²² As a result, smoking cessation should be encouraged among patients undergoing BE surveillance. Although quantifiable evidence for risk reduction with tobacco cessation among patients with BE is lacking, encouraging such behavior has pleiotropic health benefits and plausible direct advantages for BE specifically. Recent GERD guidelines suggest avoidance of tobacco among those with GERD.¹³⁰ Likewise, screening for tobacco use and providing tobacco cessation counseling for all patients is an accepted quality measure and was recently adopted within a gastroenterology core measure set.²²³

Central adiposity is another important modifiable risk factor for BE. Obesity increases GERD risk²²⁴ and weight loss is recommended for overweight and obese individuals to control GERD symptoms.¹³⁰ Although body mass index alone is imperfect for measuring risks for BE,²²⁵ markers of insulin resistance are associated with increased risk for progression to EAC.²²⁶ A recent SR/MA showed in patients with NDBE and/or LGD, increasing body mass index was associated with an increased risk of progression to HGD and EAC in a dose-dependent manner.⁵⁸ Given that behavioral modification can lead to weight loss and symptom improvement in GERD,²²⁷ it is appropriate to encourage weight loss among overweight or obese patients

with BE to reduce symptomatic GERD and reduce the risk of progression.

What is the role of antireflux surgery compared with medical management using acid suppressive therapy in the prevention of progression in patients with Barrett's esophagus?

Recommendation 8: In patients with BE, the AGA suggests use of PPIs over surgery for the prevention of neoplastic progression to HGD or EAC. (Conditional recommendation, low certainty of evidence)

The critical outcomes that informed the benefits for this PICO question were: (1) progression to EAC and (2) progression to HGD/EAC (Table 1 and Supplementary Table 12). Other patient-important outcomes we evaluated included EAC mortality.

Summary of the Evidence

Evidence informing the recommendation came from 5 observational cohort studies and 1 RCT. A prior SR/MA (4 cohort studies, 1 RCT) by Wilson et al²²⁸ evaluated the risk of progression to HGD/EAC in patients who underwent antireflux surgery vs medical management with PPI/histamine-2 receptor antagonist (search through February 2021). Disease progression was defined as progression of intestinal metaplasia to LGD, HGD, or EAC or by progression of LGD to HGD and EAC ($I^2 = 0\%$). We updated the analysis with 1 additional cohort study by Åkerström et al²²⁹ that reported on neoplastic progression to HGD/EAC in patients with BE.

A single RCT, included in the aforementioned SR/MA, compared the impact of surgical vs medical management on progression in BE.²³⁰ This RCT (101 patients) randomized 43 patients to receive medical treatment (initially histamine-2 receptor antagonists, and omeprazole from 1992 onward) and 58 patients to undergo antireflux surgery (primarily Nissen fundoplication and Collis Nissen procedure in 2 patients). Median age was 50 years (medical therapy group) vs 43 years (surgical treatment group), 71% of patients were male, and median follow-up was 5 years. The largest Nordic population-based observational study by Åkerström et al²²⁹ analyzed 33,939 patients with BE from multiple national registries. Of the cohort, 542 patients (1.6%) underwent antireflux surgery (fundoplication) and 33,397 patients underwent medical management. In the antireflux surgery cohort, 67% were men, mean age was 64 years, and mean follow-up was 4.9 years. In the medical management group, 69% were men, mean age was 53 years, and mean follow-up was 11 years. Although no formal SR/MA was conducted, indirect evidence regarding harms was obtained from a prior SR/MA examining outcomes after antireflux surgery vs medical management of GERD.^{231,232}

Benefits

For progression to EAC, pooled data from 6 studies (5 studies identified from the SR/MA and the cohort study by Åkerström et al, showed that antireflux surgery vs medical management showed no clear benefit.^{228,229} Of 33,528 patients who underwent medical management, 438 (1.3%) progressed to EAC vs 14 of 765 patients (1.8%) who underwent antireflux surgery (RR, 1.33; 95% CI, 0.29–6.16); 4 more EAC cases per 1000 in the medical management group (from 9 fewer to 67 more) (Supplementary Figure 5). The largest cohort showed that antireflux surgery did not reduce the risk of EAC among patients with BE followed up for up to 32 years (adjusted HR, 1.9; 95% CI, 1.1–3.5).²²⁹

To assess for progression to HGD/EAC, data from the same 6 studies were used.^{228,229} Of 33,528 patients who underwent medical management, 443 (1.3%) progressed to HGD/EAC vs 19 of 765 patients (2.5%) who underwent antireflux surgery (RR, 0.86; 95% CI, 0.30–2.41) (Supplementary Figure 5). The absolute risk reduction was 2 fewer per 1000 (from 9 fewer to 19 more). There was no available evidence for the impact of antireflux surgery vs medical management in patients with BE on EAC mortality.

Harms

To evaluate SAEs related to antireflux surgery and PPIs, we evaluated data from an existing review focusing on the most common major adverse events after fundoplication, as well as rates of SAEs in existing RCTs comparing antireflux surgery vs medical management for the treatment of acid reflux or BE. Adverse events related to PPI therapy are reviewed in the Prevention of Progression: Chemoprevention and Antireflux Surgery section.

A comprehensive qualitative review by Yadlapati et al²³³ summarized short and long-term outcomes of laparoscopic fundoplication for GERD, drawing from large population-based cohorts and randomized trials. In a Swedish cohort of 2655 patients, the 30-day all-cause mortality rate was 0.1% and 4.1% had early complications (within 30 days of surgery), which included infection (1.1%), bleeding (0.9%), and esophageal perforation (0.9%).²³⁴ Reflux recurred in 17.7%, and 16.4% of the cohort required secondary antireflux surgery. An older review study evaluating outcomes after 10,489 primary fundoplication procedures found similar complication rates, including mortality rate of 0.08%, perforation in 0.8%, and wound infection in 0.1%.²³⁵ The mortality estimate of 0.1%–0.2% in the qualitative review is further supported by a more recent population-based cohort study of 5 Nordic countries, which evaluated 26,193 patients who underwent primary laparoscopic antireflux surgery and found 90-day postoperative mortality of 0.13%.²³⁶

We also evaluated adverse events from multiple RCTs comparing antireflux surgery vs medical management for the treatment of acid reflux or BE. No deaths within 30 days of surgery were reported in the available RCTs.^{230,237–240} The SOPRAN study randomized 310 patients with chronic GERD to PPI vs open antireflux surgery²³⁹ with an extended follow up to 14 years, found similar rate of SAEs between both groups

(antireflux surgery: 0.1% per patient-year; PPI: 0.1% per patient-year)²⁴¹ The LOTUS RCT randomized 554 patients with chronic GERD to acid suppression vs laparoscopic antireflux surgery.²³⁸ At 5-year follow-up of 372 patients, SAEs were reported by 28.6% of patients who underwent antireflux surgery vs 24.1% of the PPI group. At 7-year follow-up, SAEs remained similar between the antireflux surgery (0.2% per patient-year) and PPI (0.2% per patient-year) groups.²⁴¹

Certainty of the Evidence

The overall certainty in the evidence was low (Supplementary Table 12). For progression to HGD/EAC and EAC the evidence was low. We largely relied on data from nonrandomized studies included in an SR/MA. There was a concern for selection bias because of lack of consecutive patient inclusion and concerns about baseline comparability of the groups. However, the larger studies were without concerns, so we did not rate down for risk of bias. Studies addressing cost-effectiveness and patient values or preferences for these 2 strategies to reduce neoplastic progression in patients with BE were not identified.

Discussion

Surgical antireflux procedures for preventing neoplastic progression are appealing, given that they restore the gastroesophageal anatomic and physiological reflux barrier and reduce gastric contents (acid and bile) from reaching the esophagus.^{242,243} In addition, antireflux surgery is highly effective in reducing esophageal acid exposure, reducing gastroesophageal reflux episodes, healing esophagitis, and reducing symptoms associated with reflux.⁵⁰ However, the existing evidence does not consistently show superiority of antireflux surgery over medical management (typically using PPIs) in reducing neoplastic progression in patients with BE. Most of the studies that helped inform this recommendation were from single centers with small sample size, short follow-up, moderate heterogeneity, and potential biases due to patients with more severe disease more likely to undergo antireflux surgery, and confounding factors, such as BE length. In addition, other risk factors, such as tobacco smoking and body mass index—factors that could influence the decision to proceed with antireflux surgery—were not available in all studies.²²⁹ Data on medication use were not available for most studies and compliance was not routinely monitored. The failure rate of antireflux surgery is 20%–30% and recurrence of GERD symptoms at 5 years is reported in approximately 15% of patients who have undergone antireflux surgery.^{234,238,244} An SR/MA of antireflux surgery in patients with GERD reported that 28% randomized to surgical intervention still reported PPI use.²³¹ The decision to recommend PPIs over antireflux surgery was also driven by the overall low risk of progression in patients with NDBE, making it difficult to justify the risks associated with antireflux surgery highlighted above. The role of antireflux surgery in patients with BE-related neoplasia undergoing EET is highlighted in the AGA EET Guidelines document.¹⁰ Finally, future studies need to better define whether there are patients with BE

Table 9. Quality Measures and Other Proposed Quality Metrics in Barrett's Esophagus Surveillance

Quality metrics	Type of metric	Rationale
Sampling technique using the Seattle biopsy protocol	Process	Adequate sampling increases neoplasia detection compared with random biopsy sampling
Patients with NDBE undergo surveillance endoscopy no sooner than 3 yr	Process	Reduction in overutilization of endoscopy
Proposed quality metrics		
Performing surveillance endoscopy using a combination of high-definition WLE with CE (dye-based or virtual CE)	Process	Combination of high-definition WLE and CE associated with higher neoplasia rates compared with WLE alone
NDR defined by percent detection of dysplasia on index endoscopy for screening for BE	Process	Reflects the overall quality of the endoscopic examination
Barrett's inspection time that suggests inspection time of 1 min/cm of circumferential BE	Process	Reflects the quality of the endoscopic examination and may lead to increased NDR
Documentation of the extent of suspected or confirmed BE using the Prague criteria	Process	Consistent reporting that facilitates evidence-based decision making, improves communication and patient monitoring
Tracking and monitoring rates of PEEC and PEEN	Outcome	Reflects the overall performance of endoscopy as most cases of PEEC and PEEN are due to missed lesions

who are most likely to benefit from antireflux procedures to reduce the risk of neoplastic progression.

Quality Assurance in Barrett's Esophagus Surveillance

This section outlines proposed quality assurance framework to improve outcomes for BE surveillance in the context of value-based and quality focused health care (Table 9). These can be measured at an individual endoscopist level or across a facility, institution or system level by comparing performance to a benchmark. In this framework, non-adherence usually reflects suboptimal care. In this section, the term *quality measures* refers to metrics that are fully specified, tested, and validated and in quality payment programs, the term *quality indicators* refers to metrics derived from guideline documents, best practice statements, and consensus recommendations that do not necessarily have a specified numerator and denominator nor are they included in quality payment programs.^{245,246} Two quality measures that have received the most attention are frequency of surveillance endoscopies at appropriate intervals, that is, avoidance of overuse by repeating a surveillance endoscopy no sooner than 3–5 years in patients with NDBE and sampling the BE segment using the Seattle biopsy protocol.^{232,247} These measures have been developed as fully specified quality measures according to the established AGA conception to implementation pathway (<https://gastro.org/practice-resources/quality-and-performance-measures/>), which requires a strong recommendation based on moderate- or high-quality evidence.²⁴⁵ Several observational studies, including data from a national benchmarking registry (GIQuIC Registry) have demonstrated suboptimal adherence and wide variability among endoscopists and participating.^{114–116,248–251}

This section provides an overview of other proposed quality metrics in BE surveillance. Similar to adenoma

detection rate, a quality metric used to measure colorectal cancer screening care and associated with the highest penetrance in clinical gastroenterology practice, neoplasia detection rate (NDR) has been proposed to monitor quality in BE screening and surveillance. NDR is defined as the prevalence of HGD or EAC (numerator) within BE during the index screening endoscopy (denominator). A meta-analysis reported a pooled HGD/EAC prevalence of 7% (95% CI, 4%–10%) and proposed 4% as the NDR threshold on screening endoscopy.²⁵² Rates of dysplasia detection rate (DDR), defined as LGD or HGD, were reported using the GIQuIC Registry among patients undergoing surveillance of NDBE and recent studies have also highlighted the wide variability among endoscopists and participating sites for DDR in patients with NDBE.^{115,249}

Similar to the phenomenon of postcolonoscopy colorectal cancer, there is a growing body of literature describing BE-associated HGD and EAC before the next recommended endoscopic evaluation after an endoscopy that was ostensibly negative for HGD/EAC.²⁵³ To address this issue in BE endoscopy quality, an AGA Clinical Practice Update and an international expert panel introduced the concepts of PEEC and PEEN. PEEC is the preferred term for EAC and PEEN is the preferred term for HGD or EAC detected before the next recommended surveillance endoscopy in a patient with prior NDBE, provided it occurs between 6 months and 3 years after a screening or surveillance endoscopy.^{111,253} It is believed that most cases of PEEC/PEEN may be attributed to missed HGD/EAC, and the remaining cases may be attributed to rapidly progressive neoplasia due to accelerated pathways of neoplasia.^{111,254} Several factors may contribute to missed neoplasia at endoscopy, including suboptimal adherence to the Seattle biopsy protocol, limited mucosal sampling, inadequate time spent inspecting the BE segment, limited knowledge in the recognition of subtle findings of early neoplasia, and interobserver

variability among pathologists for the histologic classification of dysplasia.^{1,111,253} Observational studies, including a recent population-based cohort study, have provided contemporary estimates of PEEC and PEEN.^{1,48} An SR/MA reported that the proportion of EACs that were PEEC was 21% (95% CI, 13%–31%) and the proportion of HGD/EAC that were PEEN was 26% (95% CI, 19%–34%); outcomes of PEEC/PEEN defined as HGD/EAC detected within the first year after an index endoscopy that demonstrated NDBE, IND, or LGD.⁴⁸ Similarly, a recent population-based study conducted in Denmark, Finland, and Sweden (the Nordic Barrett’s Esophagus Study) that included 20,588 patients with newly diagnosed BE and showed that 23.5% of EACs were categorized as PEEC and 17.2% of HGD/EACs were categorized as PEEN.¹ Several sensitivity analyses that varied time intervals for occurrence of PEEC/PEEN demonstrated similar results.¹ In addition, a time-trend analysis demonstrated rising incidence rates for PEEC/PEEN.¹ These findings suggest suboptimal performance among current screening and surveillance practices and provide improvement opportunities for early neoplasia detection in BE. The International Expert Panel on PEEC and PEEN and the AGA Clinical Practice Update suggested that services and individual endoscopists review PEEC/PEEN cases periodically and identify areas for improvement, provided a construct for categorizing PEEC/PEEN cases according to their most plausible explanations and best practice advice to reduce PEEC/PEEN.¹¹¹ Recent data from the Nordic Barrett’s Esophagus Study demonstrated an overall inverse association between facility NDR and the risk of PEEC/PEEN adding to the validity of NDR and PEEC/PEEN as potential quality measures in BE.²⁵⁵

Although a number of additional quality metrics specific to BE have been proposed, incorporation into value-based care plans has been limited for several reasons, including lack of formal and validated testing. Several of these proposed

quality metrics do not have established thresholds that are adjusted for risk factors. Most of these proposed quality metrics are based on weak evidence or consensus expert opinions and most importantly, not tied to clinical outcomes. Monitoring of BE-specific quality metrics, such as use of the Seattle biopsy protocol, Barrett’s inspection time of at least 1 min/cm of columnar-lined epithelium, appropriate endoscopic surveillance intervals, and monitoring of NDR/DDR must correlate with important clinical outcomes, such as PEEC and, ideally, EAC mortality, as well as drive performance improvement to be considered a high-value quality measure.²⁴⁶ Other challenges include operationalizing these, especially NDR/DDR and PEEC/PEEN, given the variable individual number of endoscopies performed for BE per endoscopist and the overall low incidence of EAC. Future efforts will need to focus on how these proposed metrics could be calculated in an automated fashion and establish minimum standards using risk-adjusted strategies.

Knowledge Gaps

This evidence review identified several important knowledge gaps that need to be addressed in future studies and highlighted in Table 10.

Plans for Updating

Considerable resources are expended for the development of guidelines, and keeping guidelines up to date is a challenging process. Future update of this guideline will depend on the availability of new evidence on the existing and new interventions. We hope to incorporate the advances in the technological platforms and models of guideline development in the future updates without duplication or reproduction of the current guideline document.

Table 10. Knowledge Gaps

Knowledge gaps
The role of surveillance needs to be assessed in study designs that minimize contamination and is adequately powered to assess differences in EAC mortality.
Future studies need to identify risk-stratification tools to better guide endoscopic surveillance intervals, risk of progression, and discontinuation of surveillance.
Future studies need to address the role of biomarker risk stratification using nonendoscopic cell collection devices to guide endoscopic surveillance for early cancer detection and efficient resource allocation.
The role of AI in enhancing dysplasia and early cancer detection among patients with BE undergoing endoscopic surveillance examinations needs to be defined (ideally in RCTs).
The role of advanced sampling techniques, such as WATS-3D as an adjunctive and substitutive technique to a structured biopsy protocol needs to be addressed in future RCTs.
Validation of biomarkers needs to be performed in prospective trials (ideally in RCTs) that assess critical end points of EAC incidence and mortality.
Studies on clinical utility of p53 (using consistent terminology, analysis, and interpretation) as a diagnostic tool to improve interrater reliability for dysplasia and as a prognostic tool with longer follow-up (3 years/5 years) for predicting progression to neoplasia.
The role of potassium-competitive acid blockers in patients with BE needs to be evaluated in future studies for the outcomes of reflux control, healing of erosive esophagitis, reduction in neoplastic progression and outcomes in patients undergoing EET.
Future research needs to define patients with BE who are most likely to benefit from antireflux procedures to prevent neoplastic progression.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2025.09.012>.

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Acknowledgments

The authors would like to thank Ms Caitlin Bakker, Archer Library at University of Regina, Regina, Saskatchewan, for designing and conducting the literature searches and Melanie Stephens-Lyman, Garrett Adams, and Krisie Gardner for their administrative support.

Conflicts of interest

These authors disclose the following: Joel H. Rubenstein has received research funding from Lucid Diagnostics. David A. Katzka has received funding for consultation for Medtronic. Sachin Wani has received funding for consultation to Exact Sciences, Lucid, Enterotracker, Castle Biosciences, and Cyted and research support from Lucid, CDx Diagnostics, Cyted, and Exact Sciences. Siddharth Singh has received research funding from Pfizer. Margaret J. Zhou has received funding for consultation to Capsovision, Inc and Neptune Medical. The remaining authors disclose no conflicts.

Funding

Sachin Wani was supported by the National Institute of Health (1U01DK129191, 5U01CA271867-02) and the Katy O. and Paul M. Rady Endowed Chair in Esophageal Cancer Research. Joel H. Rubenstein was funded in part by the National Institutes of Health (U01DK129191) and Department of Defense (W81XWH2010898). Swathi Eluri was funded in part by the National Institutes of Health (5K23DK131338).