Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE guideline on screening and surveillance of Barrett's esophagus

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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The final document was approved by the ASGE Governing Board and the Standards of Practice Committee and represents the official guideline of the ASGE on these topics.

This document is the official American Society for Gastrointestinal Endoscopy guideline on screening and surveillance in patients with Barrett's esophagus (BE) and is based on systematic reviews of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation methodology. The document addresses key clinical questions that include the role and impact of screening and surveillance and the utility of advanced imaging and sampling modalities like chromoendoscopy, volumetric laser endomicroscopy, confocal laser endomicroscopy, EUS, and wide-area transepithelial sampling. This guideline complies with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines and aims to help clinicians understand the published literature and the quality of available data with the ultimate goal of optimizing care for patients.

This American Society for Gastrointestinal Endoscopy (ASGE) guideline addresses screening and surveillance of Barrett's esophagus (BE) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.[1] BE, a premalignant condition for esophageal adenocarcinoma (EAC), is characterized by the replacement of the normal squamous epithelium of the distal esophagus with metaplastic intestinal-type columnar epithelium.[2] BE is diagnosed in 7% to 10% of individuals with chronic GERD and is estimated to be present in 1% to 2% of the general adult population.[3,4] The incidence of EAC continues to be among the fastest-rising incidence cancers in the Western population and has been closely mirrored by a rise in EAC-related mortality.[5,6] In the United States, an estimated 16,940 persons were diagnosed with esophageal cancer (>60% with EAC) in 2017, and 15,690 died from their disease.[5,7,8] Prognosis for patients with EAC is strongly related to the stage at diagnosis. Unfortunately, most patients with EAC are diagnosed with late-stage disease, and the overall 5-year survival is <20%, which decreases to <5% for patients with distant disease at diagnosis.[3,5] Although the effectiveness of treatment strategies in the management of EAC has improved over the last decade,[9,10] recent data from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results program suggest that the proportion of EAC cases with localized, regional, or distant stage disease remains relatively stable, and, strikingly, 40% of EAC patients are still diagnosed with distant disease.[5]

BE progresses to invasive EAC through stages of intestinal metaplasia (nondysplastic BE [NDBE]), low-grade dysplasia (LGD), to high-grade dysplasia (HGD), to intramucosal carcinoma, and finally to invasive EAC.[11] It is this step-wise progression in patients with BE and stage-dependent survival in EAC that provides the impetus for screening and surveillance of BE. To ultimately impact the morbidity and mortality associated with EAC, several national and international medical societies recommend screening for BE in individuals with multiple risk factors and surveillance when the diagnosis of BE is established.[4,12-14] The last decade has seen several advances that attempt to address the limitations of current screening and surveillance strategies. These include construction of models to identify individuals at risk for BE and EAC and those at the highest risk of progression when diagnosed with BE, noninvasive and less expensive tools for screening, and the use of advanced imaging and sampling techniques during endoscopy. In this guideline document, we address the best available evidence for screening and surveillance of BE. Our previous guideline, published in 2018, addressed issues related to endoscopic eradication therapy (EET) for patients with BE-associated dysplasia and intramucosal cancer.[2]

GENERAL CONSIDERATIONS FOR SCREENING AND SURVEILLANCE

Screening is the mechanism through which populations may be assessed to identify individuals who have a disease or a preclinical condition that predisposes to a disease. Surveillance is the program through which these at-risk individuals are periodically assessed or examined to identify disease at a stage amenable to cure.[15] The evidence to support screening and surveillance endoscopy, a practice that has been recommended by national guidelines,[4,12-14] is highly variable and based on observational data. As discussed later, no randomized controlled trials (RCTs) have evaluated these 2 practices.

The ideal study to assess the effectiveness of screening and surveillance is an RCT of individuals at risk for BE and EAC who are randomized to undergo screening upper endoscopy (EGD) compared with no screening. Surveillance would then be performed on individuals diagnosed with BE, and the frequency of surveillance would be based on grade of dysplasia. Patients with HGD/intramucosal carcinoma and select cases with LGD would undergo EET (ablation and/or endoscopic resection techniques) and those with invasive cancer esophagectomy.[2] Patients with NDBE would undergo surveillance endoscopy every 3 to 5 years. The primary outcome of this study would be comparison of EAC mortality (critical endpoint), and secondary outcomes would include all-cause mortality, EAC incidence, stage of diagnosis, number of EAC patients undergoing esophagectomy, and stage of diagnosis. A study designed in this fashion would provide the best evidence for the clinical practice of screening and surveillance to achieve the overall aim of reducing mortality related to EAC. However, such a study would require thousands of subjects with decades of follow-up, given the low incidence of cancer in patients with BE.[15] Such studies do not exist at this time, and to our knowledge, no such studies have been funded or are underway. It is important to recognize the risk of bias in published studies that falsely increase the apparent benefit of surveillance practices. Lead-time bias is the detection of asymptomatic preclinical cancer by endoscopy, which may only increase the detection time of individuals with cancer without truly increasing life-years. Length-time bias occurs when slowly growing cancers are more likely detected during endoscopy than rapidly growing cancers, which artificially creates the appearance that screening and surveillance prolongs survival. These considerations are important to understand in our effort to make meaningful clinical recommendations.

AIMS AND SCOPE

The aim of this document is to offer evidence-based recommendations and clinical guidelines addressing key issues related to screening and surveillance in patients with BE. The panel considered the following clinical questions:

- What is the role of surveillance endoscopy in patients with NDBE compared with no surveillance in decreasing the rate of cancer progression, EAC-related mortality, and all-cause mortality?
- What is the role of screening for BE in the general population and at-risk populations compared with no screening in decreasing the rate of cancer progression and overall mortality?
- What is the role of advanced imaging technologies in improving the detection of dysplasia in BE patients undergoing surveillance?
  - The advanced imaging techniques addressed in this document include chromoendoscopy (CE), including virtual chromoendoscopy (VC), confocal laser endomicroscopy (CLE), and volumetric laser endomicroscopy (VLE).
- What is the role of wide-area transepithelial sampling (WATS) in improving dysplasia detection rates?
- What is the role of EUS in staging BE patients with dysplasia and early EAC?

METHODS

Overview

This guideline document was based on systematic reviews (SRs) of the available literature for each clinical question. The quality or certainty in the evidence and strength of recommendations was based on the GRADE framework. When existing SRs were identified, they were used to inform the guideline when appropriate. If no existing SRs were found, a new SR (and meta-analysis [MA], when possible) was conducted with the help of an expert librarian. Evidence profiles were created with the help of GRADE methodologists (S.S., B.Q.), and recommendations were drafted by the panel at a Standards of Practice meeting convened in Nashville on March 17, 2018. For Population, Intervention, Comparator, and Outcomes (PICO) 2 and PICO 6a, a conference call including the full GRADE panel was conducted to readdress the clinical question and recommendations based on updated published data. Throughout the document, white-light endoscopy (WLE) with targeted biopsy sampling from all visible abnormalities and random 4-quadrant biopsy sampling every 1 to 2 cm starting from the top of the gastric folds up to the most proximal extent of the BE, otherwise referred to as the Seattle Protocol, was used as the criterion standard for each of the relevant clinical questions addressing surveillance and use of advanced imaging techniques to increase the yield of dysplasia detection.[4,16]

Panel composition and conflict of interest management

The panel composition consisted of content experts (J.D., S.A., B.Q., S.W.), GRADE methodologists (S.S., B.Q.),

patient representative, primary care physician (S.K.), health policy expert (B.J.), and members of the Standards of Practice committee. All members were asked to disclose conflicts of interests based on the ASGE policy (https://www.asge.org/forms/conflict-of-interest-disclosure and https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf). Panel members who received funding for any technologies or companies associated with any of the PICOs were asked to declare this before the discussion and did not vote on the final recommendation addressing that specific PICO question.

Formulation of clinical questions

These topics were conceptualized by the authors of the documents and members of the ASGE Standards of Practice committee and approved by the Governing Board. The questions followed the PICO format: P, population in question; I, intervention; C, comparator; and O, outcomes of interest. For all clinical questions, potentially relevant patient-relevant outcomes were identified a priori and rated from not important to critical through a consensus process. Relevant clinical outcomes included cancer-specific and all-cause mortality, progression to EAC, dysplasia detection rates, and performance characteristics of diagnostic tests. A list of the PICO questions is detailed in Table 1.

Literature search and study selection criteria

For each PICO question, either existing SRs/MAs were identified and reviewed or a new SR/MA was conducted. Details of the search strategies are reported in Appendix 1 (available online at www.giejournal.org) as per Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria. An expert medical librarian performed all searches. Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa), and duplicates were removed. The EndNote library was uploaded into Covidence (www.covidence.org), and 2 independent reviewers were assigned to each search. Each study was reviewed based on title and abstract using explicit inclusion and exclusion criteria. If applicable, full text was then reviewed. Differences with resolved by consensus.

Data extraction and statistical analysis

When necessary, data extraction was accomplished by 2 reviewers using Microsoft Excel (Microsoft Corporation, Redmond, Wash). The outcomes varied by PICO and included increased diagnostic yield (relative and absolute), pooled sensitivity and specificity, pooled relative risk (RR), odds ratio (OR), or proportions (risk of BE). For outcomes with limited or no available direct comparisons, indirect comparisons were used to estimate the magnitude and direction of effect. We assessed heterogeneity using the I^2 and Q statistic. We used random effects models for most analyses, and studies were weighted based on their size. Publication bias was assessed using funnel plots and the classic fail-safe. Statistical analyses were performed using Comprehensive Meta Analysis V_3 (Biostat Inc, Englewood, NJ).

For diagnostic performance, we used 2 prevalence estimates to illustrate the number of true positives, true negatives, false positives, and false negatives. These estimates were derived from content experts using the best current available evidence. The estimate of 5% represents the prevalence of BE patients with or without dysplasia in patients referred for EGD in the community, and the estimate of 30% represents the prevalence of BE patients with or without dysplasia in patients referred for EGD at tertiary care or referral centers.

Certainty in evidence (quality of evidence)

The certainty of the evidence was determined using the GRADE framework, which starts with defining the healthcare question in terms of the population of interest, alternative management strategies (intervention and comparator), and all patient-important outcomes.[17] A systematic search is then performed to identify all relevant studies, and data from individual included studies are used to generate an estimate of the effect for each patient-important outcome as well as a measure of the uncertainty associated with that estimate (typically a confidence interval [CI]). The GRADE approach to rating the quality or certainty of evidence begins with the study design (RCTs or observational studies) and then addresses 5 reasons to possibly rate down the quality of evidence (methodologic limitations, inconsistency, indirectness, imprecision, and publication bias) and 3 reasons to possibly rate up the quality (large effect, dose–response gradient, plausible confounding). The final quality of evidence ranges from *very low* to *high* (Table 2). Guideline developers then formulate the recommendation(s) and consider the direction (for or against) and grade the strength (strong or weak) of the recommendation(s) based on the criteria outlined in the GRADE approach. The GRADE evidence profile, developed using GDTpro application (http://gdt.guidelinedevelopment.org/app), contains detailed information about the quality of evidence assessment and the summary of findings for each of the included outcomes.

Considerations in the development of recommendations

The strength of a recommendation reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. GRADE specifies 2 categories of the strength of a recommendation: strong or conditional. The main factors that drive the recommendation include balance between benefits and harms, taking into account the best estimates of the magnitude of effects and importance of outcomes; overall quality of evidence; confidence in values and preferences and their variability; and cost/resource implications. The final wording of the recommendations (including direction and strength), remarks, and qualifications were decided

TABLE 1. List of Population, Intervention, Comparator, and Outcomes questions

Population	Intervention	Comparator	Outcomes	Rating
1. Nondysplastic Barrett's esophagus	Surveillance endoscopy (varying intervals)	No surveillance	1. Mortality/survival 2. Stage of diagnosis of esophageal adenocarcinoma 3. Time to progression to dysplasia or esophageal adenocarcinoma	Critical Critical Critical
2. Population at risk for Barrett's esophagus	Screening for Barrett's esophagus	No screening	1. Mortality/survival 2. Stage of diagnosis of esophageal adenocarcinoma 3. Prevalence of Barrett's esophagus based on risk factors	Critical Critical Important
3. Patients with Barrett's esophagus undergoing surveillance	Using chromoendoscopy: 1) Chromoendoscopy 2) Virtual chromoendoscopy	White-light endoscopy with random biopsy sampling	1. Increase yield in detection of dysplasia/neoplasia 2. Performance characteristics (accuracy, sensitivity, specificity, etc.)	Critical Critical
4. Patients with Barrett's esophagus undergoing surveillance	Using confocal laser endomicroscopy (endoscope-based and probe-based)	White-light endoscopy with random biopsy sampling	1. Increase yield in detection of dysplasia/neoplasia 2. Performance characteristics (accuracy, sensitivity, specificity, etc.)	Critical Critical
5. Patients with Barrett's esophagus and suspected dysplasia	EUS	No EUS	1. Increased yield in detection of dysplasia/neoplasia 2. Performance characteristics (accuracy, sensitivity, specificity, etc.) Analysis conducted at the T1a vs. T1b level and at the T1 vs. T2 level	Critical Critical
6. Patients with Barrett's esophagus undergoing surveillance	New techniques: 1) Volumetric laser endosmicroscopy 2) Wide-area transepithelial sampling	White-light endoscopy with random biopsy sampling	1. Increased yield in detection of dysplasia/neoplasia 2. Performance characteristics (accuracy, sensitivity, specificity, etc.)	Critical Critical

EUS, Endoscopic ultrasound.

by consensus and were approved by all members of the panel. According to the GRADE approach, the recommendations are either "strong" or "conditional" (Table 3). The words "the guideline panel recommends" are used for strong recommendations and "suggests" for conditional recommendations.

RESULTS

The recommendations for each clinical question are summarized in Table 4.

Question 1: What is the role of surveillance endoscopy in patients with NDBE compared with no surveillance in decreasing the rate of cancer progression, EAC-related mortality, and all-cause mortality?

Recommendation: In patients with NDBE, we suggest performing surveillance endoscopy compared with no surveillance (conditional recommendation, very low quality of evidence).

Summary of the evidence: Surveillance endoscopy for BE is predicated on the assumption that it detects dysplasia or early EAC, which can be treated by minimally invasive treatment modalities such as EET and thus reduces morbidity and mortality related to EAC. Despite the fact that surveillance endoscopy to evaluate for dysplasia is routinely performed for BE, there are no RCTs demonstrating that surveillance (vs no surveillance) leads to a reduction in the proportion of patients with advanced-stage presentation of EAC or a reduction in EAC-related or all-cause mortality.

A recent SR by Codipilly et al[18] provided a comprehensive overview of the available evidence on the impact of BE surveillance on survival in BE patients diagnosed with EAC. The panel relied on this published SR and MA to inform the recommendations for this PICO question. In this review, the authors focused on 2 groups of studies: (1) cohort studies of patients with BE who had undergone surveillance and BE patients with no surveillance (or inadequate surveillance) and (2) prospective or retrospective cohort studies that compared EAC patients with a history of BE (diagnosed ≥6 months before the diagnosis of EAC) with patients whose initial symptomatic presentation was EAC, without previously documented BE. The authors performed an MA of the

TABLE 2. GRADE categories of quality of evidence

GRADE quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.

GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

cohort studies for the following outcomes: mortality (EAC-related and all-cause), EAC stage at time of diagnosis, and rates of operative intervention. These pooled estimates were incorporated into the evidence profile (Table 5).

For EAC-related mortality, the authors identified 4 prospective cohort studies comparing regular BE surveillance (with incomplete or no surveillance) that provided unadjusted data on EAC-related mortality. MA of these studies showed that BE surveillance was associated with a reduction in EAC-related mortality (RR, .60; 95% CI, .50-.71). The authors also identified 4 cohort studies showing that EAC patients with a prior BE diagnosis had a significantly lower risk of mortality because of EAC (unadjusted RR, .73; 95% CI, .57-.94). Only 1 study adjusted for lead-time bias (using a sojourn time of 3 years) as well as stage and treatment of cancer. In this study by El-Serag et al,[19] the association between EAC mortality risk and endoscopic surveillance was no longer found (hazard ratio [HR], 1.72; 95% CI, .78-2.07). Another study by Tramontano et al[20] provided lead-time–adjusted data for EAC-related mortality (sojourn time of 3 years) and adjustment for lead-time bias eliminated the association between surveillance and mortality in those with a prior BE diagnosis versus those with no prior BE diagnosis (HR, .89; 95% CI, .78-1.01).

For all-cause mortality, MA of 3 studies showed that receiving BE surveillance (vs incomplete or no surveillance) was associated with a 25% reduction in mortality (unadjusted HR, .75; 95% CI, .59-.94). Additionally, MA of 12 studies showed that in EAC patients, having a prior diagnosis of BE was associated with a reduction in mortality (RR, .48; 95% CI, .37-.63). Because this reduction in overall mortality could have been because of lead- and length-time bias, the authors performed analyses using lead-time–adjusted estimates (using a sojourn time of 2-2.5 years). The pooled effect estimate from the 3 studies that provided HRs for survival after adjusting for lead-time bias showed an attenuation in the mortality benefit (HR, .85; 95% CI, .75-.95). This study was unable to provide length-time–adjusted analyses.

For earlier-stage EAC (stages 0 and 1) at diagnosis, the authors pooled unadjusted data from 4 studies showing that patients who had BE surveillance were more likely to be diagnosed with early-stage EAC as compared with those in the inadequate or no surveillance group (RR, 2.11; 95% CI, 1.08-4.11). Additionally, pooled data from 9 studies in EAC patients showed that individuals with prior BE diagnosis were more likely to present with an earlier stage EAC compared with those without a prior BE diagnosis (RR, 5.52; 95% CI, 3.70-8.24).

For the outcome of adverse events (AE), we used data from a previously published guideline on AEs of upper GI endoscopy by the ASGE.[21] Although the rate of AEs varies by procedure, indication, and level of sedation, AEs related to surveillance endoscopy are infrequent. The rate of overall AE in diagnostic EGDs is very low (from 1/200 to 1/10,000). The rate of AEs is higher if EET is performed.[22]

Certainty in the evidence: The overall certainty in the evidence for EAC-related mortality was very low or low because these studies were observational studies with heterogeneity (for which we rated down). For all-cause mortality the certainty in the evidence was very low; we rated down for imprecision and inconsistency. Finally, for earlier stage at diagnosis, we had very low-quality evidence and rated down for inconsistency (Table 5).

Considerations: The panel considered additional evidence on cost-effectiveness analyses, patient values and preferences, and harm. A recent SR focused on the economic impact of screening and surveillance to reduce mortality from EAC was used to guide this discussion.[15] Most economic studies on cost-effectiveness of screening incorporate surveillance among individuals diagnosed

TABLE 3. Interpretation of definitions of strength of recommendation using GRADE framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Compliance with this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

TABLE 4. Summary of recommendations and quality of evidence

Statement	Strength of recommendation	Quality of evidence
1. In patients with nondysplastic BE, we suggest performing surveillance endoscopy compared with no surveillance.	Conditional	Very low
2. There is insufficient evidence on the effectiveness of screening for BE. However, if screening endoscopy for BE is performed, we suggest a screening strategy that identifies an at-risk population. An at-risk population is defined as individuals with a family history of EAC or BE (high risk) or patients with GERD plus at least 1 other risk factor (moderate risk).	NA	NA
3. In patients with BE undergoing surveillance, we recommend using chromoendoscopy, including virtual chromoendoscopy and Seattle protocol biopsy sampling, compared with white-light endoscopy with Seattle protocol biopsy sampling.	Strong	Moderate
4. In patients with BE undergoing surveillance, we suggest against routine use of confocal laser endomicroscopy compared with white-light endoscopy with Seattle protocol biopsy sampling.	Conditional	Low
5. In BE patients with high-grade dysplasia/IMC or nodules, we recommend against routine use of EUS to differentiate mucosal vs submucosal disease.	Strong	Moderate
6a. In patients with known or suspected BE, we suggest using WATS-3D in addition to Seattle protocol biopsy sampling compared with white-light endoscopy with Seattle protocol biopsy sampling.	Conditional	Low
6b. In patients with BE undergoing surveillance, there is insufficient evidence to recommend for or against routine of VLE.	No recommendation	NA

BE, Barrett's esophagus; *NA*, not applicable; *EAC*, esophageal adenocarcinoma; *IMC*, intramucosal cancer; *VLE*, volumetric laser endomicroscopy; *WATS-3D*, wide-area transepithelial sampling with computer-assisted 3-dimensional analysis.

through screening to account for the beneficial effects of treatment of BE-related dysplasia and early EAC. Nine studies have been published that have assessed the cost-effectiveness of screening in BE (6 of these studies were conducted before the advent of EET), and all were Markov simulations.[23-28] With a willingness-to-pay threshold of <$100,000 (ie, society would be willing to pay $100,000 for each quality-adjusted life-year gained), all studies found endoscopic screening and surveillance of subjects with GERD to be cost-effective (5 studies showed that the cost was $4000-$15,000 per quality-adjusted life-year gained). There are limited data on patient values and preferences with regard to surveillance endoscopy. The panel relied heavily on the views expressed by the patient representative who expressed strong support for surveillance, placing a high value on early detection of EAC and potential benefits of treatment and a low value on any burden or harms associated with repeat surveillance endoscopies.

Discussion: The panel recognized the limitations in the current available evidence, and despite the apparent shortcomings, a decision in support of surveillance endoscopy was made (conditional recommendation). The panel acknowledged the many limitations in the existing studies: suboptimal study design, varying surveillance protocols within and among studies, and issues around lead- and

length-time bias that can skew results in favor of surveillance. An important driver for this recommendation was the potential survival benefit demonstrated in favor of surveillance. Results of the Barrett's Oesophagus Surveillance Study trial,[29] which is currently underway in the United Kingdom, are awaited. This multicenter RCT randomized BE patients to either an intensive surveillance arm (every 2 years) or a nonsurveillance arm ("at need" surveillance).[29]

Surveillance intervals are currently determined by the presence and grade of dysplasia. This PICO question does not address the frequency of surveillance intervals in patients with NDBE or the ideal approach to surveillance biopsy sampling. Several studies have demonstrated a low rate of progression to EAC in NDBE (.1%-.3% per year).[30-32] On the basis of these data, previous clinical practice guidelines recommend surveillance endoscopy every 3 to 5 years in this patient population, a recommendation that this panel endorsed until more evidence is available.[4,12,33] The distribution of dysplasia and early EAC is highly focal and variable.[34] Because a systematic biopsy sampling protocol detects more dysplasia and early EAC compared with random biopsy sampling,[16,35,36] medical societies, including this panel, recommend a biopsy sampling protocol (Seattle biopsy sampling protocol) that uses 4-quadrant biopsy sampling at 2-cm intervals in patients without dysplasia and at 1-cm intervals in patients with prior dysplasia, along with targeted biopsy sampling from any mucosal abnormality.[3,4]

As currently practiced, endoscopic surveillance of BE has numerous limitations. Compliance rates with the above recommendations in terms of surveillance intervals and obtaining biopsy specimens using the Seattle protocol are poor.[1,34,37,38] Current surveillance programs are time-consuming, and given the highly focal and variable distribution of dysplasia and early EAC, even the most thorough biopsy sampling surveillance program has the potential for sampling errors. In addition, there is significant interobserver and intraobserver variability among community and expert pathologists in the interpretation of dysplasia.[39-41] There is a growing interest in the development of risk-prediction models to identify patients with NDBE at risk for the development of HGD/EAC. A recent SR and MA identified the following factors associated with progression: increasing age (OR, 1.03; 95% CI, 1.01-1.05), male sex (OR, 2.16; 95% CI, 1.84-2.53), ever smoking (current or past; OR, 1.47; 95% CI, 1.09-1.98), increasing BE length (OR, 1.25; 95% CI, 1.16-1.36), and LGD (OR, 4.25; 95% CI, 2.58-7.0).[42] On the other hand, the use of proton pump inhibitors (OR, .55; 95% CI, .32-.96) and statins (OR, .48; 95% CI, .31-.73) have been linked to a decreased risk of progression to dysplasia/neoplasia. Another recent randomized trial[43] assessed the benefit of proton pump inhibitors and aspirin in patients with BE. They reported that high-dose proton pump inhibitor with aspirin was associated with a significant benefit on a composite endpoint of all-cause mortality, HGD, and EAC (time ratio, 1.59; 95% CI, 1.14-2.23; $P = .0068$).

The use of prediction models using demographic and clinical factors has the potential for improving the effectiveness of current surveillance strategies.[44-47] In a recent study, a scoring system based on male sex, smoking, BE length, and baseline LGD was developed that identified patients with BE at low-, intermediate-, and high-risk groups for HGD/EAC.[47] External validation before clinical application is required for these described prediction models.

Question 2: What is the role of screening for BE compared with no screening in decreasing the rate of cancer progression, EAC-related mortality, and all-cause mortality? What is the role of a screening strategy that identifies individuals at risk of having BE?

Recommendation: There is insufficient evidence on the effectiveness of screening for BE. However, if screening endoscopy for BE is performed, we suggest a screening strategy that identifies an at-risk population, defining "at-risk" individuals as those with a family history of EAC or BE (high risk) or patients with GERD plus at least 1 other risk factor (moderate risk).

Summary of the evidence: Screening for BE has been endorsed by medical societies based on the assumption that screening will detect individuals with BE and these individuals will be enrolled in surveillance programs to detect dysplasia and early EAC, who will then undergo minimally invasive procedures (EET or esophagectomy) and ultimately reduce the incidence, morbidity, and mortality associated with EAC. Screening also has the potential to identify individuals with prevalent dysplasia and early EAC who can be treated with EET. We conducted a systematic search for studies addressing screening for BE in the general population. We found no studies comparing screening with no screening in individuals at risk for BE.

We then searched for SRs and MAs assessing various risk factors for BE to identify at-risk populations who may benefit from screening. The panel decided to use a cut-off prevalence of 10% for BE in any given group (with or without risk factors) to recommend screening. The following risk factors were assessed: history of GERD, male gender, white race, smoking, obesity, and family history of BE and EAC. For the risk factor of GERD, Taylor et al[48] analyzed 26 studies and reported an OR of 2.9 (95% CI, 1.86-4.54) for the association of GERD with BE, albeit associated with high heterogeneity ($I^2 = 89\%$). This OR increased to 4.5 in 12 studies with GERD for at least 2 weeks. For the risk factor of smoking, Andrici et al[49] conducted an SR and MA of 10 studies and showed that the odds of having BE significantly increase in smokers when controlling for possible confounders. For the risk of obesity, Singh et al[50] conducted an SR and MA assessing the effect of obesity and central

TABLE 5. Evidence profile for surveillance compared with no surveillance/incomplete surveillance in patients with known Barrett's esophagus

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
*EAC-related mortality (unadjusted)**						
4	Observational studies	Serious†	Not serious	Not serious	Not serious	None
4	Observational studies	Not serious	Serious‡	Not serious	Not serious	None
EAC-related mortality (accounting for lead time bias and adjustment for patient factors including stage, and treatment)§						
1	Observational studies	Not serious	Not serious	Not serious	Serious¶	None
*All-cause mortality (unadjusted)**						
12	Observational studies	Not serious	Not serious	Not serious	Serious¶	None
3	Observational studies	Not serious	Serious‡	Not serious	Serious¶	None
*All-cause mortality adjusted (accounting for lead-time)**						
3	Observational studies	Not serious	Serious‡	Not serious	Serious¶	None
*Earlier stage of diagnosis (unadjusted)**						
4	Observational studies	Not serious	Serious‡	Not serious	Not serious	None
9	Observational studies	Serious	Serious‡	Not serious	Not serious	None
AEs from endoscopy						

EAC, Esophageal adenocarcinoma; *AE,* adverse events; *RR,* relative risk; *HR,* hazard ratio.
*Based on the SR and MA by Codipilly et al[18] these estimates were derived from (1) prospective cohort studies of BE patients who had undergone surveillance compared with BE patients with no or incomplete surveillance and (2) prospective or retrospective cohort studies that compared EAC patients with a history of BE (diagnosed >6 months before an EAC diagnosis) with patients whose initial symptomatic presentation was EAC without previously documented BE.
†There were concerns about bias based on the Newcastle-Ottowa Scale for most studies.
‡There was a large amount of heterogeneity between studies for which we rated down.
§Based on the SR and MA by Codipilly et al[18] this estimate was derived from the study by El-Serag et al,[19] which provided an EAC-mortality estimate that was adjusted for lead-time bias, stage, and treatment of EAC.
¶We rated down for imprecision.

adiposity. Based on 11 studies, they found no association with obesity but reported a significant association with central adiposity (Table 6).

In a more recent SR and MA by Qumseya et al,[51] the authors estimated the prevalence of BE in patients with specific risk factors who underwent screening and tried to synthesize the interactions between such risk factors. The authors identified 48 studies with over 300,000 patients, of which >1900 had biopsy specimen–confirmed BE. The prevalence of BE was assessed in the general or low-risk populations and in those individuals with risk factors such as GERD, family history of BE or EAC, age >50 years, obesity, and male gender. When controlling for population Western versus non-Western, mean age, and gender distribution, there was a linear relationship between the number of risk factors and the risk of BE. As the number of risk factors increased, the risk of BE increased by 1.2% per additional risk factor. In this study, all patients with multiple risk factors had either GERD or age >50.

Based on the above evidence, the panel outlined a high-risk group, a moderate-risk group, and a low-risk group. The panel recognized patients with a family history of EAC or BE as a high-risk group and recommended screening for BE in that population. The panel described a moderate-risk group to include patients with GERD and at least 1 additional risk factor who may also benefit from screening for BE. The additional risk factors were age >50, obesity/central adiposity, history of smoking, or male gender. Finally, the panel did not recommend screening in low-risk patients.

Considerations: The panel again recognized the lack of data on the impact of screening for BE on EAC incidence, EAC mortality, or all-cause mortality but acknowledged that existing guidelines from other GI societies currently endorse screening for BE in specific populations.[4] Eight studies were identified that estimated the cost-effectiveness of screening to detect individuals with BE.[23-27,52-54] Although estimates varied among studies, endoscopic screening of individuals with GERD was found

TABLE 5. Continued

No. of patients		Effect			
Surveillance	**No surveillance/incomplete surveillance**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
101/282 (35.8%)	144/249 (57.8%)	RR .60 (.50-.71)	231 fewer per 1000 (from 168 fewer to 289 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
		RR .73 (.57-.94)		⊕◯◯◯ VERY LOW	CRITICAL
71/209 (34.0%)	67/103 (65.0%)	HR 1.27 (.78-2.07)	86 more per 1000 (from 91 fewer to 236 more)	⊕◯◯◯ VERY LOW	CRITICAL
652/1256 (51.9%)	18906/23191 (81.5%)	RR .48 (.37-.63)	424 fewer per 1000 (from 302 fewer to 514 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
		HR .85 (.75-.95)		⊕◯◯◯ VERY LOW	CRITICAL
		HR .85 (.75-.95)		⊕◯◯◯ VERY LOW	CRITICAL
383/686 (55.8%)	162/453 (35.8%)	RR 2.11 (1.08-4.11)	397 more per 1000 (from 29 more to 1000 more)	⊕◯◯◯ VERY LOW	CRITICAL
597/1180 (50.6%)	2631/23100 (11.4%)	RR 5.52 (3.70-8.24)	515 more per 1000 (from 308 more to 825 more)	⊕◯◯◯ VERY LOW	CRITICAL
AE: cardiopulmonary 1/170 to 1/10,000; perforation 1/2500 to 1/11,000					

to be cost-effective if the willingness-to-pay threshold was <$100,000 per quality-adjusted life-year.[55]

Discussion: The panel acknowledged the challenges associated with this recommendation. Beyond the lack of data from RCTs, studies have shown that <10% of EAC patients have a prior diagnosis of BE, indicating that current practices have failed to identify a large majority of patients.[56,57] Symptoms of GERD have been considered a prerequisite for screening for BE and EAC. However, only 7% to 10% of individuals with chronic GERD have BE, and nearly 40% of EAC patients describe no prior history of GERD.[8,58] BE can be diagnosed in asymptomatic individuals (those without any GERD symptoms), and nearly 50% of patients with short-segment BE have no GERD symptoms.[48,59,60] These data suggest that a screening program that is limited to individuals with GERD symptoms may miss a significant proportion of high-risk individuals. Furthermore, available data from EGDs performed at the time of screening colonoscopy demonstrated a pooled prevalence of BE of more than 10%. The panel deliberated broadening the at-risk population to include individuals with multiple risk factors (age >50, male gender, white race, smoking, obesity) independent of GERD. However, this would drastically increase the number of patients eligible for BE screening and would incur increased resource use and costs for patients, insurers, and the healthcare system in general as well as increased potential harm from endoscopy and patient burden. As other less-invasive and resource-intense modalities for BE screening become available, this would influence future recommendations for screening.

Additionally, the panel recognized the value of risk prediction tools that use demographic and historical data.[61-64] However, the accuracy of these prediction models remains modest with areas under the receiver operating characteristic curve of .61 to .75.[65] Refinement and subsequent validation of these models will be critical before widespread implementation. Currently, standard upper endoscopy is the most common screening test used. However, other available modalities have been developed

TABLE 6. Association between various risk factors and BE based on literature review

Risk factor	Study	No. of studies	Effect estimate
GERD	Taylor et al[48]	26	OR = 2.9 (4.5 in 12 studies with GERD for at least 2 weeks)
Family history of BE or EAC	Chak et al[58]	1	OR = 12, adjusted for age, sex, and obesity
Male	Cook et al[119]	19	Male-to-female ratio = 2.13
Obesity	Singh et al[50]	10	OR = 1.15 [.89-1.47], adjusting for GERD
Central adiposity	Singh et al[50]	11	OR = 1.44 [1.2-1.74], adjusting for GERD
Smoking	Andrici et al[49] Andrici et al[49]	10 4	OR = 1.42 [1.15-1.76], ever smoked vs population control OR = 1.96 [1.41-2.73], adjusted for confounders

OR, Odds ratio; *BE,* Barrett's esophagus; *EAC,* Esophageal adenocarcinoma.

with the goal of improving the effectiveness, reducing cost, and minimizing invasiveness of screening. Such modalities include transnasal endoscopy, esophageal capsule endoscopy, Cytosponge (Medtronic, Fridley, Minn), tethered capsule endomicroscopy, and electronic nose device.[56] In the SR and MA by Qumseya et al,[51] standard upper endoscopy was the most common screening tool. Only 5 studies evaluated other modalities: 3 studies[66-68] used capsule endoscopy and 2 studies[69,70] used ultrathin scopes. An SR and MA of other novel screening technologies was not conducted for this guideline document and is beyond the scope of this discussion. A recent Clinical Practice Update document by the American Gastroenterological Association reviewed the current status of these technologies and recommended against the use of any alternative test to screen for BE at this time.[56] This panel also acknowledges the great potential and promise for these technologies. After careful deliberation by all stakeholders, the panel endorsed screening for BE in at-risk populations for BE using the available evidence on the prevalence of BE in specific populations.

Question 3: In patients with BE who are undergoing surveillance for dysplasia, what is the role of CE in increasing the rate of dysplasia detection?

Recommendation: In patients with BE undergoing surveillance, we recommend using CE or VC in addition to WLE and biopsy specimens obtained using the Seattle protocol compared with WLE and biopsy specimens obtained using the Seattle protocol alone (strong recommendation, moderate quality of evidence).

Summary of the evidence: The outcomes for this clinical question were the increase in diagnostic yield and performance characteristics of CE with WLE compared with WLE alone. We identified 2 existing SRs and MAs that addressed this question. We updated a previously published SR and MA that addressed the clinical question of diagnostic yield using CE.[71] Additionally, an SR and MA performed by the ASGE Technology Committee was used to inform the question addressing performance characteristics of CE in BE surveillance.[72] This document assessed whether acceptable performance thresholds outlined by the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) document[73] for clinical adoption of advanced imaging techniques have been met.

A new search was conducted using PubMed, Embase, and Web of Science to update the results from a previous SR and MA.[71] We limited our search strategy to include only RCTs published in peer-reviewed journals. A total of 1347 studies were identified, uploaded into Covidence.org, and reviewed by 2 independent reviewers. Twelve RCTs (n = 2433) were identified (1 new study in addition to the 11 included in the previously published SR and MA).[74] These studies were mostly crossover or tandem in design. Using a random effects model, the absolute increase in dysplasia detection was 9% (95% CI, 4.1%-14%; $P < .001$; $Q = 29$; $I^2 = 42\%$). This analysis also addressed the relative increase in dysplasia detection. Because the studies were crossover in design, we set the external correlation coefficient at .5. When a random effects model was used, the relative increase is dysplasia detection was 30.3% (95% CI, 16.2%-44.3%; $P < .0001$). Varying the correlation coefficient had no significant difference on the final results. In a subanalysis, there was no significant difference between VC compared with dye-based CE (risk difference, 28.5% [95% CI, 12.3%-45.5%] vs 30.7% [95% CI, 5.2%-56.3%], $P = .98$) (Fig. 1).

For the outcome of diagnostic accuracy, only 2 of the above-mentioned RCTs reported the sensitivity and specificity of CE.[75,76] However, these were reported on a per-lesion analysis and not per-patient. The SR and MA published by the ASGE Technology Committee reported an overall sensitivity of 91.9% (95% CI, 89.4%-93.8%), negative predictive value of 95.5% (95% CI, 90.8%-97.9%), and specificity of 89.9% (95% CI, 80.1%-95.2) for conventional CE using dye-spraying.[72] The diagnostic characteristics were higher using acetic acid (sensitivity, 96.6% [95% CI, 95.2%-97.7%]; negative predictive value, 98.3% [95% CI, 94.8%-99.4%], and specificity, 84.6% [95% CI, 68.5%-93.2%]) compared with methylene blue and met the thresholds set by the ASGE PIVI document.[73] VC using narrow-band imaging (NBI) had an overall sensitivity of 94.2% (95% CI, 82.6%-98.2%), negative predictive value of 97.5%

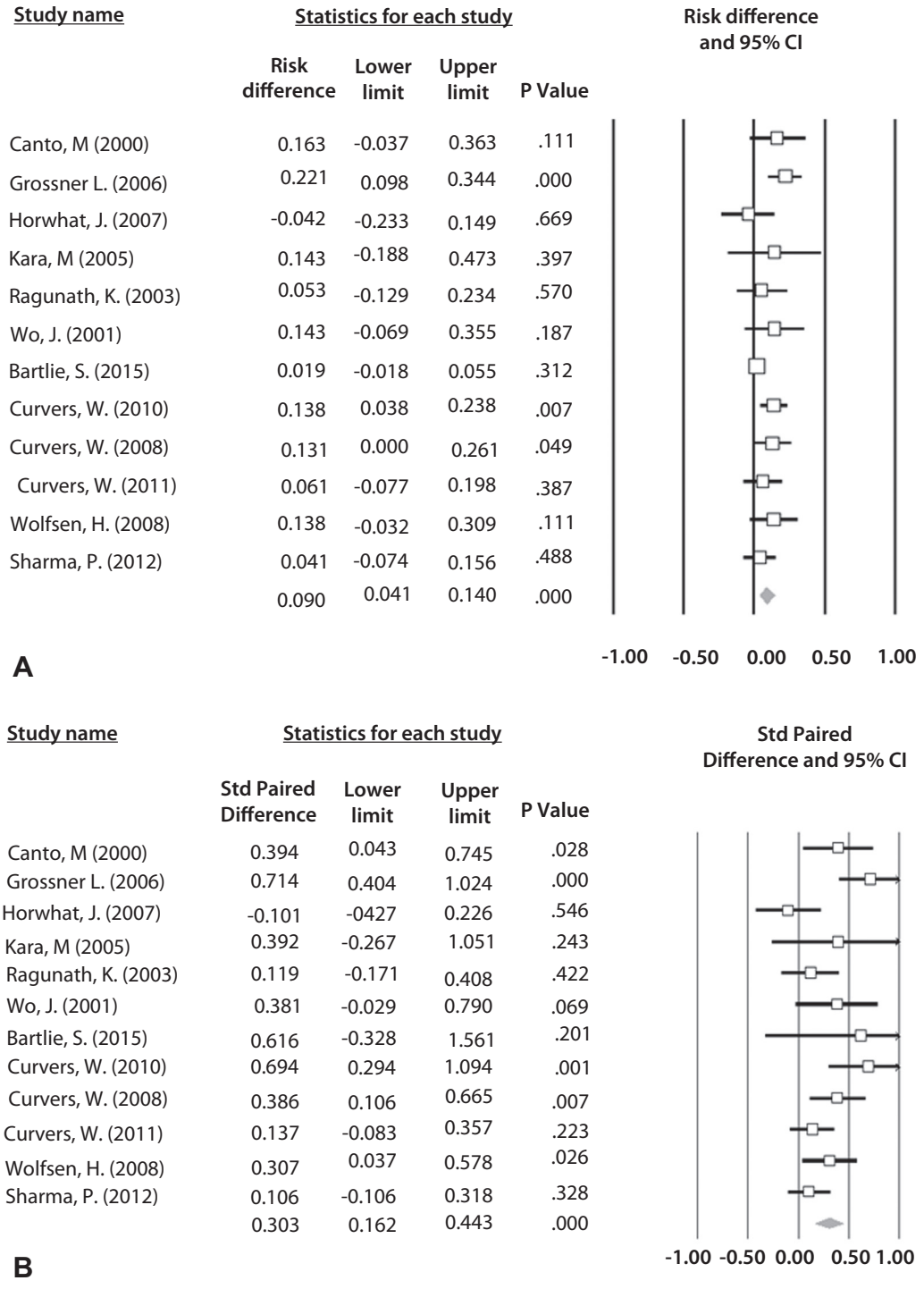


Figure 1. Forest plots of the 12 clinical trials assessing the absolute (**A**) and relative (**B**) increase in the diagnostic yield of chromoendoscopy compared with white-light endoscopy in detection of dysplasia for patients with Barrett's esophagus.

(95% CI, 95.1%-98.7%), and specificity of 94.4% (95% CI, 80.5%-98.6%), performance that exceeds the thresholds set by the ASGE PIVIC document.[73] We acknowledge that per-patient analyses are more relevant and patient-centered and allow for a more accurate determination of the impact of test findings on patient-important outcomes.

Certainty in the evidence: For the critical outcome of increase in the diagnostic yield, 12 clinical trials were included with high quality of evidence. There were no issues with inconsistency, imprecision, or publication bias (Fig. 2). However, because all studies were done at expert centers, we rated down for indirectness, because applicability to nonexpert centers may lead to different

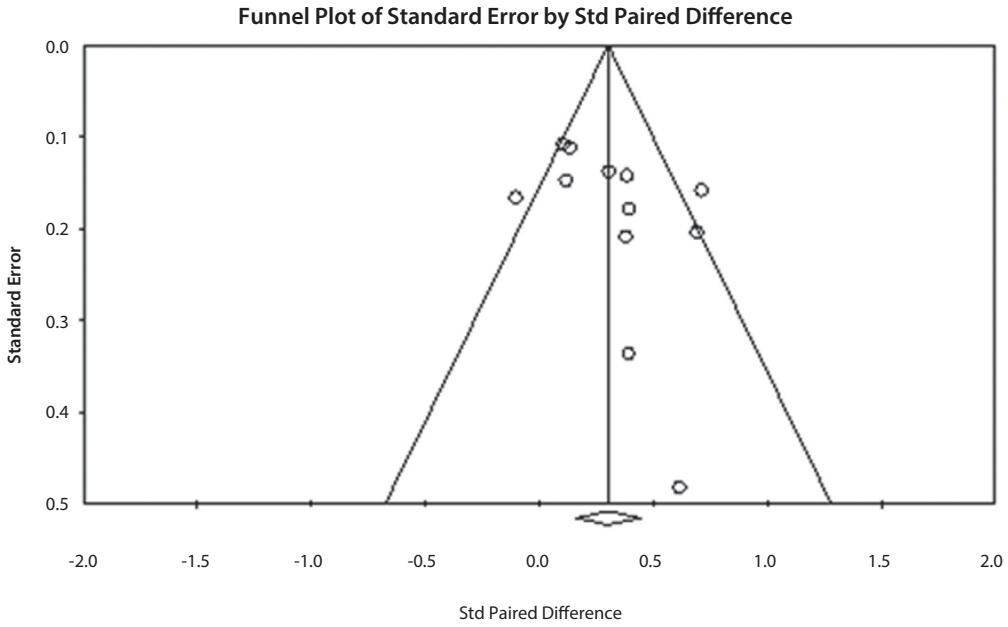


Figure 2. Funnel plot assessing publication bias among studies on the diagnostic yield of chromoendoscopy and white-light endoscopy.

estimates in diagnostic yield (Table 7). Therefore, the quality of evidence for the outcome of diagnostic yield was moderate.

Considerations: In making this recommendation, the panel noted that the use of VC was essentially cost-equivalent: No extra cost is incurred because this technology is available in most endoscopes. Additionally, VC is also risk free to the patient. The panel also reviewed the evidence for dye-based CE, which appears to be cost-effective and can be used if VC is not available. Bhandari et al[77] studied the cost-effectiveness of acetic acid in high-risk BE patients and found it to be more cost-effective than random biopsy sampling. Some dyes have been linked to potential risks, including DNA damage.[78,79]

Discussion: Several advanced imaging modalities have been investigated to improve the detection and identification of early neoplastic lesions during surveillance endoscopy.[34] Dye-based CE refers to the application of various topical dyes or solutions to the esophageal mucosa for the purpose of enhancing visibility of surface abnormalities. VC refers to using various light filters within the endoscope to achieve similar visual enhancement. The 3 available platforms for VC are NBI (Olympus, Center Valley, Pa), Fujinon intelligent color enhancement (Fujinon, Wayne, NJ), and i-Scan (Pentax Medical, Montvale, NJ). NBI is an imaging technique that is based on the optical phenomenon that the depth of light penetration into tissue depends on the wavelength; the shorter the wavelength, the more superficial the penetration. Use of blue light with narrow-band filters enables detailed imaging of the mucosal and vascular surface patterns with a high level of resolution and contrast without the need for conventional CE.[80] Fujinon intelligent color enhancement and i-Scan use proprietary postimage acquisition processing technology to modify the white-light image enhancing the superficial mucosal and vascular patterns. NBI is the most widely studied and used VC technique in clinical practice. An expert panel developed and validated a classification system to identify HGD and EAC in BE patients using NBI.[81]

Based on our results, there is a strong body of evidence to recommend this practice for all BE patients undergoing screening/surveillance with VC as its first choice. The panel did not make a specific recommendation for the type of VC to be used and acknowledged recent data demonstrating increased dysplasia detection using technologies such as the i-Scan Optical Enhancement system.[82] For dye-based CE, the panel made no specific recommendation for the type of dye, but based on available data, acetic acid is the only dye-based CE technique that meets the ASGE PIVI thresholds.[73] Acetic acid enhances mucosal surface patterns by contrast staining. Problems associated with use of dye-based CE in clinical practice include the need for dye spraying equipment; difficulty in achieving complete and uniform coating of the mucosal surface with the dye, inability to detect superficial vascular patterns, and the time-consuming and tedious nature of the procedure.

Many have hoped the use of CE would help eliminate the need for the random biopsy sampling. The processes of the Seattle protocol can be cumbersome and costly, especially in long-segment BE. The panel recognizes that areas of BE may not appear to be suspicious on CE but may still harbor dysplasia. Additionally, a meta-regression

by Qumseya et al[71] showed that the number of biopsy specimens strongly corresponded with the diagnostic yield. Therefore, the panel did not recommend CE as a replacement for the Seattle protocol but rather as an adjunct. The panel recognized that data from a single RCT reported that NBI had similar detection of BE but required fewer biopsy specimens than high-definition WLE in patients with BE undergoing screening or surveillance endoscopy.[76]

This panel also acknowledges that the studies reported in this analysis include expert endoscopists recruiting patients at tertiary care centers. There is a dearth of data on the learning curves and impact of training in the detection of early neoplasia (with or without advanced imaging techniques). The future lies in incorporating training in CE in gastroenterology fellowship programs and establishing training programs for detection of early neoplasia that are acceptable and applicable to the broader gastroenterology community.

Question 4: In patients with BE undergoing endoscopy for surveillance of dysplasia, what is the role of CLE in increasing the rate of dysplasia detection?

Recommendation: In patients with BE undergoing surveillance, we suggest against routine use of CLE compared with WLE with Seattle protocol biopsy sampling (conditional recommendation, low quality of evidence).

Summary of the evidence: The outcomes of interest for this question were the increase in diagnostic yield of CLE (critical) and performance characteristics of CLE (important). We identified 2 existing SRs: the previously described SR and MA by the ASGE Technology Committee[72] and another study by Xiong et al.[83] We updated the more recent SR by Xiong et al and used this to address our clinical question. An updated search from June 2015 until June 2017 identified 205 new studies, and none was eligible for inclusion. Therefore, four RCTs detailing the diagnostic yield in CLE versus WLE were included.[84-87] Two studies reported using probe-based CLE, whereas the other 2 used endoscope-based CLE. Using a random effects model and a per-patient analysis, the absolute increase in dysplasia detection using CLE was 10.2% (95% CI, 1.4%-19.1%; $P = .024$; $I^2 = 42\%$). Note that the CI for this measure was very close to zero. The relative increase in dysplasia detection was not significant: 36% (95% CI, –5.4% to 77.5%; $P = .088$; $I^2 = 64\%$) (Fig. 3, Table 8).

For performance characteristics (sensitivity and specificity), Xiong et al[83] analyzed 7 studies totaling 473 patients and reported a pooled sensitivity of 89% (95% CI, 82%-94%) and a pooled specificity of 83% (95% CI, 78%-86%). The overall prevalence of dysplasia/neoplasia varied significantly by study ranging from 12.5% to 100%. Table 9 highlights the performance of CLE varying the prevalence of dysplasia (5% and 30%) in the underlying population.

The panel also considered AEs associated with CLE. The main risks of CLE relate to the need to inject intravenous fluorescein to conduct these procedures. Wallace et al[88] conducted a cross-sectional international survey of 16 academic centers. Based on 2272 CLE procedures, they found no major AEs. The rate of minor adverse outcomes was 1.4%, and this included epigastric pain, nausea/vomiting, rash, injection site erythema, and transient hypotension.

Certainty in the evidence: The certainty in the evidence for the diagnostic yield was based on data from the 4 RCTs. We rated down for inconsistency given the high I^2 and for indirectness given that all studies were done at tertiary referral centers. Therefore, the overall quality of evidence was rated as low (Table 8). For the outcome of sensitivity and specificity, we rated down for imprecision given the wide CIs and inconsistency on account of the high I^2. Therefore, the quality of evidence was also rated as low (Table 9).

Considerations: The panel considered the AEs for CLE as described above.[88] The panel also considered that this technology requires up-front investment in equipment and significant training to achieve proficiency.[89] There were no studies regarding patient values and preferences using this technology, and the overall cost-effectiveness of CLE has not been adequately studied. A cost-utility analysis using Markov modeling showed that the routine use of CLE and optical coherence tomography was not cost-effective compared with the use of WLE with the Seattle protocol biopsy sampling.[90]

Discussion: CLE uses blue laser light to illuminate issues after application of intravenous fluorescence agents. This can produce magnification up to 1250-fold, allowing visualization at the cellular level, with the resulting ability to identify areas of dysplasia/neoplasia. For CLE, as with CE, the panel placed a higher level of importance on the increase in the diagnostic yield compared with the performance characteristics because of reasons discussed earlier. Our results showed that the absolute increase in the diagnostic yield for CLE was 10%, similar to that reported for CE. However, the CI was very close to zero. Additionally, the relative increase in the diagnostic yield was 36%, but this was not statistically significant (CI crossed zero). The panel assumed that a minimum of 20% relative increase in diagnostic yield would be an appropriate threshold that might warrant a recommendation for CLE. This threshold was partly based on a recent study among a group of international BE experts who reported the minimum incremental diagnostic yield for the use of advanced imaging techniques in BE surveillance.[91] In this study, experts reported a minimum incremental increase in the diagnostic yield of 27% (interquartile range, 20%-50%) for CLE before implementation in clinical practice.

TABLE 7. Evidence profile for use of chromoendoscopy compared with white-light endoscopy for detection of dysplasia in patients with Barrett's esophagus

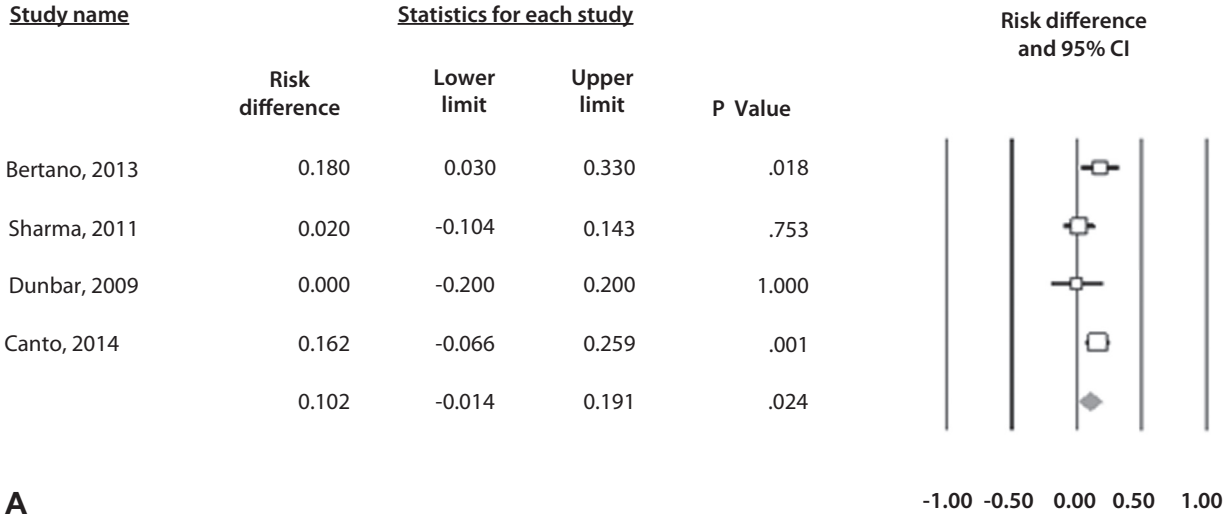
Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Chromoendoscopy: increased yield in dysplasia detection						
12	Randomized trials	Not serious	Not serious	Serious*	Not serious	None

RR, Relative risk.
*Most studies were done at tertiary centers with gastroenterologists who have expertise and skills in detecting Barrett's esophagus, and these findings may not be generalizable to all gastroenterologists

TABLE 8. Evidence profile for use of confocal laser endomicroscopy compared with white-light endoscopy for detection of dysplasia in patients with Barrett's esophagus

Certainty assessment							No. of patients	
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Confocal laser endomicroscopy**	**White-light endoscopy**
Increased yield in dysplasia detection								
4	Randomized trials	Not serious	Serious*	Serious†	Not serious	None	75/284 (26.4%)	49/288 (17.0%)

RR, Relative risk.
*We rated down for inconsistency.
†Studies were done at tertiary centers with gastroenterologists who have expertise and skills in detecting Barrett's esophagus, and these findings may not be generalizable to all gastroenterologists.



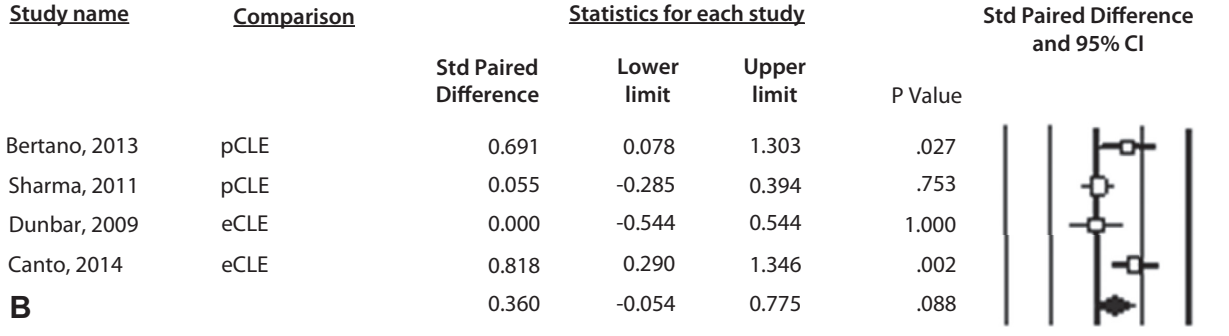


Figure 3. Forest plots of the 4 clinical trials assessing the absolute (**A**) and relative (**B**) increase in the diagnostic yield of confocal laser endomicroscopy compared with white-light endoscopy in detection of dysplasia for patients with Barrett's esophagus. *pCLE*, probe-based confocal laser endomicroscopy; *eCLE*, endoscope-based confocal laser endomicroscopy.

TABLE 7. Continued

No. of patients		Effect			
Chromoendoscopy	White-light endoscopy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
408/848 (48.1%)	329/848 (38.8%)	RR 1.31 (1.21-1.41)	120 more per 1000 (from 81 more to 159 more)	⊕⊕⊕◯ MODERATE	CRITICAL

TABLE 8. Continued

Effect			
Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
RR 1.50 (.93-2.08)	85 more per 1000 (from 12 fewer to 184 more)	⊕⊕◯◯ LOW	CRITICAL

Furthermore, the 4 RCTs had a prevalence of dysplasia ranging from 19% to 35%, much higher than the prevalence of dysplasia in the BE population seen by most gastroenterologists at nonspecialized centers. Therefore, in practice, CLE is likely to have a lower diagnostic yield. Therefore, our results indicate that the benefit from CLE is small at best in the general surveillance population. The added cost of equipment, training, and possible risk of intravenous dye administration makes the routine use of CLE less desirable.

With regard to the diagnostic characteristics, there are limited data on patient-related outcomes. For example, there are no data on how many patients who had a negative CLE subsequently developed dysplasia. The SR and MA by the ASGE Technology Committee reported an overall (combining endoscope-based CLE and probe-based CLE) sensitivity of 90.4% (95% CI, 75.7%-96.6%), negative predictive value 96.2% (95% CI, 93.1%-97.9%), and specificity of 89.9% (95% CI, 83.8%-93.9%), thresholds that did not meet the ASGE PIVI thresholds.[72] Although endoscope-based CLE met the ASGE PIVI thresholds, this was based on data from studies conducted at tertiary care centers. In addition, this technology (endoscope-based CLE) is no longer available in clinical practice. As illustrated in the evidence profile (Table 9), in a low-prevalence population, the false-positive rate was relatively high at 16.3% (95% CI, 13.4%-21.1%), but even with a prevalence of 30%, the false-positive rate remains high at 12%. Although this guideline suggests against the *routine use* of CLE in BE patients, we acknowledge that CLE may be a helpful tool in increasing the diagnostic yield of dysplasia in centers with a high prevalence of dysplasia and significant local expertise.

Question 5: What is the role of EUS in staging BE patients with dysplasia or early EAC?

Recommendation: In BE patients with dysplasia or early EAC, we recommend against routine use of EUS to differentiate mucosal versus submucosal disease (strong recommendation, moderate quality of evidence).

Summary of the evidence: This guideline statement pertains to the use of EUS in differentiating mucosal (T1a) from submucosal (T1b) EAC. The rationale for using EUS in this patient population is to detect advanced disease into and beyond the submucosa with the goal of avoiding potentially invasive EMR or endoscopic submucosal dissection in patients with advanced disease and avoiding esophagectomy in patients with EAC limited to the mucosa (T1a disease). The patient-important outcomes in this analysis were mortality and cancer progression and the diagnostic performance of EUS to detect advanced disease. We identified no studies that addressed the outcome of mortality and cancer progression. For the outcome of diagnostic characteristics of EUS in BE patients with dysplasia and early EAC, we started with 2 MAs by Qumseya et al.[92,93] These analyses focused on the performance characteristics of EUS at the T1a versus T1b level using data from 11 studies. The pooled sensitivity, specificity, and accuracy from this analysis were 41% (95% CI, 35%-48%), 89% (95% CI, 86%-91%), and 75% (95% CI, 59%-86%), respectively. As with other diagnostic studies, we reviewed performance characteristics based on the prevalence of disease. In the included studies, the prevalence of advanced disease ranged from 5% to 45%. The evidence profile illustrates how the false-positive rate increases from 6% in patients with high prevalence of advanced disease to

TABLE 9. Evidence profile for performance characteristics of confocal laser endomicroscopy compared with white-light endoscopy for detection of dysplasia in patients with Barrett's esophagus using a prevalence of 5% and 30%*

Sensitivity	.89 (95% CI, .82-.94)	Prevalences	5% 30%
Specificity	.83 (95% CI, .78-.86)		

Outcome	No. of studies (no. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested		Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pretest probability of 5%	Pretest probability of 30%	
True positives (patients with dysplasia)	7 studies patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious†	Serious‡	None	45 (41-47)	267 (246-282)	⊕⊕◯◯ LOW
False negatives (incorrectly classified as not having dysplasia)								5 (3-9)	33 (18-54)	
True negatives (patients without dysplasia)	7 studies patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious†	Serious‡	None	789 (741-817)	581 (546-602)	⊕⊕◯◯ LOW
False positives (incorrectly classified as having dysplasia)								161 (133-209)	119 (98-154)	

*The illustrated prevalences of 5% and 30% were used as estimates of the prevalence of Barrett's esophagus and/or dysplasia in patients referred for EGD in the community and at tertiary care centers. These estimates were based on expert opinion and the best available published evidence.
†We rated down for inconsistency, as there was significant heterogeneity.
‡We rated down for imprecision.

10.5% in patients with low prevalence of advanced disease (Table 10). Of the 11 studies in the MA, the prevalence of HGD/EAC was 100% in all but 2 studies, where the prevalence of dysplasia was 49% and 65%.[94,95] A prior MA by Yousef et al[96] reported a crude HGD/EAC prevalence rate of 4% (178 patients with HGD/EAC among 4491 BE patients).

Certainty in the evidence: We rated down for inconsistency given heterogeneity. There was no evidence of publication bias, inconsistency, or indirectness. Therefore, the quality of evidence was rated as moderate (Table 10).

Considerations: There are no studies assessing the cost-effectiveness of EUS for this patient population. Similarly, there are no direct data on AEs from EUS in this patient group. However, based on indirect evidence, EUS is associated with a risk of cervical esophageal perforation estimated at .03% to .06%[97] and mortality of .002%.[98] Bleeding after EUS with FNA has been reported in .13% based on a MA.[99] Finally, rare cases of tumor seeding have been reported.[100] There were no reports on patient values or preferences other than the input we received from the patient representative on our panel.

Discussion: The use of EUS in BE continues to be controversial, although there seems to be a trend toward doing less EUS in this patient population because of the lack of reliability of EUS in accurately distinguishing between patients with HGD/T1a cancer from those with T1b cancer. Our evidence profiles showed that EUS is associated with a relatively high false-positive rate ranging from 6% to 10%.

Of all patients who test positive for advanced disease on EUS, around one third will be false positive for advanced disease. In light of the possible AEs of EUS, potential costs of procedure and sedation, and the high false-positive rate, the panel decided to recommend against the routine use of EUS for this specific indication. It should also be emphasized that the most recent ASGE guideline document on EET strongly recommends endoscopic resection of all visible lesions in BE patients as first-line modality for diagnostic and therapeutic purposes.[2] This recommendation is in line with other GI society guidelines and quality indicator documents.[4,101] This recommendation should not be confused with the role of EUS in patients with EAC. EUS is indicated in patients with EAC for accurate staging of advanced cancer (≥T1b) and to evaluate for nodal disease.

A study that used the Surveillance, Epidemiology, and End Results Medicare database showed that the receipt of EUS was a significant predictor of improved 1-year (HR, .49; 95% CI, .39-.59; $P < .0001$), 3-year (HR, .57; 95% CI, .48-.66; $P < .0001$), and 5-year survival (HR, .59; 95% CI, .5-.68) driven primarily by provision of stage-appropriate treatment for EAC patients.[102] Receipt of EUS also increased the likelihood

TABLE 10. Evidence profile for performance characteristics of EUS compared with no EUS for diagnosing advanced neoplasia using a prevalence of 5% and 30%*

Sensitivity	.41 (95% CI, .35-.48)				Prevalences		5%		30%	
Specificity	.89 (95% CI, .86-.91)									
			Factors that may decrease certainty of evidence					Effect per 1000 patients tested		
Outcome	No. of studies (no. of patients)	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pretest probability of 5%	Pretest probability of 30%	Test accuracy
True positives (patients with advanced neoplasia)	11 studies 228 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious†	Not serious	None	21 (17-24)	123 (105-144)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having advanced neoplasia)								29 (26-33)	177 (156-195)	
True negatives (patients without advanced neoplasia)	11 studies 679 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious†	Not serious	None	845 (817-864)	623 (602-637)	⊕⊕⊕◯ MODERATE
advanced neoplasia)								105 (86-133)	77 (63-98)	

*The illustrated prevalence of 5% and 30% were used as estimates of the prevalence of Barrett's esophagus and/or dysplasia in patients referred for EGD in the community and at tertiary care centers. These estimates were based on expert opinion and the best available published evidence.
†We rated down for inconsistency.

of receiving endoscopic therapies, esophagectomy, and chemoradiation. Therefore, the panel acknowledged several circumstances in which a clinician may consider performing EUS. However, EUS should not be used for T staging of early disease instead of EMR or endoscopic submucosal dissection of such lesions.

Question 6a: In patients with known or suspected BE, what is the role of WATS with computer-assisted 3-dimensional analysis (WATS-3D) in increasing the rate of dysplasia detection?

Recommendation: In patients with known or suspected BE, we suggest using WATS-3D in addition to WLE with Seattle protocol biopsy sampling compared with WLE with Seattle protocol biopsy sampling alone (conditional recommendation, low quality of evidence).

Summary of the evidence: A new SR was conducted to address this clinical question. The search strategy resulted in 1554 studies (search date December 15, 2018). After review by 2 independent reviewers, 40 studies were reviewed in detail and 6 studies (5 trials and 1 meeting abstract) were included in the final analysis.

Of the 6 studies, 3 studies[102-104] were in patients with BE and dysplasia (high-risk group) who were undergoing surveillance and 3 studies[105-107] included patients with and without a history of dysplasia. Patients without a history of BE were removed from all analyses. Therefore, 6271 patients with BE were analyzed. WLE with random biopsy sampling detected 125 cases of dysplasia. The performance of WATS resulted in identification of 137 additional cases missed by WLE with random biopsy sampling. Using a random effects model, the relative increase in dysplasia detection was 48% (95% CI, 34%-60%%; I^2 = 68%, Q = 16). All heterogeneity in this analysis resulted from 1 study by Smith et al.[105] Removing the study reduced I^2 to zero.

For patients with history of dysplasia, the relative increase in dysplasia detection using WATS was 47% (95% CI, 32%-61%). The absolute increase in dysplasia detection using WATS was 10.6% (95% CI, 1.5%-19.8%). The relative increase in LGD detection was 21% (95% CI, 24%-40%) (Table 11, Fig. 4). For studies reporting all patients with or without a history of dysplasia, referred to as all-comers, the relative increase in dysplasia detection was 52% (95% CI, 21%-82%), whereas the absolute increase in dysplasia detection was 2% (95% CI, 1.5%-2.5%) (Table 11, Fig. 4). Four of the 6 studies reported the yield of WATS in detection of LGD. When the random effects model was used, the absolute increase in LGD detection was 1.8% (95% CI, 1.4%-2.3%) (Fig. 5).

TABLE 11. Evidence profile for use of wide-area transepithelial sampling for detection of dysplasia in patients with Barrett's esophagus

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Dysplasia detection						
6	Randomized trials	Serious*	Serious†	Not serious	Not serious	None
Adverse events						
1	Observational studies	Serious‡	Not serious	Not serious	Not serious	None

WATS-3D, Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis; *WLE+RB,* white-light endoscopy with random biopsies; *RR,* relative increase in dysplasia detection.
*Dysplasia definition varied.
†Moderate heterogeneity in some of the analyses.
‡Only 1 study in abstract form.

Certainty in the evidence: We rated down for risk of bias, inconsistency, and indirectness. The dysplasia definition varied across studies; some studies included LGD, whereas others did not. Additionally, most studies were funded by the manufacturer. There was no evidence of publication bias (Fig. 6). Therefore, the quality of evidence was low (Table 11).

Considerations: To date, we found no studies assessing cost-effectiveness of WATS-3D in routine surveillance of BE patients. With respect to AEs, we contacted the authors who reported no significant adverse outcomes from using this technology. We also identified 1 abstract by Smith et al[108] that surveyed 33 physicians using WATS-3D with over 4881 cases of WATS-3D. They reported rate of serious adverse outcomes at .06%. Patient preferences have not been reported to date.

Discussion: The use of WATS-3D has received much attention in recent years. The idea of WATS-3D is novel in that although previous technologies have focused on attempting to increase dysplasia detection by improving visualization of dysplastic areas, WATS-3D attempts to improve dysplasia detection by increasing the surface area sampled. Unlike standard soft cytology brushes, the WATS-3D biopsy instrument samples deeper layers of the more firmly attached glandular epithelium in the esophagus. Unlike histology specimens from forceps biopsy sampling that are sliced to a 1- to 3-μm thickness, samples using this technology are uncut to preserve the 3D representation of the intact cellular structure. The analysis of the sample is aided by a high-speed computer scan, which identifies potentially abnormal cells, cell clusters, and abnormal glandular cells on a high-resolution video monitor for pathology review. The most suspicious cells are flagged by the computer as a starting point for the pathologists to review.

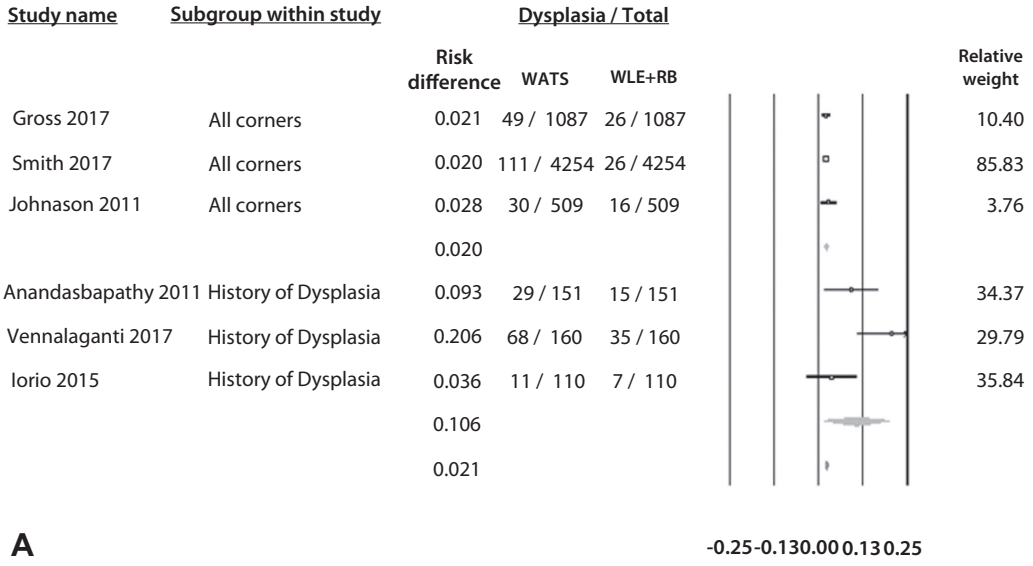
An important limitation of the above studies was how dysplasia was defined. All the aforementioned studies were funded by the manufacturer (CDx Diagnostics, Suffern, NY). In an attempt to stratify data by dysplasia type, the manufacturer was contacted by the lead author (B.Q.) and the chair of the Standards of Practice committee (S.W.). For Anandasabapathy et al,[102] Johanson et al,[107] and Iorio et al,[104] the outcome reported was dysplasia. The manufacturer confirmed that indefinite for dysplasia was excluded from the analyses in 2 of the 3 studies. In Iori et al, 3 of the 4 cases detected by WATS were LGD and 1 was HGD. In the study by Smith et al,[108] WATS detected 10 cases of HGD/EAC and 75 cases with LGD. For our analyses, the cases of indeterminate for dysplasia were removed. Therefore, we note that the increase in dysplasia detection reported on WATS-3D may be largely related to LGD. In a subanalysis of 4 studies, the absolute increase in LGD detection was 1.8%. However, the question remains of what LGD means on cytology compared with LGD dysplasia on histology. The minimum incremental diagnostic yield of dysplasia for the use of WATS-3D, based on a recent survey of an international group of BE experts,[91] was 27% (95% CI, 20%-50%). Results from our SR and MA demonstrate that WATS-3D exceeds this threshold.

Another related question is the diagnosis of crypt dysplasia reported on WATS specimens. This is diagnosed when the pathologist reports dysplasia-like changes that seem to be isolated to the crypts and not to the surface epithelium. Shaheen et al[109] recently presented data on disease progression in patients with crypt dysplasia (n = 310) and noted a progression rate of 2.1% per patient year for an endpoint of HGD/EAC. In the same study, the rate of disease progression in 83 patients with LGD was 7.7% per patient-year. This rate of 2.1% reported by Shaheen et al is very similar to the incidence rate of 2.2% reported in a MA by Qumseya et al[11] assessing disease progression rates in BE patients with LGD. This suggests that patients with the diagnosis of crypt dysplasia may be at a higher risk for progression and future prospective studies should define the natural history of this entity before management plans are altered based on this diagnosis.

The panel initially made no recommendation for WATS-3D at the face-to-face meeting. After a complete review of additional published literature (including data on AEs) and

TABLE 11. Continued

No. of patients		Effect		Certainty	Importance
WATS-3D	WLE + RB	Relative (95% CI)	Absolute (95% CI)		
137/6271 (2.2%)	125/6271 (2.0%)	RR 2.25 (1.79-2.83)	25 more per 1000 (from 16 more to 36 more)	⊕⊕◯◯ LOW	CRITICAL
Rate of serious adverse events .06% in survey of 33 physicians				⊕◯◯◯ VERY LOW	CRITICAL



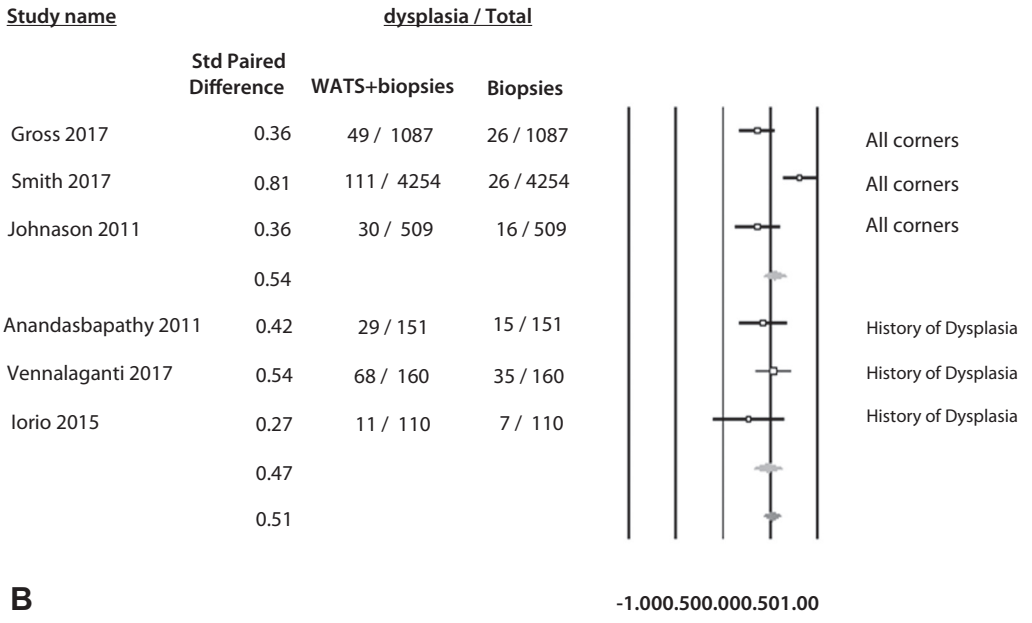


Figure 4. Forest plots of the 6 studies assessing the absolute (**A**) and relative (**B**) increase in the diagnostic yield of wide-area transepithelial sampling compared with white-light endoscopy in detection of dysplasia for patients with Barrett's esophagus. *WATS*, Wide-area transepithelial sampling; *WLE+RB*, white-light endoscopy with random biopsies.

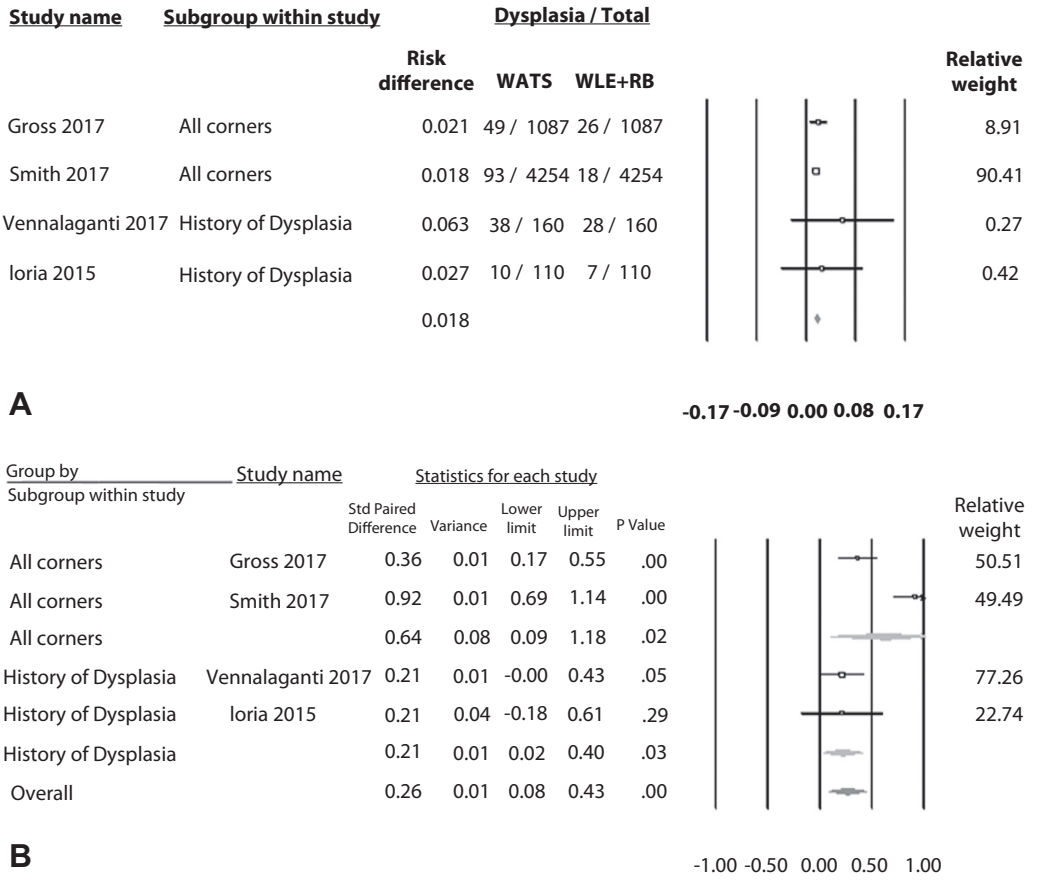


Figure 5. Forest plots of the assessing the absolute (**A**) and relative (**B**) increase in the diagnostic yield of wide-area transepithelial sampling compared with white-light endoscopy in detection of low-grade dysplasia for patients with Barrett's esophagus. *WATS*, Wide-area transepithelial sampling; *WLE+RB*, white-light endoscopy with random biopsies.

an additional phone conference, the panel made a conditional recommendation for the use of WATS-3D in addition to WLE with Seattle protocol biopsy sampling.

Question 6b: In patients with BE undergoing endoscopy for surveillance of dysplasia, what is the role of VLE in increasing the rate of dysplasia detection?

Recommendation: There is insufficient evidence to make a recommendation for or against routine use of VLE in surveillance of patients with BE (no recommendation).

Summary of the evidence: For this clinical question, we started with an existing SR and MA currently published in abstract form.[110] This study included a search of Medline, Embase, Web of Science, and Cochrane Central ending in October 2016. Of 487 studies, only 4 abstracts were identified. When the random effects model was used, the pooled absolute increase in dysplasia detection was 2.3% (95% CI, 1.5%-3.4%) with a false-positive rate of 44%. However, this study was only in abstract form and the 4 studies included stemmed from the same database, and therefore we could not rely on this study for our panel. The main issue with CLE is that the technology has continued to evolve. Most recently, the technology now includes the ability to use laser tagging that allows better marking of areas of suspected dysplasia identified by VLE. After tagging such areas, biopsy sampling can be done to confirm the presence or absence of dysplasia. Henceforth, the evidence on this technology is still evolving. Based on our updated search and after contacting the manufacturer, only 1 study[111] was identified that assessed the increase in dysplasia detection using the new VLE laser device. This study by Alshelleh et al[111] compared results from biopsy specimens obtained using the Seattle protocol, random biopsy sampling, VLE, and VLE laser (with laser marking). This study used an historical analysis comparing these techniques. The authors analyzed 386 patients. Overall, the study reported higher dysplasia detection in the VLE laser group (33.7%) compared with the Seattle protocol group (19.6%). In post-treatment surveillance, total dysplasia detection was higher in VLE laser compared with the Seattle biopsy sampling group (8.3% vs 32.7%, $P = .02$). Finally, in treatment-naïve patients undergoing surveillance, the rate of dysplasia detection was not different in VLE laser compared with the Seattle protocol group (16.7% vs 35.3%) (Table 12).

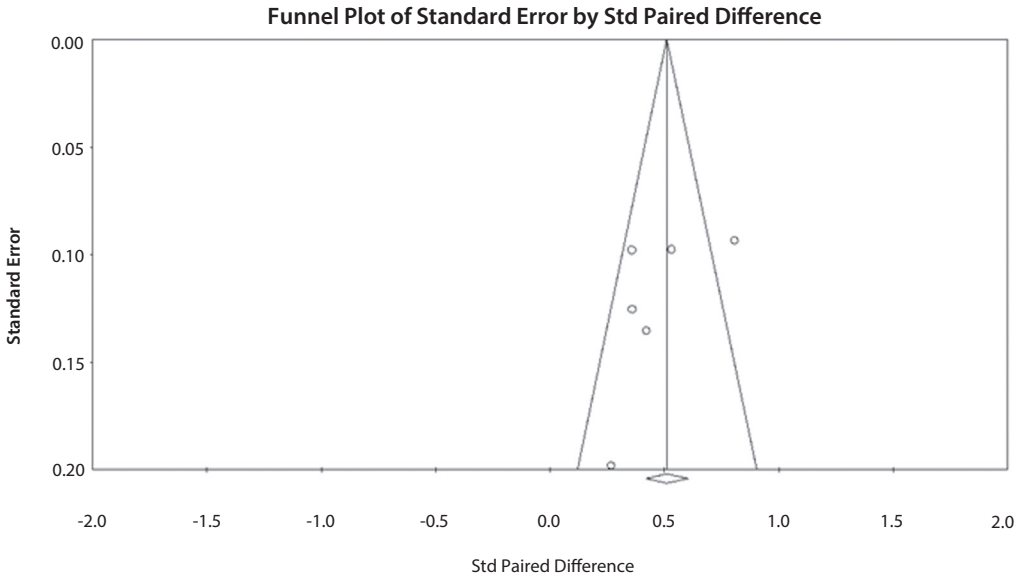


Figure 6. Funnel plots showing risk of publication bias for studies assessing wide-area transepithelial sampling in patients with Barrett's esophagus.

TABLE 12. Overall dysplasia detection as presented by Alshelleh et al[111]

Group	RB (n = 79)	SP (n = 95)	Volumetric laser endomicroscopy (n = 168)	Volumetric laser endomicroscopy laser (n = 106)
Years	2011-2015	2011-2015	2014-2016	2016-2017
Overall dysplasia detection, %	5.7	19.6	24.8	33.7

RB, Random biopsies; *SP,* Seattle protocol.

Certainty in the evidence: Because there was only 1 cohort study and limited data available in abstract form, the overall quality of evidence was very low.

Considerations: There are no data on patient preferences or cost-effectiveness of VLE in routine surveillance of BE patients. Similarly, detailed reports on AEs are unavailable. However, the panel noted that the procedure does include balloon inflation, which has the potential to cause pain or even perforation. The procedure does also require additional time to introduce the device, inflate the balloon, and obtain and interpret images. The exact cost of such measures is not clear at this time.

Discussion: VLE is based on optical coherence tomography and is an advanced imaging technique that produces a complete scan of the esophageal wall, including subsurface layers, with a resolution comparable with low-power microscopy.[112] Optical coherence tomography uses light waves instead of sound waves to form 2-dimensional images based on differences in optical scattering of tissue structures. With second-generation optical coherence tomography, it is possible to perform high-resolution, high-speed acquisition of large luminal surfaces and ultimately creating 3D imaging of the esophagus wall.[113] VLE scans 6 cm of the esophagus over 90 seconds and provides a resolution of 10 μm and an imaging depth of 3 mm.

The use of VLE, especially VLE laser, is an emerging area. The panel acknowledged the limitations in the current studies. In light of evidence gaps, the panel concluded there was insufficient evidence to make a recommendation for this question. In addition to the thresholds set by the ASGE PIVI document, international experts in BE reported a minimum incremental increase in the diagnostic yield of dysplasia of 30% (95% CI, 18%-50%) for the use of VLE in routine clinical practice.[91] Validation of VLE features and the VLE prediction score for neoplasia and demonstrating that these thresholds can be achieved in large prospective trials is required.[114,115] Finally, studies defining the role of computer-aided analysis as an aid in VLE interpretation are awaited.[116]

FUTURE DIRECTIONS

This document highlights several knowledge gaps in the field of screening and surveillance for BE. First and foremost, we still lack high-quality evidence on the benefits of screening and surveillance in patients with BE specifically addressing key outcomes such as incidence, morbidity, and mortality associated with EAC. In this document, we discuss the best design for future studies to address this critical issue. Future studies that refine and validate existing prediction tools for screening of BE and EAC are required. These tools may require the addition of noninvasive genetic or blood biomarkers to

demographic and historical variables to improve the areas under the receiver operating characteristic curves and overall performance.[117] Before we embrace the new generation of less-invasive and potentially less-expensive screening techniques and replace our current approach of using standard endoscopy for screening, these new techniques need to demonstrate high diagnostic performance characteristics, easy implementation at a primary care level, high uptake in the at-risk population, and low cost.[118] Future studies also need to focus on improved risk stratification of BE patients undergoing surveillance with the intent of performing EET for high-risk populations and extending or discontinuing surveillance in low-risk groups. Finally, effectiveness and validation data regarding advanced imaging and sampling techniques among nonexpert endoscopists are needed.

SUMMARY AND CONCLUSIONS

In this document, the ASGE offers evidence-based clinical practice guidelines on topics regarding screening and surveillance for BE. These guidelines follow the GRADE framework and offer guidance on several key clinical questions such as the role and impact of screening and surveillance in patients with BE and the role of advanced imaging techniques in BE patients undergoing surveillance endoscopy. This guideline complies with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines and aims to help clinicians understand the published literature and the quality of available data with the ultimate goal of optimizing care for patients with BE.

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Abbreviations: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett's esophagus; CE, chromoendoscopy; CI, confidence interval; CLE, confocal laser endomicroscopy; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapies; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HGD, high-grade dysplasia; HR, hazard ratio; LGD, low-grade dysplasia; MA, meta-analysis; NBI, narrow-band imaging; NDBE, nondysplastic Barrett's esophagus; OR, odds ratio; PICO, Population, Intervention, Comparator and Outcomes; PIVI, Preservation and Incorporation of Valuable Endoscopic Innovations; RCT, randomized controlled trial; RR, relative risk; SR, systematic review; VC, virtual chromoendoscopy; VLE, volumetric laser endomicroscopy; WATS, wide-area transepithelial sampling; WATS-3D, WATS with computer-assisted 3-dimensional analysis; WLE, white-light endoscopy.

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APPENDIX 1. Search strategies for the PICO question 2 (screening), 3 (update CE), 4 (update CLE), 5

Search strategies screening for Barrett's esophagus (PICO 2)

Date of last Search: 09/06/2017

Medline	1387
Embase	1610
Web of Science	1235
Total	4232

After removing duplicates 2502 records

MEDLINE (Ovid)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

20170905

1387 Records

(exp Endoscopy, Digestive System/ OR (esophagogastroduodenoscop* OR egd OR oesophagogastroduodenoscop* OR ogd).ab,ti OR ((oesophago gastro OR esophago gastro) adj duodenoscop*).ab,ti OR ((screen* OR surveill* OR upper) adj3 endoscop*).ab,ti) AND (exp mass screening/ OR exp early detection of cancer/exp OR (screen* OR surveillance).ab,ti)

AND (exp barrett esophagus/ OR ((esophag* OR oesophag*) AND barrett*).ab,ti)

Embase (Elsevier)

20170905

1610 Records

('esophagogastroduodenoscopy'/exp OR (esophagogastroduodenoscop* OR egd OR oesophagogastroduodenoscop* OR ogd):ab,ti OR (('oesophago-gastro' OR 'esophago gastro') NEXT/1 duodenoscop*):ab,ti OR ((screen* OR surveill* OR upper) NEAR/3 endoscop*):ab,ti) AND ('mass screening'/exp OR 'early cancer diagnosis'/exp OR (screen* OR surveillance):ab,ti) AND ('Barrett esophagus'/exp OR ((esophag* OR oesophag*) AND barrett*):ab,ti)

Web of Science (Clarivate Analytics)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years

20170905

1235 Records

TS = ("esophagogastroduodenoscop*" OR "egd" OR "oesophagogastroduodenoscop*" OR "ogd" OR "oesophago gastro duodenoscop*" OR "esophago gastro duodenoscop*" OR (("screen*" OR "surveill*" OR "upper") NEAR/3 "endoscop*")) AND TS = ("screen*" OR "surveillance") AND TS = (("esophag*" OR "oesophag*") AND "barrett*")

Search strategies for update on chromoendoscopy for Barrett's esophagus (PICO 3)

Date of original search: 10/1/2012

This search was run on 06/12/2017

In both PubMed and Embase, the search was limited by the date the record was entered into the database (the entrez date, or EDAT) set to 20120101 (Jan. 1, 2012). For Web of Science, the publication year was used and set to 2012.

PubMed	493
Embase	983
Web of Science	458
Total	1934

1354 Records after removing duplicates.

PubMed (NCBI)

20170612

493 Records

((Esophagoscopy[mesh] AND Image Enhancement [mesh]) OR "Acetic Acid"[Mesh] OR "Indigo Carmine" [Mesh] OR "Methylene Blue"[Mesh] OR "Congo Red" [mesh] OR "Gentian Violet"[mesh] OR "Phenolsulfonphthalein"[mesh] OR "Coloring Agents"[Mesh] OR "Chromogenic Compounds"[mesh] OR "Iodides"[mesh] OR acetic acid[tiab] OR indigo[tiab] OR carmine[tiab] OR methylene blue[tiab] OR phenolsulfonphthalein[tiab] OR congo red [tiab] OR gentian violet[tiab] OR phenol red[tiab] OR crystal violet[tiab] OR lugol*[tiab] OR iodine[tiab] OR coloring agent*[tiab] OR colouring agent*[tiab] OR chromoendoscop*[tiab] OR chromo endoscop*[tiab] OR chromoscop*[tiab] OR narrow band imag*[tiab] OR nbi[tiab] OR autofluoresc*[tiab] OR trimodal[tiab] OR fujinon intelligent[tiab]) AND ("Barrett Esophagus"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR ((esophag*[tiab] OR oesophag*) AND (neoplasm*[tiab] OR neoplasia*[tiab] OR cancer*[tiab] OR dysplas*[tiab] OR carcinoma*[tiab] OR precancer*[tiab] OR metaplas*[tiab] OR barrett* [tiab]))) AND ("2012/01/01"[EDAT] : "3000/12/31"[EDAT])

Embase (Elsevier)

20170612

983 records

('chromoendoscopy'/exp OR 'acetic acid'/exp OR 'indigo carmine'/exp OR 'methylene blue'/exp OR 'congo red'/exp OR 'crystal violet'/exp OR 'phenolsulfonphthalein'/exp OR 'coloring agent'/exp OR 'chromogenic substrate'/exp OR 'iodide'/exp OR 'acetic acid':ab,ti OR indigo:ab,ti OR carmine:ab,ti OR 'methylene blue':ab,ti OR phenolsulfonphthalein:ab,ti OR 'congo red':ab,ti OR 'gentian violet':ab,ti OR 'phenol red':ab,ti OR 'crystal violet':ab,ti OR lugol*:ab,ti OR iodine:ab,ti OR 'coloring agent*':ab,ti OR 'colouring agent*':ab,ti OR chromoendoscop*:ab,ti OR (chromo NEXT/1 endoscop*):ab,ti OR chromoscop*:ab,ti OR ('narrow band' NEXT/1 image*):ab,ti OR nbi:ab,ti OR autofluoresc*:ab,ti OR trimodal:ab,ti OR

'fujinon intelligent':ab,ti) AND ('Barrett esophagus'/exp OR 'esophagus tumor'/exp OR ((esophag* OR oesophag*) AND (neoplasm* OR neoplasia* OR cancer* OR dysplas* OR carcinoma* OR precancer* OR metaplas* OR barrett*)):ab,ti) AND
[1-1-2012]/sd NOT [31-12-2017]/sd

Web of Science (Thomson Reuters)
20170612
458 Records

TS = ("acetic acid" OR "indigo" OR "carmine" OR "methylene blue" OR "phenolsulfonphthalein" OR "congo red" OR "gentian violet" OR "phenol red" OR "crystal violet" OR "lugol*" OR "iodine" OR "coloring agent*" OR "colouring agent*" OR "chromoendoscop*" OR "chromo endoscop*" OR "chromoscop*" OR "narrow band image*" OR "nbi" OR "autofluoresc*" OR "trimodal" OR "fujinon intelligent") AND TS = (("esophag*" OR "oesophag*") AND ("neoplasm*" OR "neoplasia*" OR "cancer*" OR "dysplas*" OR "carcinoma*" OR "precancer*" OR "metaplas*" OR "barrett*"))

Search strategy for update on confocal laser endomicroscopy in Barrett's esophagus

Date of last search: 06/20/2017
Previous search
578 Records on 09/06/2016
This Update

PubMed	226
Embase	479
Web of Science	396
BIOSIS	
Total	1101
After removing duplicates	778

After substracting original search, 205 new records remained; 5 old records did not match records in the new search

PubMed (NCBI)
20170620
226 Records (truncated "Barrett", added "dysplasia*"; 157 Records previously)

("Microscopy, Confocal"[mesh] OR (confocal[tiab] AND (endomicroscop*[tiab] OR mircoscop*[tiab])) OR cle[tiab] OR pcle[tiab]) AND ("Barrett Esophagus"[mesh] OR (barrett*[tiab] AND (esophag*[tiab] OR oesophag*[tiab] OR neoplas*[tiab] OR dysplasia*[tiab])))

Embase (Elsevier)
20170620
479 Records

('confocal laser microscopy'/exp OR (confocal NEAR/3 (endomicroscop* OR microscop*)):ab,ti OR cle:ab,ti OR pcle:ab,ti) AND ('barrett esophagus'/exp OR (barrett* AND (esophag* OR oesophag* OR neoplas* OR dysplasia*)):ab,ti)

Web of Science (Thomson Reuters)
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years
20170620
396 Records

TS = (("confocal" NEAR/3 ("endomicroscop*" OR "microscop*")) OR "cle" OR "pcle") AND TS = ("barrett*" AND ("esophag*" OR "oesophag*" OR "neoplas*" OR "dysplasia*"))

BIOSIS Previews (Thomson Reuters)
20170620
176 Records

TS = (("confocal" NEAR/3 ("endomicroscop*" OR "microscop*")) OR "cle" OR "pcle") AND TS = ("barrett*" AND ("esophag*" OR "oesophag*" OR "neoplas*" OR "dysplasia*"))