ASGE Technology Committee systematic review and meta-analysis assessing the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations thresholds for adopting real-time imaging–assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus

Prepared by: ASGE TECHNOLOGY COMMITTEE

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

Background and Aims: Endoscopic real-time imaging of Barrett's esophagus (BE) with advanced imaging technologies enables targeted biopsies and may eliminate the need for random biopsies to detect dysplasia during endoscopic surveillance of BE. This systematic review and meta-analysis was performed by the American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee to specifically assess whether acceptable performance thresholds outlined by the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) document for clinical adoption of these technologies have been met.

Methods: We conducted meta-analyses calculating the pooled sensitivity, negative predictive value (NPV), and specificity for chromoendoscopy by using acetic acid and methylene blue, electronic chromoendoscopy by using narrow-band imaging, and confocal laser endomicroscopy (CLE) for the detection of dysplasia. Random effects meta-analysis models were used. Statistical heterogeneity was evaluated by means of I^2 statistics.

Results: The pooled sensitivity, NPV, and specificity for acetic acid chromoendoscopy were 96.6% (95% confidence interval [CI], 95-98), 98.3% (95% CI, 94.8-99.4), and 84.6% (95% CI, 68.5-93.2), respectively. The pooled sensitivity, NPV, and specificity for electronic chromoendoscopy by using narrow-band imaging were 94.2% (95% CI, 82.6-98.2), 97.5% (95% CI, 95.1-98.7), and 94.4% (95% CI, 80.5-98.6), respectively. The pooled sensitivity, NPV, and specificity for endoscope-based CLE were 90.4% (95% CI, 71.9-97.2), 98.3% (95% CI, 94.2-99.5), and 92.7% (95% CI, 87-96), respectively.

Conclusions: Our meta-analysis indicates that targeted biopsies with acetic acid chromoendoscopy, electronic chromoendoscopy by using narrow-band imaging, and endoscope-based CLE meet the thresholds set by the ASGE PIVI, at least when performed by endoscopists with expertise in advanced imaging techniques. The ASGE Technology Committee therefore endorses using these advanced imaging modalities to guide targeted biopsies for the detection of dysplasia during surveillance of patients with previously nondysplastic BE, thereby replacing the currently used random biopsy protocols. (Gastrointest Endosc 2016;83:684-98.)

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee periodically performs systematic reviews and meta-analyses to evaluate endoscopic technologies to determine whether these have met previously established Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) thresholds. A subcommittee of the ASGE Technology Committee, comprising committee members chosen for their individual expertise, invited outside expert in the subject area, and the Technology Committee Chair performed the

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systematic review and meta-analysis. The results are then reviewed and approved by the entire Technology Committee. The systematic review and meta-analysis are ultimately submitted to the ASGE Governing Board for approval. The systematic review and meta-analysis undergo peer review by outside experts in statistics and meta-analysis before receiving final ASGE Governing Board approval.

The PIVI initiative is an ASGE program, the objectives of which are to identify important clinical questions related to endoscopy and to establish a priori diagnostic and/or therapeutic thresholds for endoscopic technologies designed to resolve these clinical questions. Once endoscopic technologies meet an established PIVI threshold, those technologies are appropriate to incorporate into clinical practice, presuming the appropriate training in that endoscopic technology has been achieved. ASGE encourages and supports the appropriate use of technologies that meet its established PIVI thresholds.

INTRODUCTION

Barrett's esophagus (BE) is defined as histologic identification of characteristic specialized intestinal metaplasia within the normal stratified squamous mucosa of the esophagus.[1] BE is a known risk factor for the development of esophageal adenocarcinoma (EAC).[2,3] BE evolves into EAC via a sequence of low-grade dysplasia, high-grade dysplasia (HGD), and eventually EAC.[4] Under traditional white-light endoscopy, dysplasia and EAC may be indistinguishable from nondysplastic BE.[5,6] Moreover, the distribution of dysplasia and EAC is highly variable within the length of BE.[5,6] Therefore, current guidelines recommend endoscopic surveillance in patients with BE with random 4-quadrant biopsy specimens obtained at every 1 to 2 cm to detect dysplasia, in addition to targeted biopsies of suspicious lesions under white-light endoscopy.[7]

Current approaches for endoscopic surveillance of BE are problematic on several fronts.[8-11] Obtaining multiple biopsy specimens, especially for long-segment BE, is labor-intensive and time-intensive. Pathologic interpretation of the multiple biopsy specimens obtained is expensive. Dysplasia and EAC may not be readily distinguishable endoscopically from background BE.[5,6,12] Given the variable distribution of dysplasia and EAC, current biopsy surveillance programs also have the potential for sampling error.[5,6,12] Studies indicate that current practice guidelines are not widely followed, with marked variability noted in both technique and intervals of surveillance.[9-11]

Over the last decade, various advanced imaging techniques have been evaluated in an attempt to improve the detection of dysplasia and EAC within BE.[13] The most studied techniques include chromoendoscopy by using acetic acid or methylene blue, confocal laser endomicroscopy (CLE), and electronic chromoendoscopy with use of narrow-band imaging with or without autofluorescence imaging. In addition, other modalities of electronic chromoendoscopy including i-SCAN (Pentax Medical, Montvale, NJ) and Fujinon Intelligent Chromoendoscopy (FICE; Fujinon Inc, Wayne, NJ), endocytoscopy, volumetric laser endomicroscopy, and spectroscopy are also being evaluated for the ability to improve detection of dysplasia and EAC within BE.

The American Society for Gastrointestinal Endoscopy (ASGE) created a new initiative in 2011 entitled Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI). The key objectives of the PIVI initiative are to identify important clinical questions related to endoscopy and to establish a priori, diagnostic, and/or therapeutic thresholds for endoscopic technologies designed to resolve these clinical questions. The ASGE has identified endoscopic real-time imaging of BE as a key area for new endoscopic technologies and has outlined, in a PIVI document entitled "Imaging in Barrett's Esophagus PIVI," the performance thresholds for an imaging technology with targeted biopsies to eliminate the need for random biopsies during endoscopic surveillance of BE.[14] The performance thresholds established in the PIVI document are (1) imaging technology with targeted biopsies should have a per-patient sensitivity of $\geq$90% and a negative predictive value (NPV) of $\geq$98% for detecting HGD or early EAC, compared with the current standard protocol, and (2) the imaging technology should have a specificity that is sufficiently high (80%) to allow a reduction in the number of biopsies (compared with random biopsies).

These PIVI thresholds were selected based on the fact that despite a marked increase in the incidence of EAC, the incidence of HGD and EAC in patients with BE remains low, with an estimate of 0.6% to 1% per year.[15] Given the low prevalence of HGD and EAC in patients with nondysplastic BE, sensitivity and NPV were selected as important metrics for new imaging technologies seeking to eliminate the need for random biopsies.[14] Prior clinical trials have indicated that the sensitivity of current surveillance biopsy protocols ranges from 28% to 85%.[16-19] In addition, prior analyses assessing cost-effectiveness of BE surveillance have assumed a sensitivity of 85% to 90% for surveillance programs.[20-22] This was the basis for selecting a sensitivity of $\geq$90% as the threshold for replacing the current biopsy protocol with advanced imaging targeted biopsies.[14] To allow a reduction in the number of biopsies compared with random biopsy protocols, a threshold specificity of $\geq$80% was set, because prior clinical trials indicate that the specificity of current biopsy protocols ranges from 56% to 100%.[14,16,19]

The systematic review and meta-analyses were performed by the ASGE Technology Committee to specifically assess whether these PIVI thresholds have been met, based on the existing literature. Input also was sought from the

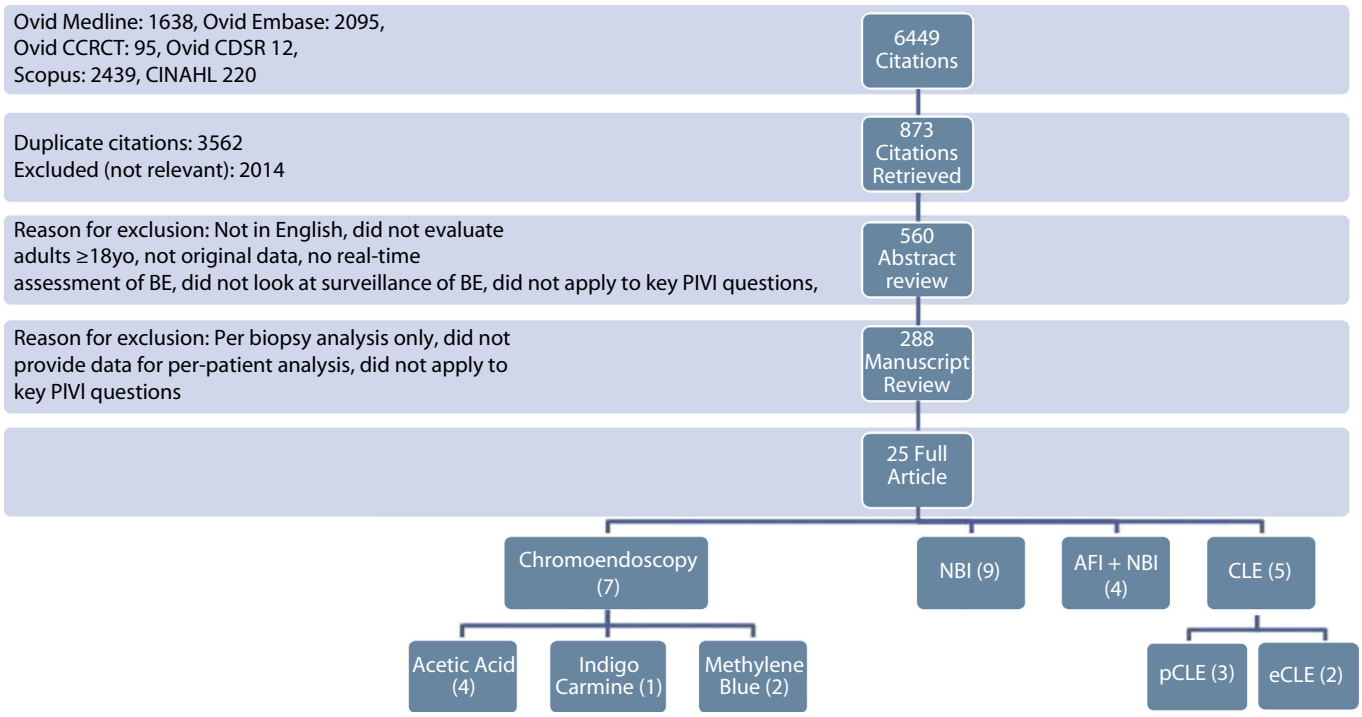

Figure 1. Flow diagram depicting included studies selection for the meta-analysis. *CINAHL*, Cumulative Index to Nursing and Allied Health Literature; *BE,* Barrett's esophagus; *CLE,* confocal laser endomicroscopy; *NBI,* narrow-band imaging; *eCLE,* endoscope-based CLE; *pCLE,* probe-based CLE; *PIVI,* ASGE Preservation and Incorporation of Valuable Endoscopic Innovations.

chair (P.S.) of the ASGE committee that wrote the original PIVI document.

METHODS

Data sources and search strategies

A comprehensive search of several English-language databases was conducted for studies published between January 1, 1980 and August 10, 2015. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy was designed and conducted by an experienced librarian with input from the study team. Controlled vocabulary supplemented with keywords was used to search for studies evaluating advanced imaging technologies in BE. The search strategy is depicted in Appendix 1 (available online at www.giejournal.org). Relevant studies also were identified from the bibliography of studies obtained through the search.

Study selection

We reviewed titles and abstracts of studies retrieved by our search strategy for potential eligibility for inclusion in the meta-analysis. Based on the initial review of study titles and abstracts, we narrowed the search to 288 relevant, full-length studies evaluating chromoendoscopy, electronic chromoendoscopy with or without autofluorescence imaging, and CLE. We reviewed the full text of these articles, and included in the meta-analyses (1) studies that included data on per-patient sensitivity and NPV of real-time imaging–assisted (targeted) biopsies in detecting HGD and EAC compared with the standard biopsy protocol and (2) studies that reported specificity of real-time imaging–assisted (targeted) biopsies compared with the standard biopsy protocol.

Two reviewers performed study selection (N.T., B.K.A.D.). When a disagreement occurred, a third blinded reviewer (S.B.) was consulted to resolve the disagreement. Both reviewers eventually agreed on all included studies. For inclusion in the meta-analysis, a study had to meet the following inclusion criteria: human trial, published in English (full-text) in a peer-reviewed journal, and evaluated the ability of real-time imaging–assisted targeted biopsies by using chromoendoscopy, electronic chromoendoscopy with or without autofluorescence imaging, or CLE compared with the standard biopsy protocol in achieving the thresholds set by the ASGE PIVI document on BE. Abstracts, letters, editorials, expert opinions, reviews without original data, case reports, and studies not directly assessing at least one of the PIVI thresholds were excluded. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to assess the quality of each

TABLE 1. Included studies for the meta-analysis

Author	Technology	Endoscope/equipment	Patients, no.	Male, %	Average length of BE	Endoscopist, no.
Hoffman[24]	AA 1.5%	GIF 160z	31	68	4.3	2
Vázquez-Iglesias[25]	AA 3%	NA	100	69	NA	1
Longcroft-Wheaton[26]	AA 2.5%	EG 590 ZW, EG 590 WR	119	75	4	1
Pohl[27]	AA 1.5%	EG 590 HR, EG 450 WR	701	79	4	4
Sharma[28]	IC	GIF 160z	56	93	3	
Lim[29]	MB 0.5%	–	30	67	5	2
Horwhat[30]	MB 0.5%	GIF 130, GIF140	48	92	2	4
Kara[31]	NBI	GIF 240z	28	86	5	2
Sharma[32]	NBI	GIF 240z	51	98	3.5	
Goda[33]	NBI	GIF 240z	58	88	1.5	1
Anagnostopoulos[34]	NBI	GIF 240z	50	68	4	3
Singh[35]	NBI	GIF 240z	109	71	4.5	4
Wolfsen[36]	NBI	GIF H 180	65	82	4	2
Sharma[37]	NBI	GIF H 180	101	86	3.6	2
Singh[38]	NBI	GIF H 190	40	77.5	4.35	1
Sharma[39]	NBI	GIF H 180	123	94	1.8	–
Kara[40]	AFI-NBI	GIF 240z	20	85	6	2
Curvers[41]	AFI-NBI	GIF 240z	84	83	7	5
Curvers[42]	AFI-NBI	GIF 240z	87	82	7	9
Giacchino[43]	AFI+NBI	GIF 240z	42	100	5.7	6
Trovato[44]	eCLE	EC-3870CIK	48	79	3	2
Canto[45]	eCLE	EC-3870CIK	94	74	3	5
Bajbouj[46]	pCLE	pCLE miniprobe	68	82	4	5
Sharma[37]	pCLE	UHD probe	101	86	3.6	2
Bertani[47]	pCLE	UHD probe	50	78	2.7	2

AA, Acetic acid; *AFI,* autofluorescence imaging; *BE,* Barrett's esophagus; *EAC,* esophageal adenocarcinoma; *eCLE,* endoscope-based confocal laser endomicroscopy; *HDG,* high-grade dysplasia; *IC,* indigo carmine; *MB,* methylene blue; *NA,* not available; *NBI,* narrow-band imaging; *NPV,* negative predictive value; *pCLE,* probe-based confocal laser endomicroscopy; *QUADAS,* Quality Assessment of Diagnostic Accuracy Studies.

study.[23] For each question in the QUADAS tool, responses were either yes = 1 point, unclear = 0.5 point, and no = 0 points were assigned by 2 independent reviewers (N.T., B.K.A.D.). The maximum number of points awarded to a study was 14.

Data extraction

Two reviewers (N.T., B.K.A.D.) independently performed data extraction from each selected citation. When ambiguity on outcomes determination was present, a third reviewer (S.B.) was consulted, and the outcome was determined by consensus. Data extracted included the year the study was published, the country where the study was conducted, setting (academic center vs community practice), expertise of the operator, advanced imaging technology used (chromoendoscopy, electronic chromoendoscopy with or without autofluorescence imaging, or CLE), median length of BE, percentage of men within the study population, overall prevalence of dysplasia and EAC within the study population, and data to calculate sensitivity, specificity, and NPV of advanced imaging techniques compared with the current standard biopsy protocol.

Statistical analysis

To best summarize the available evidence, we conducted direct meta-analyses calculating the pooled sensitivity and pooled NPV with 95% confidence intervals (CI) for advanced imaging–guided targeted biopsies for predicting dysplasia and EAC compared with the standard biopsy protocol. We also calculated the pooled specificity for advanced imaging–guided targeted biopsies compared with the standard biopsy protocol. We used random-effects meta-analysis models to calculate pooled sensitivity, NPV, and specificity. Statistical heterogeneity was evaluated by means of Q value and I^2 statistics; an I^2 value >50% was considered to indicate high statistical heterogeneity. Whenever heterogeneity was present, we performed subgroup analysis or meta-regression to analyze the effects of prevalence of BE in the

TABLE 1. Continued

Blinded pathologist	Magnification	Prevalence of HGD/EAC (%)	Sensitivity	NPV	Specificity	QUADAS
Yes	Yes	6.4	100	100	100	14
No	No	13	100	100	92.3	10
No	No	38	95.4	95.3	81	12
No	No	13	97	99	67	10
No	NA	11	67	96	100	12
No	NA	27	33	50	92	13
Yes	NA	44	76	84	100	14
Yes	NA	50	86	–	–	14
No	Yes	29	100	100	98	14
No	Yes	10	100	100	100	13
Yes	Yes	12	83	98	98	11
Yes	Yes	13	93	99	97	13
Yes	No	32	100	100	–	12
Yes	No	30	97	97.5	56	13
Yes	Yes	2.5	100	100	86.2	13
Yes	Yes	49	50	94	95	14
Yes	Yes	70	100	–	–	11
Yes	Yes	36	90	–	–	11
Yes	Yes	63	83.6	–	–	13.5
Yes	Yes	33	71	76	46	13
Yes	NA	12.5	83.3	97.6	95.2	13
Yes	NA	20	95	98.5	92	12
Yes	NA	16	60	93	95	12
Yes	NA	30	93.5	96	67	13
Yes	NA	3	100	100	61	12

study population, median length of BE, percentage of male population, and blinding of pathologist on the pooled primary outcomes. We also performed sensitivity analyses to rule out bias by removing 1 study at a time to evaluate the impact of individual studies in the overall results of the meta-analyses. A funnel plot and classic fail-safe test were used to assess for potential publication bias. Analyses were performed by using the Comprehensive Meta-analysis software version 2 (Biostat Inc, Englewood, NJ).

RESULTS

The search strategy is summarized in Figure 1. The literature search captured a total of 6449 citations for various advanced imaging techniques in BE. Review for citation duplication (3562) or inapplicable studies (2014) based on title reviews led to the exclusion of 5576 citations. After the abstract reviews, 288 full-length manuscripts were selected for comprehensive review. Of these, 263 citations were excluded because they did not meet inclusion and/or exclusion criteria. A total of 25 remaining citations were ultimately included in the meta-analysis (Table 1). There were 7 studies focusing on chromoendoscopy with acetic acid (4 studies),[24-27] indigo carmine (1 study),[28] and methylene blue (2 studies)[29,30] that compared per-patient sensitivity, specificity, and NPV for chromoendoscopy-assisted targeted biopsies against standard protocol biopsies. Nine studies evaluated electronic chromoendoscopy by using narrow-band imaging,[31-39] and an additional 4 studies evaluated combined used of autofluorescence imaging with narrow-band imaging.[40-43] Five studies evaluated confocal endomicroscopy by using either endoscope-based CLE (eCLE, 2 studies)[44,45] or probe-based CLE (pCLE, 3 studies).[37,46,47] One study evaluated the utility of both pCLE and narrow-band imaging in consecutive patients undergoing surveillance for BE, and this study was included for meta-analysis of pCLE as well as narrow-band imaging.[37]

Overall Sensitivity, Chromoendoscopy

	Model	Group by Dye	Study name	Statistics for each study				
				Event rate	Lower limit	Upper limit	*P* Value	Total
		Acetic Acid	Hoffman _2006	0.984	0.794	0.999	.004	31
		Acetic Acid	Vazquez-Iglesias _2007	0.995	0.926	1.000	.000	100
		Acetic Acid	Longcroft-Wheaton _2010	0.954	0.898	0.980	.000	119
		Acetic Acid	Pohl _2010	0.967	0.951	0.978	.000	701
	Random	Acetic Acid		0.966	0.952	0.977	.000	
		Indigo carmine	Sharma _2006	0.670	0.538	0.780	.013	56
	Random	Indigo carmine		0.670	0.538	0.780	.013	
		Methylene Blue	Lim _2006	0.500	0.328	0.672	1.000	30
		Methylene Blue	Horwhat _2008	0.760	0.620	0.860	.001	48
	Random	Methylene Blue		0.642	0.367	0.847	.310	
A	Random	Overall		0.919	0.894	0.938	.000	

Sensitivity 90%

Overall NPV, Chromoendoscopy

	Model	Group by Dye	Study name	Statistics for each study			
				Event rate	Lower limit	Upper limit	*P* Value
		Acetic Acid	Hoffman _2006	0.984	0.794	0.999	.004
		Acetic Acid	Vazquez-Iglesias _2007	0.995	0.926	1.000	.000
		Acetic Acid	Longcroft-Wheaton _2010	0.953	0.897	0.979	.000
		Acetic Acid	Pohl _2010	0.990	0.979	0.995	.000
	Random	Acetic Acid		0.983	0.948	0.994	.000
		Indigo carmine	Sharma _2006	0.960	0.863	0.989	.000
	Random	Indigo carmine		0.960	0.863	0.989	.000
		Methylene Blue	Lim _2006	0.500	0.328	0.672	1.000
		Methylene Blue	Horwhat _2008	0.844	0.712	0.922	.000
	Random	Methylene Blue		0.698	0.306	0.923	.322
B	Random	Overall		0.955	0.908	0.979	.000

NPV 98%

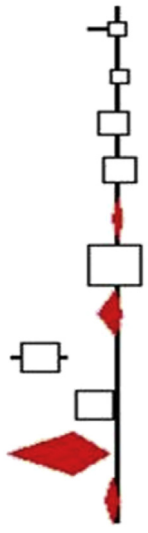

Figure 2. **A**, Forest plot of studies evaluating sensitivity. **B**, Forest plot of studies evaluating negative predictive value. **C**, Forest plot of studies evaluating specificity of chromoendoscopy-guided targeted biopsy against current standard biopsy protocol during surveillance of nondysplastic Barrett's esophagus. *NPV*, negative predictive value.

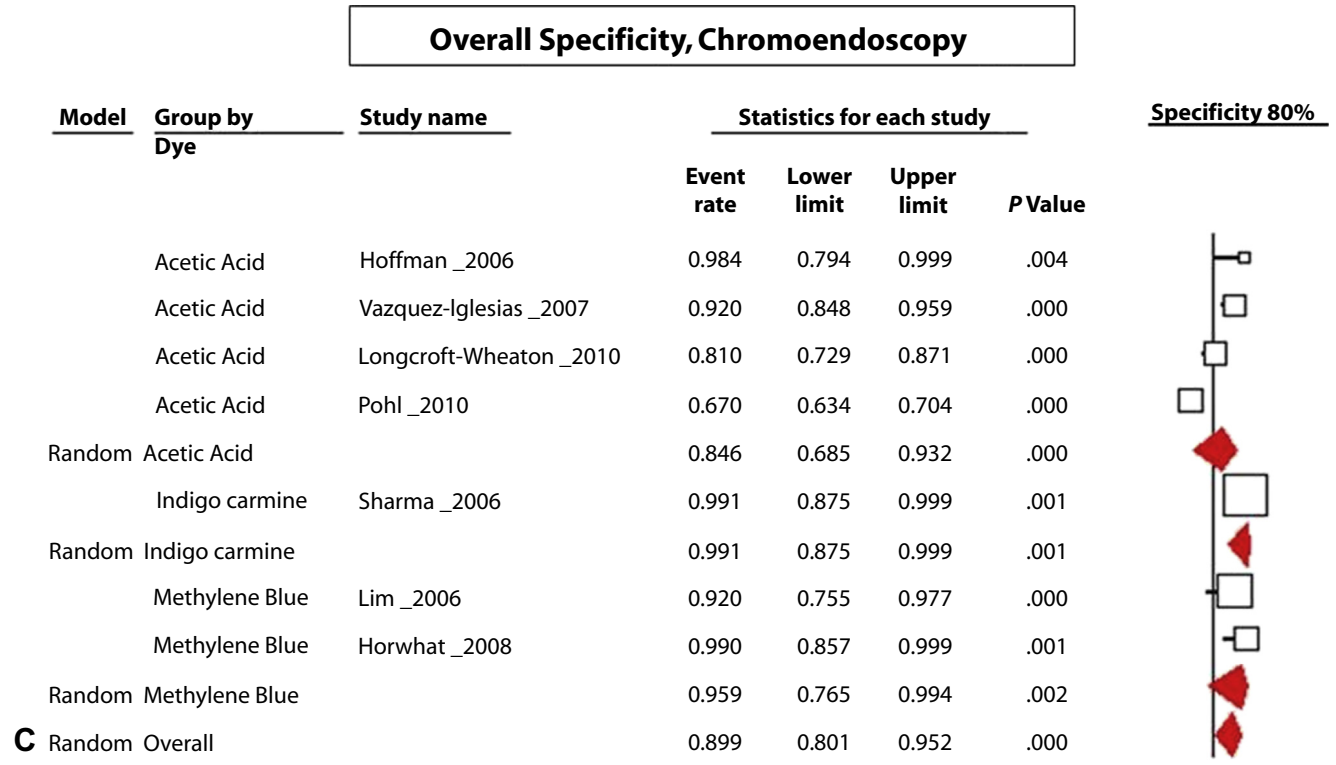

Figure 2. Continued

Meta-analysis of chromoendoscopy studies

Seven studies reported or provided information enabling the calculation of the sensitivity, specificity, and NPV in detecting dysplasia or EAC by using chromoendoscopy-guided targeted biopsies compared with standard protocol biopsies during endoscopic surveillance for BE. Collectively, these studies examined a total of 1085 patients with BE undergoing endoscopic surveillance. The median overall prevalence of dysplasia or EAC in the included studies was 13% (range 6%-44%).

Sensitivity. The pooled sensitivity using the random-effects model was 91.9% (95% CI, 89-94) (Fig. 2A). This finding was associated with a high degree of heterogeneity ($I^2 = 95$).

NPV. The pooled NPV using the random-effects model was 95.5% (95% CI, 91-98) (Fig. 2B). This finding was associated with a high degree of heterogeneity ($I^2 = 93$).

Specificity. The pooled specificity using the random-effects model was 89.9% (95% CI, 80-95) (Fig. 2C). This finding was associated with a high degree of heterogeneity ($I^2 = 89$).

To further explore heterogeneity, we performed subgroup analysis based on the type of dye used during chromoendoscopy.

Acetic acid chromoendoscopy

This subgroup meta-analysis included 4 studies, with 951 patients undergoing surveillance for BE.

Sensitivity. The pooled sensitivity using the random-effects model was 96.6% (95% CI, 95-98). No heterogeneity was noted ($I^2 = 0$).

NPV. The pooled NPV using the random-effects model was 98.3% (95% CI, 95-99). This finding was associated with heterogeneity ($I^2 = 65$).

Specificity. The pooled specificity using the random-effects model was 84.6% (95% CI, 69-93). This finding was associated with a high degree of heterogeneity ($I^2 = 91$).

Methylene blue chromoendoscopy

This meta-analysis included 2 studies, with 78 patients undergoing surveillance for BE.

Sensitivity. The pooled sensitivity using the random-effects model was 64.2% (95% CI, 36-85). This finding was associated with a high degree of heterogeneity ($I^2 = 82$).

NPV. The pooled NPV using the random-effects model was 69.8% (95% CI, 31-92). This finding was associated with a high degree of heterogeneity ($I^2 = 90$).

Specificity. The pooled specificity using the random-effects model was 95.9% (95% CI, 77-99). This finding was associated with a low degree of heterogeneity ($I^2 = 46$).

Indigo carmine chromoendoscopy

The impact of indigo carmine chromoendoscopy on targeted biopsies during surveillance of nondysplastic

Overall Sensitivity, NBI

Model	Study name	Statistics for each study				Sensitivity 90%
		Event rate	Lower limit	Upper limit	*P* Value	
	Kara _2005	0.860	0.679	0.947	.001	
	Sharma _2006	0.990	0.864	0.999	.001	
	Goda _2007	0.992	0.879	0.999	.001	
	Anagnostopoulos _2007	0.830	0.700	0.911	.000	
	Singh _2008	0.930	0.864	0.965	.000	
	Wolfsen _2008	0.992	0.890	1.000	.001	
	Sharma _2011	0.970	0.912	0.990	.000	
	Singh _2013	0.988	0.833	0.999	.002	
	Sharma _2013	0.500	0.413	0.587	1.000	
A Random		0.942	0.826	0.982	.000	

Overall NPV, NBI

Model	Study name	Statistics for each study				NPV 98%
		Event rate	Lower limit	Upper limit	*P* Value	
	Sharma_2006	0.990	0.864	0.999	.001	
	Goda _2007	0.992	0.879	0.999	.001	
	Anagnostopoulos _2007	0.980	0.871	0.997	.000	
	Singh _2008	0.990	0.838	0.998	.000	
	Wolfsen _2008	0.992	0.890	1.000	.001	
	Sharma _2011	0.975	0.918	0.993	.000	
	Singh _2013	0.988	0.833	0.999	.002	
	Sharma _2013	0.937	0.878	0.969	.000	
B Random		0.975	0.951	0.987	.000	

Figure 3. **A**, Forest plot of studies evaluating sensitivity. **B**, Forest plot of studies evaluating negative predictive value. **C**, Forest plot of studies evaluating specificity of narrow-band imaging–guided targeted biopsy against current standard biopsy protocol during surveillance of nondysplastic Barrett's esophagus. *NBI*, narrow-band imaging; *NPV*, negative predictive value.

BE was evaluated in only a single study.[28] This study reported per-patient sensitivity, NPV, and specificity of 67% (95% CI, 54-78), 96% (95% CI, 86-99), and 99% (95% CI, 87-99.9), respectively.[28]

Meta-analysis of electronic chromoendoscopy studies

Nine studies reported or provided information enabling the calculation of sensitivity, specificity, and NPV in

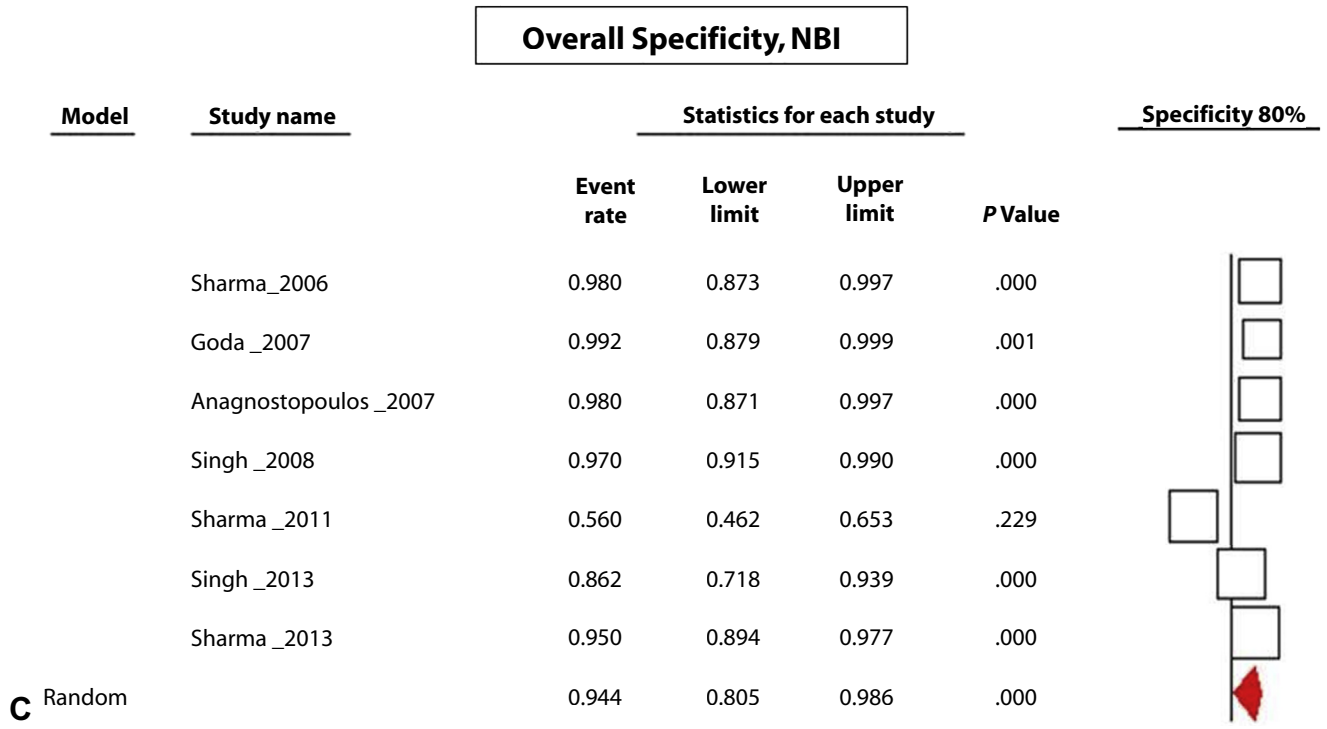

Figure 3. Continued

detecting dysplasia or EAC by using NBI-guided targeted biopsies compared with standard protocol biopsies during endoscopic surveillance for BE. Collectively, these studies examined 625 patients, with BE undergoing endoscopic surveillance. The median overall prevalence of dysplasia or EAC among the included studies was 29% (range 2.5%-50%).

Sensitivity. The pooled sensitivity using the random-effects model was 94.2% (95% CI, 83-98) (Fig. 3A). This finding was associated with a high degree of heterogeneity ($I^2 = 92$).

NPV. The pooled NPV using the random-effects model was 97.5% (95% CI, 95-99) (Fig. 3B). This finding was associated with a low degree of heterogeneity ($I^2 = 20$).

Specificity. The pooled specificity using the random-effects model was 94.4% (95% CI, 81-99) (Fig. 3C). This finding was associated with a high degree of heterogeneity ($I^2 = 92$).

Reduction in number of random biopsies

Two of the included studies provided details in overall reduction in total biopsies with the use of narrow-band imaging–targeted biopsies compared with random 4-quadrant biopsies.[38,39] In a prospective, international, randomized, controlled trial, Sharma et al[39] reported that narrow-band imaging examination required fewer biopsies than did high-definition white-light endoscopy examination in both patients with <3 cm BE (3.0 vs 3.9; $P = .02$) and ≥3 cm BE (4.1 vs 10.9; $P < .0001$), whereas narrow-band imaging detected a higher proportion of areas with dysplasia (30% vs 21%; $P = .01$). Similarly, in a preliminary feasibility study using a novel, dual-focus magnification narrow-band imaging system, Singh et al[38] reported that with use of dual-focus narrow-band imaging, biopsies could have been avoided in 86% of the areas examined while accurately identifying all early cancers and HGD.

Meta-regression for electronic chromoendoscopy

We performed a series of univariate meta-regressions to examine the potential relationship between overall sensitivity and each of the following variables: proportion of men in the study population, average length of BE in the study participants, total number of endoscopists participating in the study, overall prevalence of HGD and EAC within the study population, and blinding of the pathologist to the population. A higher proportion of men in the study population ($P < .01$), shorter average length of BE within the study participants ($P < .01$), a lower prevalence of HGD and/or EAC within the study population ($P < .01$), and blinded pathologists ($P < .01$) were all significant factors associated with overall lower sensitivities.

Meta-analysis of autofluorescence imaging with NBI studies

This meta-analysis included 4 studies, with 233 patients undergoing surveillance for BE.

	Model	Group by Probe Type	Study name	Event rate	Lower limit	Upper limit	*P* Value
		eCLE	Trovato _2013	0.833	0.700	0.914	.000
		eCLE	Canto _2014	0.950	0.883	0.980	.000
	Random	eCLE		0.904	0.719	0.972	.001
		pCLE	Bajbouj _2010	0.600	0.480	0.709	.101
		pCLE	Sharma _2011	0.935	0.867	0.969	.000
		pCLE	Bertani _2013	0.990	0.862	0.999	.001
	Random	pCLE		0.903	0.541	0.987	.034
A	Random	Overall		0.904	0.757	0.966	.000

	Model	Group by Probe Type	Study name	Event rate	Lower limit	Upper limit	*P* Value
		eCLE	Trovato _2013	0.980	0.867	0.997	.000
		eCLE	Canto _2014	0.985	0.926	0.997	.000
	Random	eCLE		0.983	0.942	0.995	.000
		pCLE	Bajbouj _2010	0.930	0.840	0.971	.000
		pCLE	Sharma _2011	0.960	0.899	0.985	.000
		pCLE	Bertani _2013	0.990	0.862	0.999	.001
	Random	pCLE		0.951	0.907	0.975	.000
B	Random	Overall		0.962	0.931	0.979	.000

Figure 4. A, Forest plot of studies evaluating sensitivity. **B**, Forest plot of studies evaluating negative predictive value. **C**, Specificity of confocal laser endomicroscopy–guided targeted biopsy against current standard biopsy protocol during surveillance of nondysplastic Barrett's esophagus. *CLE*, confocal laser endomicroscopy; *eCLE*, endoscope-based confocal laser endomicroscopy; *pCLE*, probe-based confocal laser endomicroscopy; *NPV*, negative predictive value.

Sensitivity. The pooled sensitivity using the random-effects model was 80.6% (95% CI, 62-91). This finding was associated with a high degree of heterogeneity (I^2 = 83).

NPV. Only 1 study reported per-patient NPV of 88.7% (95% CI, 42-99).

Specificity. Only 1 study reported per-patient specificity of 46% (95% CI, 32-61).

Meta-analysis of CLE studies

Five studies reported or provided information enabling the calculation of sensitivity, specificity, and NPV in detecting dysplasia or EAC for CLE-guided targeted biopsies compared with standard protocol biopsies during endoscopic surveillance of BE. Collectively, these studies examined 361 patients with BE undergoing endoscopic

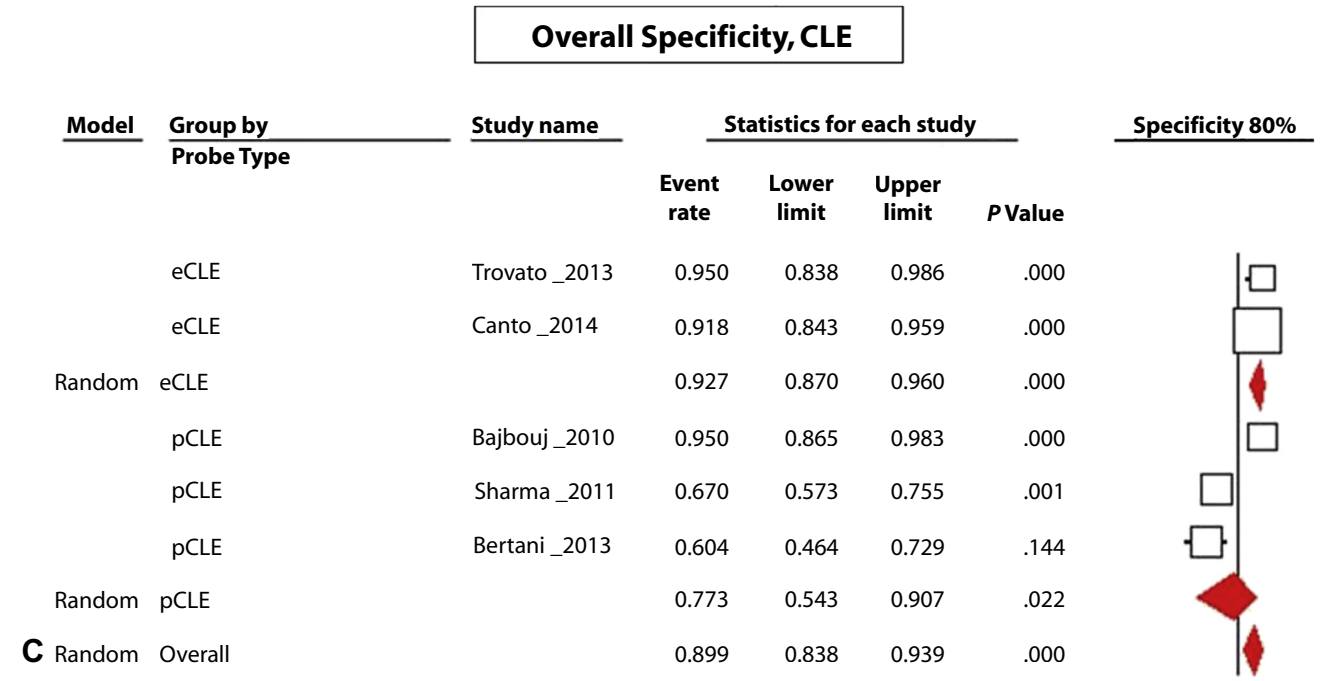

Figure 4. Continued

surveillance. The median overall prevalence of dysplasia or EAC among the included studies was 16% (range 3%-30%).

Sensitivity. The pooled sensitivity using the random-effects model was 90.4% (95% CI, 76-97) (Fig. 4A). This finding was associated with a high degree of heterogeneity ($I^2 = 91$).

NPV. The pooled NPV using the random-effects model was 96.2% (95% CI, 93-98) (Fig. 4B). This finding was associated with a low degree of heterogeneity ($I^2 = 10$).

Specificity. The pooled specificity using the random-effects model was 89.9% (95% CI, 84-94) (Fig. 4C). This finding was associated with a high degree of heterogeneity ($I^2 = 90$).

To further explore heterogeneity, we performed subgroup analysis for endoscope-based CLE (eCLE) and probe-based CLE (pCLE).

eCLE

This meta-analysis included 2 studies, with 142 patients undergoing surveillance for BE.

Sensitivity. The pooled sensitivity using the random-effects model was 90.4% (95% CI, 72-97). This finding was associated with a high degree of heterogeneity ($I^2 = 79$).

NPV. The pooled NPV using the random-effects model was 98.3% (95% CI, 94-99.5). No heterogeneity was noted ($I^2 = 0$).

Specificity. The pooled specificity using the random-effects model was 92.7% (95% CI, 87-96). No heterogeneity was noted ($I^2 = 0$).

pCLE

This meta-analysis included 3 studies, with 219 patients undergoing surveillance for BE.

Sensitivity. The pooled sensitivity using the random-effects model was 90.3% (95% CI, 72-99). This finding was associated with a high degree of heterogeneity ($I^2 = 93$).

NPV. The pooled NPV using the random-effects model was 95.1% (95% CI, 91-98). This finding was associated with a low degree of heterogeneity ($I^2 = 7$).

Specificity. The pooled specificity using the random-effects model was 77.3% (95% CI, 54-91). This finding was associated with a high degree of heterogeneity ($I^2 = 88$).

Overall results of meta-analyses are summarized in detail in Table 2.

Publication bias

A potential publication bias was noted based on asymmetry on graphic assessment of the funnel plots (Supplemental Fig. 1A-D, available online at www.giejournal.org) for chromoendoscopy, narrow-band imaging, narrow-band imaging-autofluorescence imaging, and CLE meta-analyses. To further quantify the degree of publication bias, we performed the classic fail-safe test (file-drawer analysis). For chromoendoscopy, narrow-band imaging, and autofluorescence imaging with narrow-band imaging, and CLE meta-analyses, the classic fail-safe N test indicated that an additional 332, 318, 296, and 48 null studies, respectively, would be needed for the *P* value to exceed .05.

TABLE 2. Results of the meta-analysis

Technology	Total no. of studies	Sensitivity	95% CI	NPV	95% CI	Specificity	95% CI	Meets ASGE PIVI thresholds
Chromoendoscopy	7	91.9	89.4-93.8	95.5	90.8-97.9	89.9	80.1-95.2	No
Acetic acid	4	96.6	95.2-97.7	98.3	94.8-99.4	84.6	68.5-93.2	Yes
Methylene blue	2	64.2	36.2-84.7	69.8	30.6-92.3	95.9	76.5-99.4	No
NBI	9	94.2	82.6-98.2	97.5	95.1-98.7	94.4	80.5-98.6	Yes
NBI AFI	4	80.6	62.0-91.3	88.7	41.5-98.9	46	31.7-61.0	No
CLE	5	90.4	75.7-96.6	96.2	93.1-97.9	89.9	83.8-93.9	No
eCLE	2	90.4	71.9-97.2	98.3	94.2-99.5	92.7	87.0-96.0	Yes
pCLE	3	90.3	54.1-98.7	95.1	90.7-97.5	77.3	54.3-90.7	No

CI, Confidence interval; *NPV,* negative predictive value; *ASGE,* American Society for Gastrointestinal Endoscopy; *PIVI,* ASGE Preservation and Incorporation of Valuable Endoscopic Innovations; *NBI,* narrow-band imaging; *AFI,* autofluorescence imaging; *CLE,* confocal laser endomicroscopy; *eCLE,* endoscope-based CLE; *pCLE,* probe-based CLE.

DISCUSSION

The PIVI document on imaging in BE was created by the ASGE to address the problems of effectiveness, cost, and compliance associated with current surveillance protocols. It sought to promote and facilitate a potential paradigm shift in the endoscopic surveillance of BE, namely that of eliminating the need for random biopsies and promoting instead, targeted biopsies under the guidance of advanced imaging technologies. Such an approach would allow for a decrease in the number of biopsy specimens obtained, which would favorably impact procedure time and associated costs, including pathology charges, while minimizing sampling error and thereby improving accuracy. These advantages may promote endoscopist compliance with new guidelines incorporating advanced imaging technologies. The PIVI document established performance thresholds (per-patient sensitivity of ≥90% and an NPV of ≥98% for detecting HGD or EAC and specificity of ≥80%) that needed to be met before widespread adoption of targeted biopsies using these technologies could be endorsed.[14] Our meta-analysis indicates that chromoendoscopy using acetic acid, electronic chromoendoscopy using NBI, and eCLE all meet the sensitivity, NPV, and specificity thresholds established in the PIVI document for surveillance of patients with nondysplastic BE. However, most of the studies evaluated in this meta-analysis were performed by experts in BE at referral centers in an enriched population, and limited data exist regarding experience with these technologies by gastroenterologists in community practice.

Dye-based chromoendoscopy has been studied by using various agents including methylene blue, indigo carmine, and acetic acid used at various concentrations. Our meta-analysis of all 7 studies focusing on chromoendoscopy found that overall sensitivity, NPV, and specificity were 91.9% (95% CI, 89-94), 95.5% (95% CI, 91-98), and 89.9% (95% CI, 80-95) and did not meet the PIVI thresholds. However, significant heterogeneity was noted in the analysis. Further subgroup analyses of studies focusing on chromoendoscopy with methylene blue indicated that overall sensitivity, NPV, and specificity were 64.2% (95% CI, 36-85), 69.8% (95% CI, 31-92), and 95.9 (95% CI, 77-99), respectively. These values do not meet the thresholds established by the ASGE PIVI. Our results align with the results of a previous meta-analysis assessing the diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in BE, which found no incremental yield of methylene blue chromoendoscopy over random biopsies for the detection of specialized intestinal metaplasia, dysplasia, and HGD and/or EAC.[48] Given its lack of efficacy and potential risks,[49] its use for this purpose cannot be recommended. Similarly, a single study evaluating the performance of indigo carmine chromoendoscopy showed very poor sensitivity of 67% (95% CI, 54-78).[28]

In contrast, subgroup analysis of studies focusing on acetic acid chromoendoscopy indicated an overall sensitivity, NPV, and specificity of 96.6% (95% CI, 95-98), 98.3% (95% CI, 95-99), and 84.6% (95% CI, 69-93), respectively. These values meet the thresholds established by the ASGE PIVI, and acetic acid chromoendoscopy can therefore be incorporated into routine clinical practice. However, despite its efficacy, chromoendoscopy has not been widely adopted for a variety of reasons. Chromoendoscopy requires use of a spraying catheter and is disadvantaged by the perception that the technique is time-consuming and tedious.[13] Moreover, dye-based chromoendoscopy does not have a specific CPT (Current Procedural Terminology, American Medical Association, Chicago, Ill) code for billing and reimbursement, and costs for dye have increased, which may be factors limiting its adoption.[48]

Electronic chromoendoscopy is increasingly used in clinical practice rather than dye-based chromoendoscopy because of the advantages of ease of use and safety. There are limited published data on surveillance of BE by using FICE[50] and I-SCAN,[51] and our meta-analysis was therefore

performed only on narrow-band imaging. BE HGD and/or EAC are identified with the use of narrow-band imaging based on abnormal mucosal and vascular patterns. Our meta-analysis of 9 studies focusing on surveillance of nondysplastic BE with narrow-band imaging indicated a pooled sensitivity, NPV, and specificity of 94.2% (95% CI, 83-98), 97.5% (95% CI, 95-99), and 94.4% (95% CI, 81-99), respectively. These values meet the thresholds established by the ASGE PIVI, and narrow-band imaging targeted biopsies can therefore be incorporated into routine clinical practice. Our results are similar to another recent meta-analysis that reported per-patient pooled sensitivity and specificity of 91% (95% CI, 75-98) and 95% (95% CI, 91-97) for detection of HGD with the use of NBI.[52] A recent study using narrow-band imaging with dual-focus endoscopes (190 series Exera III NBI system, Olympus Co, Tokyo, Japan) indicated an overall 86% reduction in need for biopsies, while detecting all HGD and early adenocarcinoma.[38] Narrow-band imaging offers several advantages, including relative ease of use, wide-field imaging, and relative cost savings because it is readily available and does not require an additional probe and/or processor. The main limitation with use of narrow-band imaging for BE surveillance is that no single classification system has been universally adopted.[53] Currently, 3 different classifications[32,35,54] of mucosal and vascular patterns have been proposed, with inadequate interobserver agreement. A new consensus-driven, international narrow-band imaging classification system (BING criteria) has been developed recently and validated by a group of expert endoscopists.[55]

Autofluorescence imaging is a wide-field imaging technology that has been used in conjunction with narrow-band imaging and high-resolution white-light endoscopy. We found a per-patient pooled sensitivity of 80.6% (95% CI, 62-91) in our meta-analysis of 4 published studies. Only 1 of the published studies reported NPV and specificity, which were 89% (95% CI, 42-99) and 46% (95% CI, 32-61), respectively. This does not meet the ASGE PIVI thresholds.

Our meta-analysis of 5 CLE studies indicated a pooled sensitivity of 90.4% (95% CI, 76-97), NPV of 96.2% (95% CI, 93-98), and specificity of 89.9% (95% CI, 84-94). These results do not meet the established PIVI thresholds. However, significant heterogeneity was noted in the analysis. Subgroup analysis of studies focusing on eCLE indicates an overall sensitivity, NPV, and specificity of 90.4% (95% CI, 72-97), 98.3% (95% CI, 94-99), and 92.7% (95% CI, 87-96), respectively. Although these values meet the PIVI thresholds, this endoscope is no longer commercially available.

Most recent CLE studies have used pCLE. Subgroup analysis of studies that used pCLE indicates an overall sensitivity, NPV, and specificity of 90.3% (95% CI, 54-99), 95.1% (95% CI, 91-98), and 77.3% (95% CI, 54-91), respectively. These values for pCLE are high but do not meet the established a priori PIVI thresholds. Our results are consistent with another recent meta-analysis on pCLE, which found overall per-patient sensitivity and specificity of 86% (95% CI, 74-96) and 83% (95% CI, 77-88), respectively.[56] There are important limitations with the use of pCLE. The pCLE probe is capable of imaging only a small field of mucosa, and performing targeted biopsy of mucosa at the exact site visualized by pCLE is challenging, raising the possibility of sampling error.

As with any meta-analysis, there are several potential limitations in our analysis. One important limitation is that the sensitivity, NPV, and specificity of new technologies were derived by comparing them against the current random biopsy protocol, which was considered the criterion standard. Dysplasia and EAC can be missed with current biopsy protocols because of sampling error, and, therefore, in the absence of surgical removal or complete BE excision, the true disease status of any given patient remains unknown.[57] Therefore, determination of sensitivity, NPV, and specificity compared with the current criterion standard biopsy protocol is potentially biased.[57] Sample sizes in the included studies are small and raise the possibility of selection bias.[48] By pooling data from individual small studies, potential selection bias could have been amplified. A high degree of heterogeneity was present among the included studies. Whenever possible, we corrected for this by performing subgroup analysis and meta-regression analysis. We did find that the overall prevalence of HGD and/or EAC within the study population, proportion of men within the study, average length of BE, and blinding of the pathologist did contribute to the heterogeneity between the studies. In addition, it is likely that operator experience, difference in the overall BE inspection time with a given technology, and variability between different image interpretation classification systems all contributed to heterogeneity between the studies. We also included only studies that reported per-patient sensitivity, NPV, and specificity and excluded many studies that reported per-biopsy analysis.

This ASGE Technology Committee systematic review and meta-analysis confirms that the thresholds set by ASGE PIVI for real-time imaging–assisted endoscopic targeted biopsy during endoscopic surveillance of BE have been met by acetic acid chromoendoscopy, narrow-band imaging, and eCLE, at least by endoscopists with expertise in advanced imaging techniques at referral centers. The ASGE Technology Committee therefore endorses the use of these modalities during surveillance of nondysplastic BE for obtaining targeted biopsy specimens by endoscopists proficient in these techniques. Results with autofluorescence imaging and pCLE are encouraging but do not yet meet the established PIVI thresholds. Other advanced imaging technologies including i-Scan, FICE, optical coherence tomography, high-resolution microendoscopy, endocytoscopy, and spectroscopy have the potential to improve targeting of biopsies for BE surveillance, but few data currently exist, and further studies are needed.

Further challenges therefore remain before widespread implementation of these technologies into clinical practice, including proving the cost-effectiveness of new advanced imaging technologies for BE surveillance, standardization of imaging-based BE classification systems, establishing training and quality standards in advanced imaging–guided targeted biopsies for BE surveillance to ensure consistent high-confidence examinations, and finally, appropriate patient selection based on individualized risk for the development of esophageal cancer. The ASGE Standards of Practice, Training, Educational Products, and Quality Assurance in Endoscopy committees will address all of these issues to promote and facilitate widespread adoption of advanced imaging–guided targeted biopsies during surveillance of nondysplastic BE.

DISCLOSURE

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett's esophagus; CLE, confocal laser endomicroscopy; EAC, esophageal adenocarcinoma; eCLE, endoscope-based CLE; FICE, Fujinon Intelligent Chromoendoscopy; HGD, high-grade dysplasia; NBI, narrow-band imaging; NPV, negative predictive value; pCLE, probe-based CLE; PIVI, ASGE Preservation and Incorporation of Valuable Endoscopic Innovations; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

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APPENDIX 1

Ovid

Database(s): Embase 1988 to 2015 Week 37, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials August 2015, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 2015

SEARCH STRATEGY:

#	Searches	Results
1	exp Barrett Esophagus/	19089
2	exp Esophageal Neoplasms/	92589
3	(((barrett or barretts) and (esophagus or oesophagus or syndrome or epithelium or metaplasia)) or ((esophag* or oesophag*) and (neoplasm* or cancer* or dysplas* or carcinoma* or adenocarcinoma* or precancer* or "pre-cancer*" or premalignan* or "pre-malignan*" or metaplas*)) or "columnar epithelium lined lower esophagus" or "columnar epithelium lined lower oesophagus").mp.	151326
4	1 or 2 or 3	153015
5	exp chromoendoscopy/	1974
6	exp acetic acid/	43580
7	exp Methylene Blue/	19969
8	exp Esophagoscopy/	21125
9	exp Image Enhancement/	467342
10	8 and 9	633
11	exp narrow band imaging/	2713
12	exp Microscopy, Confocal/	91479
13	exp confocal laser microscopy/	15028
14	exp Coloring Agents/	189425
15	exp autofluorescence imaging/	24651
16	exp Optical Imaging/	34185
17	exp Indigo Carmine/	2261
18	((enhanc* adj3 imag*) or "acetic acid" or "advanced imag*" or AFI or "astrazone blue" or autofluorescen* or "basic blue 9" or "Blue No 2" or "Blue NO 6" or "carminum coeruleum" or CE or chromoendoscop* or chromoscop* or chromosmon or CLE or CLSM or "colorant agent*" or "coloring agent*" or "confocal endomicroscop*" or "confocal laser endomicroscop*" or "confocal laser microscop*" or "Confocal Laser Scanning Microscop*" or "Confocal Microscop*" or "confocal scanning laser microscop*" or CSLM or eCLE or endocytoscop* or "endoscopic vital stain*" or FICE or "Fluorescence Imag*" or "four quadrant biops*" or "Fuji intelligent chromo endoscop*" or "Fuji intelligent chromoendoscop*" or "Fuji Intelligent Color Enhance*" or "Fujinon intelligent chromo endoscop*" or "Fujinon intelligent chromoendoscop*" or "Fujinon intelligent color enhance*" or "high-resolution microendoscop*" or HRME or "HR-WLE" or indicamine or indicarmin or Indigo or indigocarmine or Indigotin or "indigotin disulfonate" or Indigotindisulfonate or "Indigotindisulfonic Acid" or IScan or "I-Scan" or "Laser Microscop*" or "Laser Scanning Confocal Microscop*" or "laser scanning cytometr*" or "Laser Scanning Microscop*" or "methylene blue" or "methylthionine chloride" or "methylthioninium chloride" or "narrow band imag*" or "narrowband imag*" or NBI or OCT or "optical coherence tomograph*" or "optical imag*" or pCLE or "real time histolog*" or "real time imag*" or "realtime histolog*" or "realtime imag*" or spectroscop* or "Swiss Blue" or "tetramethylthionine chloride" or "tissue dye*" or "tissue stain*" or "urolene blue" or "video capsule endoscop*" or VLE or "volumetric laser endomicroscop*" or "white light endoscop*").mp.	1372896
19	5 or 6 or 7 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1530763
20	4 and 19	5551
21	limit 20 to english language [Limit not valid in CDSR; records were retained]	5039
22	limit 21 to yr="1980 -Current"	5029
23	22 not "conference abstract".pt.	4143
24	limit 23 to (editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	315
25	from 24 keep 1-303	303
26	23 not 25	3840
27	remove duplicates from 26	2627

Scopus

1 TITLE-ABS-KEY(((barrett or barretts) and (esophagus or oesophagus or syndrome or epithelium or metaplasia)) or ((esophag* or oesophag*) and (neoplasm* or cancer* or dysplas* or carcinoma* or adenocarcinoma* or precancer* or "pre-cancer*" or premalignan* or "pre-malignan*" or metaplas*)) or "columnar epithelium lined lower esophagus" or "columnar epithelium lined lower oesophagus")
2 TITLE-ABS-KEY((enhanc* W/3 imag*) OR "acetic acid" OR "advanced imag*" OR AFI OR "astrazone blue" OR autofluorescen* OR "basic blue 9" OR "Blue No 2" OR "Blue NO 6" OR "carminum coeruleum" OR CE OR chromoendoscop* OR chromoscop* OR chromosmon OR CLE OR CLSM OR "colorant agent*" OR "coloring agent*" OR "confocal endomicroscop*" OR "confocal laser endomicroscop*" OR "confocal laser microscop*" OR "Confocal Laser Scanning Microscop*" OR "Confocal Microscop*" OR "confocal scanning laser microscop*" OR CSLM OR eCLE OR endocytoscop* OR "endoscopic vital stain*" OR FICE OR "Fluorescence Imag*" OR "four quadrant biops*" OR "Fuji intelligent chromo endoscop*" OR "Fuji intelligent chromoendoscop*" OR "Fuji Intelligent Color Enhance*" OR "Fujinon intelligent chromo endoscop*" OR "Fujinon intelligent chromoendoscop*" OR "Fujinon intelligent color enhance*" OR "high-resolution microendoscop*" OR HRME OR "HR-WLE" OR indicamine OR indicarmin OR Indigo OR indigocarmine OR Indigotin OR "indigotin disulfonate" OR Indigotindisulfonate OR "Indigotindisulfonic Acid" OR IScan OR "I-Scan" OR "Laser Microscop*" OR "Laser Scanning Confocal Microscop*" OR "laser scanning cytometr*" OR "Laser Scanning Microscop*" OR "methylene blue" OR "methylthionine chloride" OR "methylthioninium chloride" OR "narrow band imag*" OR "narrowband imag*" OR NBI OR OCT OR "optical coherence tomograph*" OR "optical imag*" OR pCLE OR "real time histolog*" OR "real time imag*" OR "realtime histolog*" OR "realtime imag*" OR spectroscop* OR "Swiss Blue" OR "tetramethylthionine chloride" OR "tissue dye*" OR "tissue stain*" OR "urolene blue" OR "video capsule endoscop*" OR VLE OR "volumetric laser endomicroscop*" OR "white light endoscop*")
3 PUBYEAR AFT 1979 AND LANGUAGE(english)
4 1 and 2 and 3
5 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ab)
6 4 and not 5
7 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
8 6 and not 7

CINAHL

#	Query	Limiters/Expanders	Last Run Via	Results
S26	S4 AND S24	Limiters - Published Date: 19800101-20151231; Language: English Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	220
S25	S4 AND S24	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	220
S24	S22 OR S23	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	22,764
S23	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	21,154

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#	Query	Limiters/Expanders	Last Run Via	Results
S22	S7 OR S8 OR S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	2,665
S21	Indigotin OR "indigotin disulfonate" OR Indigotindisulfonate OR "Indigotindisulfonic Acid" OR IScan OR "I-Scan" OR "Laser Microscop*" OR "Laser Scanning Confocal Microscop*" OR "laser scanning cytometr*" OR "Laser Scanning Microscop*" OR "methylene blue" OR "methylthionine chloride" OR "methylthioninium chloride" OR "narrow band imag*" OR "narrowband imag*" OR NBI OR OCT OR "optical coherence tomograph*" OR "optical imag*" OR pCLE OR "real time histolog*" OR "real time imag*" OR "realtime histolog*" OR "realtime imag*" OR spectroscop* OR "Swiss Blue" OR "tetramethylthionine chloride" OR "tissue dye*" OR "tissue stain*" OR "urolene blue" OR "video capsule endoscop*" OR VLE OR "volumetric laser endomicroscop*" OR "white light endoscop*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	11,433
S20	"high-resolution microendoscop*" OR HRME OR "HR-WLE" OR indicamine OR indicarmin OR Indigo OR indigocarmine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	57
S19	"Fujinon intelligent chromoendoscop*" OR "Fujinon intelligent color enhance*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	6
S18	"Fuji Intelligent Color Enhance*" OR "Fujinon intelligent chromo endoscop*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	4
S17	"Fuji intelligent chromo endoscop*" OR "Fuji intelligent chromoendoscop*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	1
S16	"endoscopic vital stain*" OR FICE OR "Fluorescence Imag*" OR "four quadrant biops*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	103
S15	"Confocal Microscop*" OR "confocal scanning laser microscop*" OR CSLM OR eCLE OR endocytoscop*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	529
S14	"confocal laser endomicroscop*" OR "confocal laser microscop*" OR "Confocal Laser Scanning Microscop*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	235

(*continued on the next page*)

Continued

#	Query	Limiters/Expanders	Last Run Via	Results
			Database - CINAHL with Full Text	
S13	chromosmon OR CLE OR CLSM OR "colorant agent*" OR "coloring agent*" OR "confocal endomicroscop*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	210
S12	chromoendoscop* OR chromoscop*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	135
S11	"basic blue 9" OR "Blue No 2" OR "Blue NO 6" OR "carminum coeruleum" OR CE	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	4,874
S10	(enhanc* N3 imag*) OR "acetic acid" OR "advanced imag*" OR AFI OR "astrazone blue" OR autofluorescen*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	4,320
S9	(MH "Dyes+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	2,028
S8	(MH "Acetic Acid")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	597
S7	S5 AND S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	47
S6	(MH "Image Enhancement+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	38,475
S5	(MH "Esophagoscopy")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	525

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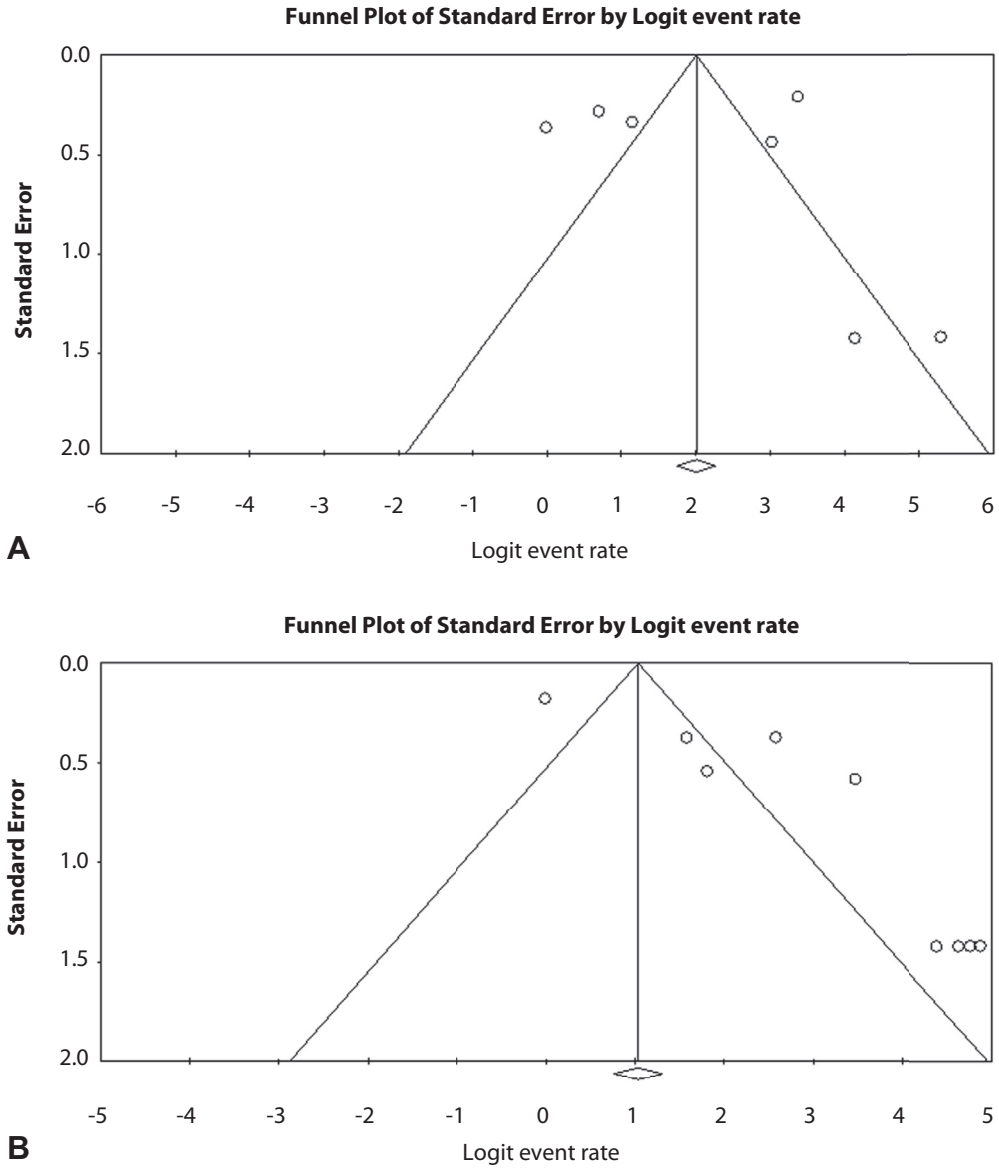
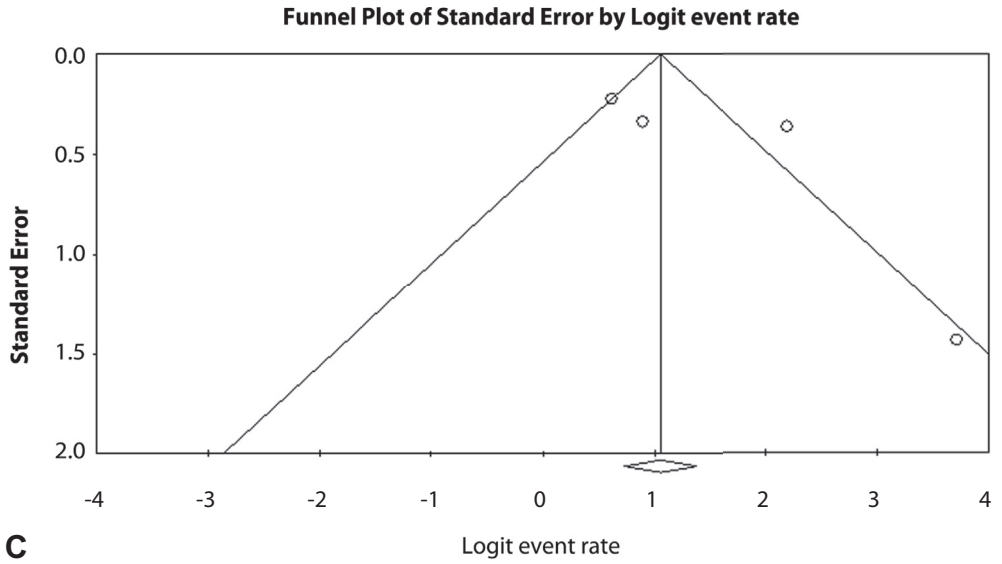
Continued

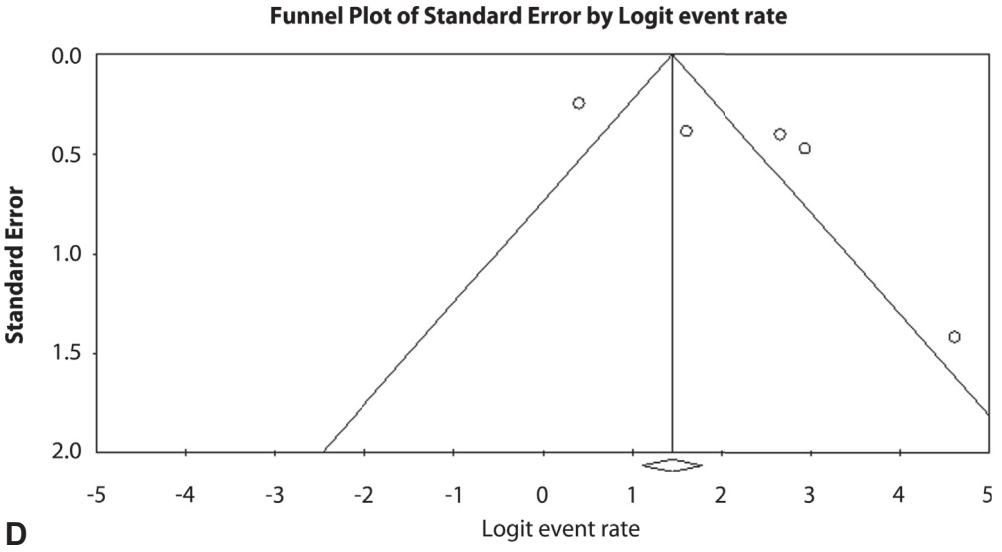
#	Query	Limiters/Expanders	Last Run Via	Results
S4	S1 OR S2 OR S3	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	3,688
S3	(((barrett or barretts) and (esophagus or oesophagus or syndrome or epithelium or metaplasia)) or ((esophag* or oesophag*) and (neoplasm* or cancer* or dysplas* or carcinoma* or adenocarcinoma* or precancer* or "pre-cancer*" or premalignan* or "pre-malignan*" or metaplas*)) or "columnar epithelium lined lower esophagus" or "columnar epithelium lined lower oesophagus")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	3,688
S2	(MH "Esophageal Neoplasms")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	2,155
S1	(MH "Barrett Esophagus")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	760



Supplemental Figure 1. Publication bias funnel plot for chromoendoscopy **(A)**, narrow-band imaging **(B)**, autofluorescence imaging with NBA **(C)**, and confocal laser endomicroscopy **(D)**.



C



D

Supplemental Figure 1. Continued