Communication from the ASGE Technology Committee

ASGE TECHNOLOGY COMMITTEE
SYSTEMATIC REVIEW AND META-ANALYSIS

ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps

Abstract: In vivo real-time assessment of the histology of diminutive (≤5 mm) colorectal polyps detected at colonoscopy can be achieved by means of an "optical biopsy" by using currently available endoscopic technologies. 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 an ASGE Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) document for clinical adoption of these technologies have been met. We conducted direct meta-analyses calculating the pooled negative predictive value (NPV) for narrow-band imaging (NBI), i-SCAN, and Fujinon Intelligent Color Enhancement (FICE)–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps. We also calculated the pooled percentage agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm. Random-effects meta-analysis models were used. Statistical heterogeneity was evaluated by means of I^2 statistics. Our meta-analyses indicate that optical biopsy with NBI, exceeds the NPV threshold for adenomatous polyp histology, supporting a "diagnose-and-leave" strategy for diminutive predicted nonneoplastic polyps in the rectosigmoid colon. The pooled NPV of NBI for adenomatous polyp histology by using the random-effects model was 91% (95% confidence interval [CI], 88–94). This finding was associated with a high degree of heterogeneity (I^2 = 89%). Subgroup analysis indicated that the pooled NPV was greater than 90% for academic medical centers (91.8%; 95% CI, 89-94), for experts (93%; 95% CI, 91-96), and when the optical biopsy assessment was made with high confidence (93%; 95% CI, 90-96). Our meta-analyses also indicate that the agreement in assignment of postpolypectomy surveillance intervals based on optical biopsy with NBI of diminutive colorectal polyps is 90% or greater in academic settings (91%; 95% CI, 86-95), with experienced endoscopists (92%; 95% CI, 88-96) and when optical biopsy assessments are made with high confidence (91%; 95% CI, 88-95). Our systematic review and meta-analysis confirms that the thresholds established by the ASGE PIVI for real-time endoscopic assessment of the histology of diminutive polyps have been met, at least with NBI optical biopsy, with endoscopists who are expert in using this advanced imaging technology and when assessments are made with high confidence. (Gastrointest Endosc 2015;81:502-16.)

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(s) in the subject area, and the Technology Committee Chair performed the 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

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that endoscopic technology has been achieved. ASGE encourages and supports the appropriate use of technologies that meet its established PIVI thresholds.

INTRODUCTION

The majority of colorectal polyps found at screening colonoscopy are diminutive (≤5 mm). These polyps seldom harbor advanced histological features (villous features or high-grade dysplasia) and very rarely harbor cancer. However, based on current management guidelines, endoscopists encountering diminutive polyps are obliged to remove them and submit them to histopathology to determine the next surveillance colonoscopy interval based on the histology of these polyps (adenomatous vs hyperplastic).[1,2] The costs associated with resection and pathology evaluation of these diminutive polyps add substantially to the total cost of colonoscopy, especially in countries such as the United States, where colonoscopy is a common modality for colorectal cancer screening.[3]

If a sufficiently accurate in vivo assessment of the histology of these diminutive polyps can be achieved by means of an "optical biopsy," this may allow for a paradigm shift in the assessment and management of these polyps, which could significantly reduce the total cost of colonoscopy without affecting its efficacy in reducing future risk of colorectal cancer. This paradigm shift would incorporate the adoption of a "diagnose-and-leave" strategy, in which the endoscopist leaves in situ diminutive rectosigmoid hyperplastic polyps, and a "resect-and-discard" strategy, in which diminutive adenomatous polyps are resected after endoscopic assessment of histology to allow determination of surveillance colonoscopy intervals, but not submitted for histopathology evaluation.

Several in vivo endoscopic technologies exist that allow for real-time characterization of diminutive colorectal polyps that are superior to that achievable with white-light endoscopy. Electronic chromoendoscopy technologies facilitate polyp characterization by enhancing the surface pit pattern and highlighting the microvasculature of these polyps. These technologies include narrow-band imaging (NBI) (Olympus, Tokyo, Japan), i-SCAN (Pentax, Tokyo, Japan), and Fujinon Intelligent Color Enhancement (FICE) (Fujinon Inc, Saitama, Japan).[4] Confocal laser endomicroscopy (CLE) has also been evaluated for this purpose.

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 polyp characterization as a key area for new endoscopic technologies and has outlined in a PIVI document entitled "The ASGE PIVI on Real-Time Endoscopic Assessment of the Histology of Diminutive Colorectal Polyps" the performance thresholds that these technologies should meet before adoption into clinical practice.[5] Two thresholds have been established in this PIVI document:

1. For a technology to be used to guide the decision to leave suspected rectosigmoid hyperplastic polyps 5 mm or smaller in place (without resection), the technology should provide a 90% or greater negative predictive value (NPV) (when used with high confidence) for adenomatous histology.
2. For colorectal polyps 5 mm or smaller to be resected and discarded without pathologic assessment, endoscopic technology (when used with high confidence) used to determine histology of these polyps, when combined with the histopathologic assessment of polyps larger than 5 mm, should provide 90% or greater agreement in assignment of postpolypectomy surveillance intervals when compared with decisions based on pathology assessment of all identified polyps.

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 was also sought from the chair (D.K.R.) 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 May 14, 2014. 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 Web of Science. 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 electronic chromoendoscopy (NBI, i-SCAN, and FICE) for the characterization of colonic polyps. The detailed search strategy is available upon request. Relevant studies were also identified from the bibliography of studies obtained through the search. A similar process was also used for studies evaluating confocal laser endomicroscopy (CLE) for the characterization of colonic polyps.

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 49 relevant full-length studies evaluating NBI and 25 studies evaluating

i-SCAN and FICE. We reviewed the full text of these studies, and included in the meta-analysis:

1. Studies that included data on the NPV of real-time NBI, i-SCAN, or FICE for adenomatous histology of small and diminutive colorectal polyps detected during colonoscopy and/or
2. Studies that assessed agreement in assigning postpolypectomy surveillance intervals when combining real-time NBI, i-SCAN, or FICE in situ optical biopsy of colorectal polyps 5 mm or smaller along with histopathologic assessment of polyps larger than 5 mm compared with decisions based on histopathologic assessment alone of all identified polyps.

Two reviewers performed study selection (B.K.A.D. and N.T.); 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 evaluating the ability of NBI, i-SCAN, or FICE in performing real-time in situ optical biopsy of small and diminutive colorectal polyps, compared with the criterion standard of histopathology, in achieving 1 or both of the PIVI thresholds. Abstracts, letters, editorials, expert opinions, reviews without original data, case reports, and studies not directly assessing at least 1 of the 2 PIVI thresholds were excluded. All prospective, randomized trials included in the meta-analysis met the majority of the criteria set forth by the Evidence-Based Gastroenterology Steering Group for methodologic quality, indicating studies of reasonable quality.[6]

A similar review process for CLE revealed only 5 published studies with a mix of endoscopy-based and probe-based CLE, reporting real-time classification of polyps. Given the variability of these studies in assessing the PIVI thresholds, we could not combine them in a meta-analysis.

Data extraction

Two independent reviewers performed data extraction (B.K.A.D. and N.T.) 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 endoscopist in performing optical biopsy of colorectal polyps by using NBI, i-SCAN, or FICE (expert vs novice), training in optical NBI biopsy as part of the study protocol (yes vs no), criteria used for optical biopsy (vascular pattern intensity [VPI], Kudo, Sano, Modified Narrow Band Imaging International Colorectal Endoscopic Classification [M-NICE], NICE, or combination), use of high-definition white-light endoscopy (yes vs no), use of magnification (yes vs no), processor type, high confidence interpretation of the optical biopsy (yes vs no), number of small and diminutive polyps detected, number of polyps per patient, percentage of polyps with adenomatous histology, NPV of NBI, i-SCAN, or FICE optical biopsy for predicting adenomatous polyp histology of small and diminutive colorectal polyps, and percentage of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time NBI, i-SCAN, or FICE optical biopsy of colorectal polyps 5 mm or smaller along with histopathologic assessment of polyps larger than 5 mm in size.

Statistical analysis

To best summarize the available evidence, we conducted direct meta-analyses calculating the pooled NPV with 95% confidence intervals (CI) for NBI-, i-SCAN-, and FICE-assisted optical biopsy for predicting adenomatous polyp histology of small and diminutive colorectal polyps. We also calculated the pooled percentage of agreement with histopathology and 95% CI when assigning postpolypectomy surveillance intervals based on combining real-time NBI-, i-SCAN, and FICE-assisted optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm. Random-effects meta-analysis models were used. Statistical heterogeneity was evaluated by means of the I^2 statistic; an I^2 value greater than 50% was considered to indicate high statistical heterogeneity. A funnel plot and Egger regression asymmetry were used to assess potential publication bias. We also performed subgroup analysis to analyze the effects of expertise, setting, and high confidence interpretation on the pooled primary outcomes. Analyses were performed by using Comprehensive Meta-analysis software version 2 (Biostat, Inc, Englewood, NJ).

RESULTS

The search results are summarized in Figure 1. The literature search captured a total of 771 citations for NBI and 159 citations for i-SCAN and FICE. Review for citation duplication eliminated 377 citations for NBI and 85 citations for i-SCAN and FICE. Of the 74 remaining citations for i-SCAN and FICE, 39 citations were for FICE and 35 citations were for i-SCAN. Title reviews led to the exclusion of 244 citations for NBI, 13 citations for FICE, and 11 citations for i-SCAN. Of the subsequently reviewed abstracts (150 for NBI, 26 for FICE, and 24 for i-SCAN), 101, 14, and 11 citations, respectively, were excluded because they were not applicable to the current meta-analysis. The full-length manuscripts of the remaining 49 NBI citations, 12 FICE citations, and 13 i-SCAN citations were reviewed. Of these, 29 citations for NBI, 4 citations for FICE, and 5 citations for i-SCAN were excluded because they did not meet inclusion/exclusion criteria.

Twenty remaining citations were ultimately included in the NBI meta-analysis, of which 19 evaluated the NPV of optical NBI biopsy and 10 evaluated agreement in postpolypectomy surveillance intervals. The 20 included studies were published between 2008 and 2014, with the majority (17/20)

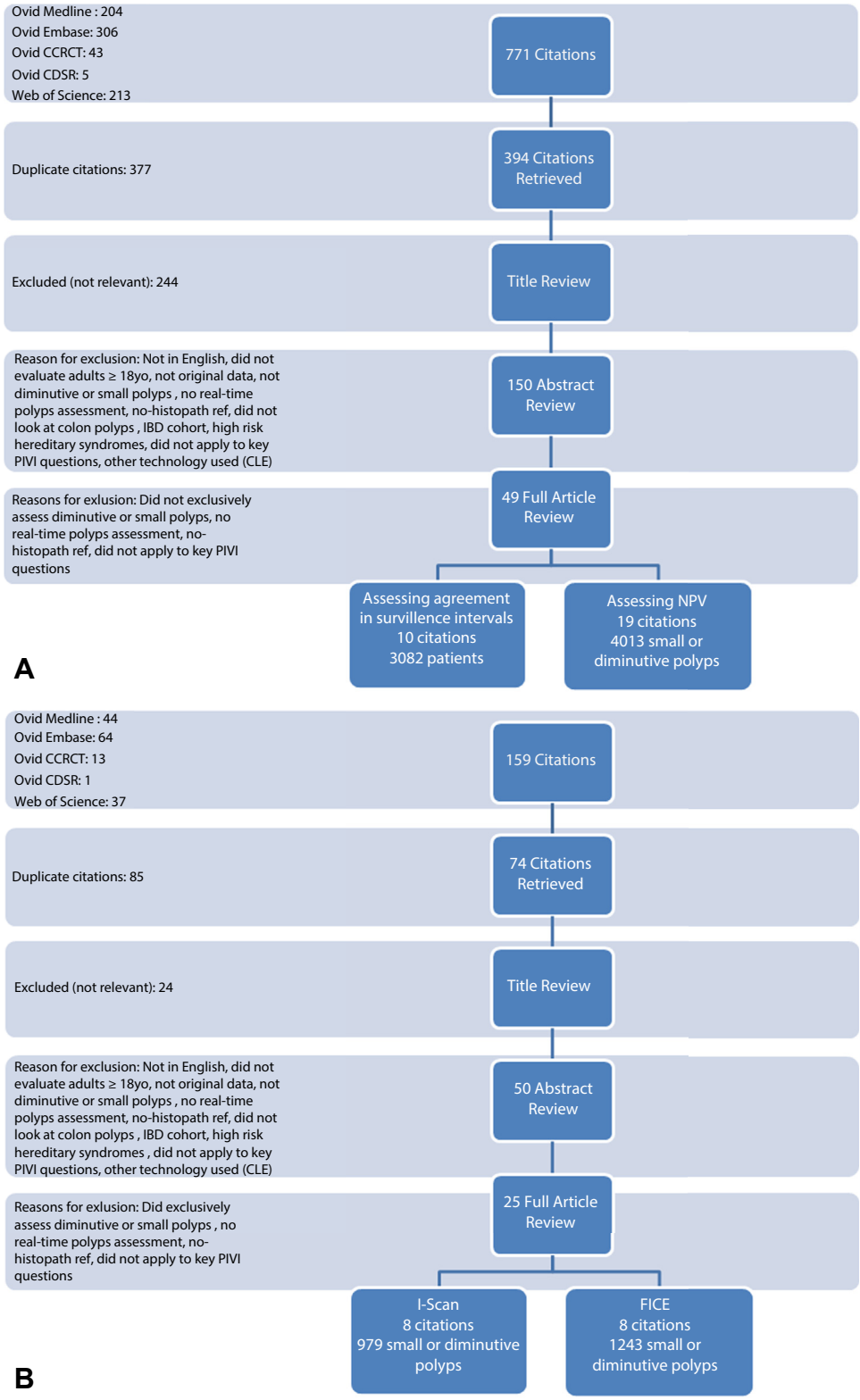

Figure 1. Flow diagram depicting included studies selected for NBI meta-analysis (**A**) and i-SCAN and FICE meta-analyses (**B**). *CLE*, confocal laser endoscopy; *FICE*, Fujinon Intelligent Color Enhancement; *IBD*, inflammatory bowel disease; *NPV*, negative predictive value; *PIVI*, Preservation and Incorporation of Valuable endoscopic Innovations.

of the studies conducted at academic medical centers. Twelve studies were performed by experts in optical NBI biopsy of colorectal polyps. Seventeen of the included studies used high-definition white-light endoscopy in addition to NBI. Eleven of the 20 included studies designating the confidence level of interpreting the optical biopsies (Table 1).

TABLE 1. Narrow-band imaging studies

Study (year), country	Setting (academic vs community)	Expertise in NBI	Training	Criteria for optical biopsy	High definition	Magnification	High confidence	NPV	Surveillance intervals
East et al (2008), UK	Academic	Yes	No	VPI	Yes	Yes	No	Yes	No
Rogart et al (2008), USA	Academic	No	Yes	Kudo/VPI	Yes	Yes	No	Yes	No
Ignjatovic et al (2009), UK	Academic	Mixed	Yes	VPI	Yes	No	Yes	Yes	Yes
Rex et al (2009), USA	Academic	Yes	Yes	Kudo/VPI	Yes	On demand	Yes	Yes	Yes
Sano et al (2009), Japan	Academic	Yes	No	Sano	No	Yes	No	Yes	No
Van Den Broek et al (2009), the Netherlands	Academic	No	No	Kudo/VPI	No	Yes	No	Yes	No
Henry et al (2010), USA	Academic	Yes	Yes	Sano/Emura	Yes	On demand	No	Yes	No
Lee et al (2011), South Korea	Academic	Yes	No	Pit vascular pattern	Yes	No	Yes	Yes	No
Gupta et al (2012), USA	Academic	Yes	No	Pit vascular pattern	Yes	No	No	Yes	Yes
Paggi et al (2012), Italy	Community	Yes	Yes	Pit vascular pattern	Yes	No	Yes	Yes	Yes
Hewett et al (*GIE*) (2012), USA	Academic	Yes	No	M-NICE	Yes	Yes	Yes	Yes	No
Hewett et al (*Gastroenterology*) (2012), USA	Academic	No	Yes	NICE	Yes	No	Yes	Yes	No
Shahid et al (2012), USA	Academic	Yes	No	Sano	Yes	No	No	Yes	No
Kuiper et al (2012), the Netherlands	Community	No	Yes	Kudo	Yes	No	Yes	Yes	Yes
Coe et al (2012), USA	Academic	No	Yes	Pit vascular pattern	Yes	No	No	No	Yes
Sakamoto et al (2012), Japan	Academic	No	Yes	Sano	No	Yes	No	Yes	No
Repici et al (2013), Italy and the Netherlands	Academic	Yes	Yes	M-NICE	Yes	Yes	Yes	Yes	Yes
Singh et al (2013), Australia and Japan	Academic	Yes	No	Sano	Yes	Yes/dual focus	Yes	Yes	Yes
Ladabaum et al (2013), USA	Community	No	Yes	NICE	Yes	No	Yes	Yes	Yes
Wallace et al (2014), USA	Academic	Yes	Yes	NICE	Yes	Yes	Yes	Yes	Yes
	Academic	Yes	Yes	NICE	Yes	Yes/dual focus	Yes	Yes	Yes

NBI, Narrow-band imaging; *NPV*, negative predictive value; *VPI*, vascular pattern intensity; *NICE*, Narrow Band Imaging International Colorectal Endoscopic Classification; *M-NICE*, Modified Narrow Band Imaging International Colorectal Endoscopic Classification.

Sixteen remaining citations were ultimately included in the i-SCAN and FICE meta-analyses, of which 8 evaluated i-SCAN and 8 evaluated FICE. The NPV of optical i-SCAN or FICE biopsy was evaluated in all studies; however, only 2 studies evaluated agreement in postpolypectomy surveillance intervals for FICE and 1 for i-SCAN. The 16 included studies were published between 2008 and 2014, with the majority (13/16) conducted at academic medical centers. Ten studies were performed by experts in optical biopsy of colorectal polyps. All included i-SCAN and FICE studies used high-definition white-light endoscopy in addition to the respective technology. Only 1 of the 16 included i-SCAN/FICE studies designated the confidence level of interpreting the optical biopsies (Table 2).

Meta-analysis of NBI studies evaluating NPV for adenomatous polyp histology

Nineteen studies reported or provided information enabling the calculation of the NPV of optical biopsy performed by using NBI for predicting adenomatous polyp histology of small and diminutive colorectal polyps.[7-25] These studies collectively evaluated 4013 in situ small or diminutive colorectal polyps in real-time by using NBI and compared it with criterion standard histopathology. The median prevalence of adenomas among these polyps was 48.5% (range 18%–88%). There was no evidence of publication bias based on a review of the funnel plot (Appendix 1, available online at www.giejournal.org). The pooled NPV by using the random effects model was 91%

TABLE 2. i-SCAN and FICE studies

Study (year), country	Setting (academic vs community)	Expertise in i-SCAN or FICE	Training	Criteria for optical biopsy	High definition	Magnification	High confidence	NPV	Surveillance intervals
				i-SCAN					
Lee et al (2011), Korea	Academic	Yes	No	Kudo/VPI	Yes	No	Yes	Yes	No
Hoffman et al 2 (2010), Germany	Academic	Yes	No	Kudo/VPI	Yes	No	No	Yes	No
Hoffman et al 1 (2010), Germany	Academic	Yes	No	Kudo	Yes	No	No	Yes	No
Chan et al (2012), USA	Academic	No	Yes	Kudo	Yes	No	No	Yes	No
Hong 2 et al (2012) South Korea	Academic	No	No	Kudo/VPI	Yes	No	No	Yes	No
Hong 1 et al (2012), South Korea	Academic	No	No	Kudo/VPI	Yes	No	No	Yes	No
Pigo et al (2013), Italy	Community	Yes	No	NICE	Yes	No	No	Yes	No
Schachschal et al (2014), Germany	Mixed	No	Yes	Kudo	Yes	No	No	Yes	Yes
				FICE					
Pohl et al (2008), Germany	Community	No	Yes	Kudo/VPI	Yes	No	No	Yes	No
Togashi et al (2009), Japan	Academic	No	Yes	Vascular pattern	Yes	No	No	Yes	No
Buchner et al (2010), USA	Academic	Yes	Yes	Kudo/VPI	Yes	No	No	Yes	No
Dos Santo et al (2010), Brazil	Academic	Yes	No	Vascular pattern	Yes	Yes	No	Yes	No
Kim et al (2011) South Korea	Academic	Yes	Yes	Kudo/VPI	Yes	Yes	No	Yes	No
Longcroft et al (2011), England	Academic	Yes	No	Vascular pattern	Yes	No	No	Yes	Yes
Dos Santo et al (2012), Brazil	Academic	Yes	No	Vascular pattern	Yes	Yes	No	Yes	No
Longcroft et al (2012), England	Academic	Yes	No	Vascular pattern	Yes	Yes	No	Yes	Yes

FICE, Fujinon Intelligent Color Enhancement; *NPV*, negative predictive value; *VPI*, vascular pattern intensity.

(95% CI, 88–94) (Fig. 2). This finding was associated with high degree of heterogeneity (I^2 = 89%). Therefore, we performed multiple subgroup analyses to account for some of the factors contributing to this high degree of heterogeneity.

1. *Effect of practice setting*: No significant difference was noted in the pooled NPV of studies conducted at academic medical centers (91.8%; 95% CI, 89-94) compared with community practices (88.3%, 95% CI, 82-94) (Fig. 3).
2. *Effect of operator experience*: A subgroup analysis based on experience in interpreting real-time optical biopsies of colorectal polyps indicated that only experts met the PIVI threshold of a 90% or higher NPV with a pooled NPV for experts of 93% (95% CI, 91-96). This finding was associated with a lesser degree of heterogeneity (I^2 = 78%) (Fig. 4). The NPV for novice operators was 87% (95% CI, 83-91).
3. *Effect of confidence level*: The pooled NPV was higher (93%; 95% CI, 90-96) when the optical biopsy assessment was made with high confidence compared with when no information on the confidence level was provided (88%; 95% CI, 84-92) (Fig. 5).
4. *Effect of combined operator experience and confidence level*: Novice operators approached the PIVI NPV threshold when their optical biopsies were performed with high confidence (90%; 95% CI, 86-94). Experienced operators exceeded PIVI thresholds when reporting assessments with high confidence (95%; 95% CI, 92-98).

Meta-analysis of the degree of agreement in assignment of postpolypectomy surveillance intervals based on NBI optical biopsy versus those based on histopathology

Ten studies including 3082 patients reported on the degree of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time NBI optical biopsy of colorectal polyps

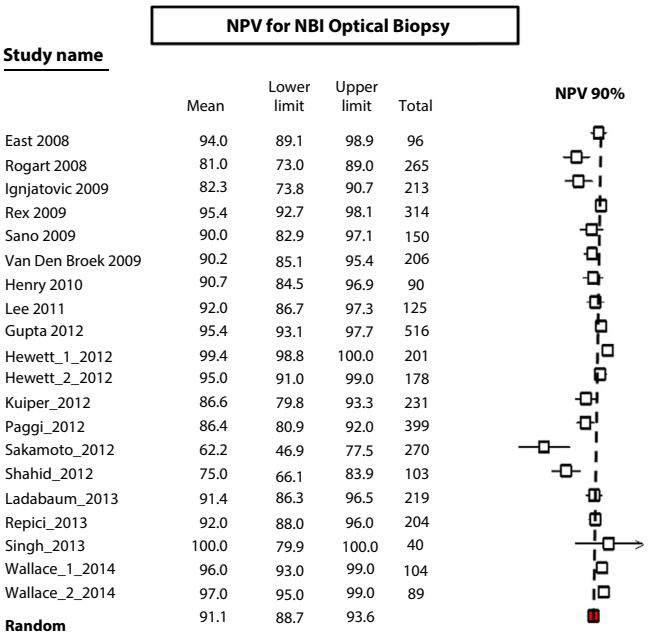

Figure 2. Forest plot of studies evaluating the negative predictive value (NPV) for narrow-band imaging (NBI)–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps.

5 mm or smaller with histopathologic assessment of polyps larger than 5 mm using the U.S. Multi-Society Task Force (MSTF) postpolypectomy surveillance intervals.[7-12,15,18,20,26] The pooled percentage of agreement using the random-effects model was 89% (95% CI, 85-93) (Fig. 6). This finding was associated with a significant degree of heterogeneity (I^2 = 93%). Therefore, we performed multiple subgroup analyses to account for some of the factors contributing to this high degree of heterogeneity.

1. *Effect of practice setting*: The pooled percentage of agreement was higher for studies conducted in academic medical centers (91% [95% CI, 86-95]) compared with community practices (82% [95% CI, 74-90]) (Fig. 7).
2. *Effect of operator experience*: A subgroup analysis based on endoscopist experience in interpreting real-time optical biopsies of colorectal polyps indicated that experts reached the PIVI threshold of 90% or higher agreement (92%; 95% CI, 88-96). This finding was associated with lesser degree of heterogeneity (I^2 = 72%) (Fig. 8). Experts outperformed novice endoscopists, who had a lower pooled percentage of agreement (82%; 95% CI, 75-88).
3. *Effect of confidence level*: The pooled percentage of agreement was higher when the optical biopsy was made with high confidence (91%; 95% CI, 88-95) compared with when no information on the confidence level was provided (79%; 95% CI, 71-86) (Fig. 9).
4. *Effect of combined operator experience and confidence level*: Novice operators improved their agreement with postpolypectomy surveillance intervals when their optical biopsies were performed with high confidence (87%; 95% CI, 82-93). Experienced operators when reporting with high confidence exceeded PIVI thresholds (93%; 95% CI, 90-96).

Meta-analyses of i-SCAN and FICE studies in meeting PIVI thresholds

i-SCAN. Eight studies reported or provided information enabling the calculation of the NPV of optical biopsies performed by using i-SCAN for predicting adenomatous polyp histology of small and diminutive colorectal polyps.[14,27-32] These studies collectively evaluated 979 small or diminutive colorectal polyps in real-time using i-SCAN and compared their evaluation with the criterion standard histopathology. There was no evidence of publication bias based on review of the funnel plot (Appendix 2). The pooled NPV by using the random-effects model was 84% (95% CI, 76–91). This finding was associated with a significant degree of heterogeneity (I^2 = 95). Therefore, we performed a subgroup analyses based on endoscopist experience in performing and interpreting optical biopsies of colorectal polyps. Experienced endoscopists meet the PIVI NPV threshold for adenomatous histology of small and diminutive colorectal polyps with a NPV of 96% (95% CI, 94-98) compared with a NPV of 72% (95% CI, 69-76) for novice endoscopists (Fig. 10). Only 1 i-SCAN study[27] evaluated the degree of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time i-SCAN optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm in size using the MSTF postpolypectomy surveillance intervals. The reported degree of agreement of i-SCAN optical biopsy with histopathology in the assignment of postpolypectomy surveillance intervals based on this study was 69.5% (95% CI, 63-75), which did not meet the PIVI threshold.

Fujinon Intelligent Color Enhancement. Eight studies reported or provided information enabling the calculation of the NPV of optical biopsy performed by FICE for adenomatous polyp histology of small and diminutive colorectal polyps.[33-40] These studies collectively evaluated 1243 small or diminutive colorectal polyps in real-time by using FICE and compared the evaluation with the criterion standard histopathology. There was no evidence of publication bias based on a review of the funnel plot (Appendix 3). The pooled NPV by using the random-effects model was 80% (95% CI, 76–85). This finding was associated with a significant degree of heterogeneity (I^2 = 70). Subgroup analyses based on operator experience and use of magnification with the FICE optical biopsy indicated that operator experience did not improve the NPV of FICE for predicting adenomatous polyp histology; however, the use of magnification did improve FICE performance with a NPV of 85% (95% CI, 79–91) (Fig. 11). Only 2 FICE studies[33,35] evaluated the degree

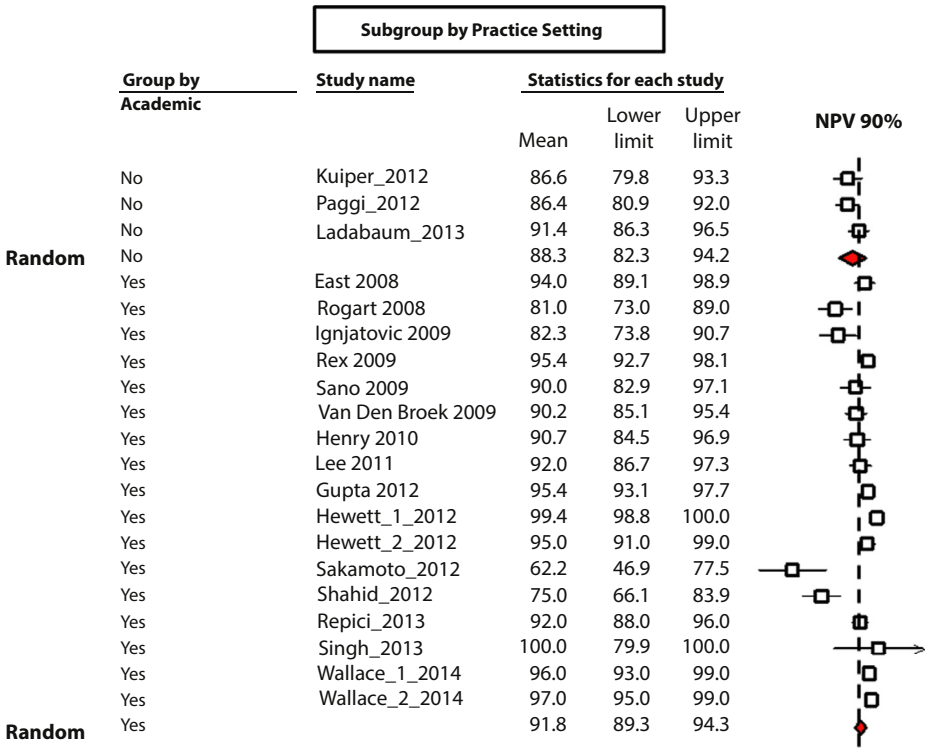

Figure 3. Forest plot of studies evaluating the negative predictive value (NPV) for narrow-band imaging–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps stratified by practice setting (academic vs community).

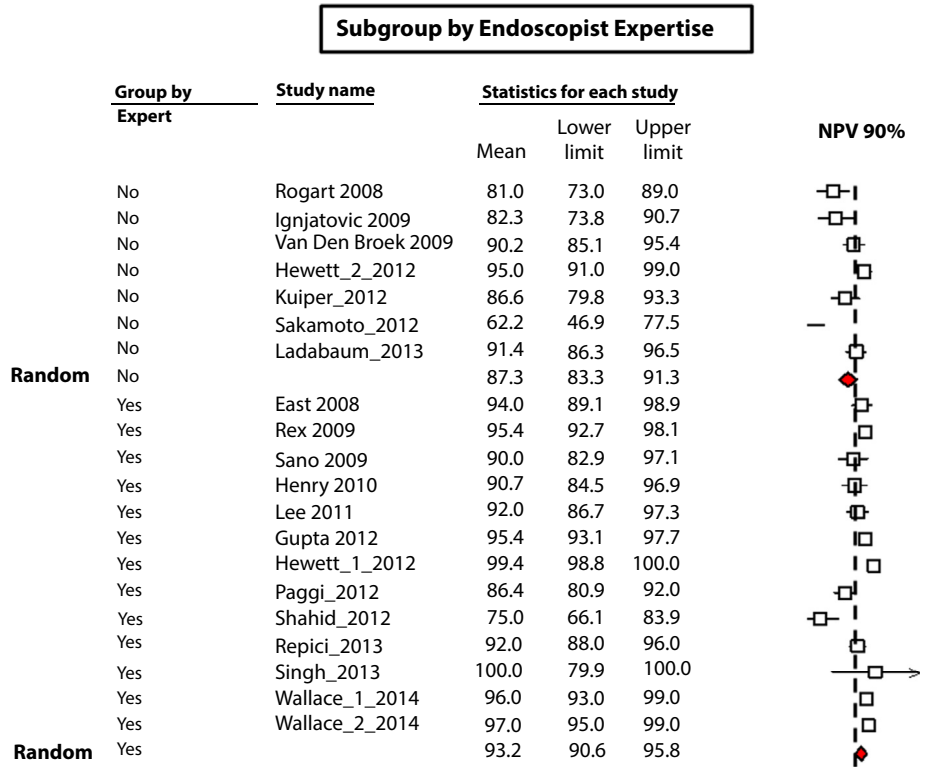

Figure 4. Forest plot of studies evaluating the negative predictive value (NPV) for narrow-band imaging–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps stratified by endoscopist expertise (expert vs novice).

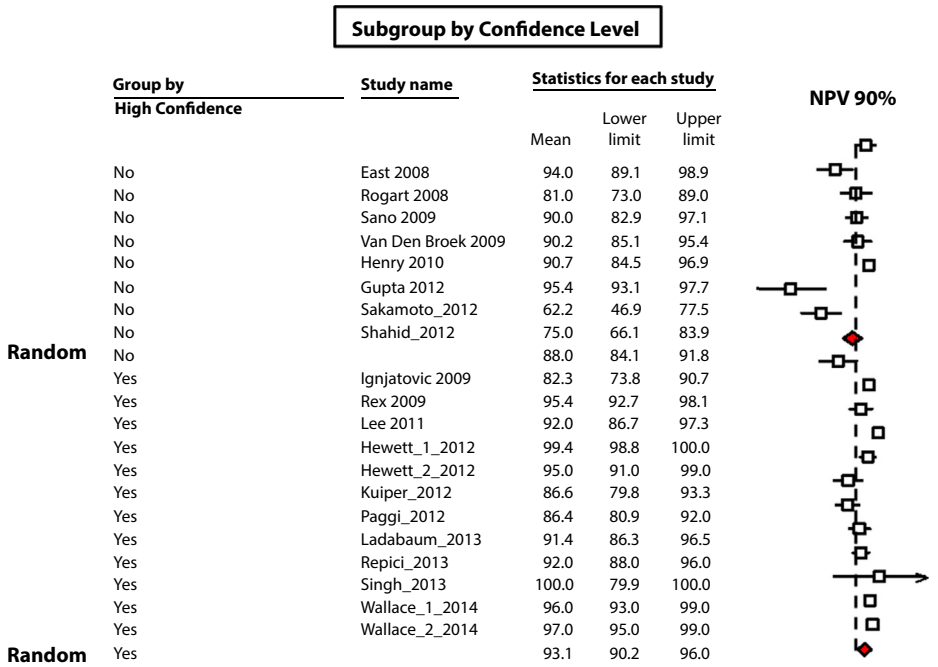

Figure 5. Forest plot of studies evaluating the negative predictive value (NPV) for narrow-band imaging (NBI)–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps, stratified by high confidence interpretation of the optical biopsy.

of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time FICE optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm by using the MSTF postpolypectomy surveillance intervals. The reported degree of agreement of FICE optical biopsy with histopathology in assigning postpolypectomy surveillance intervals based on these 2 studies was 100% (95% CI, 91-100) and 97% (95% CI, 89 -100).

Confocal laser endomicroscopy

Relatively few CLE studies have assessed this technology in achieving PIVI thresholds. Several studies were performed by using postprocedure "offline" evaluation of CLE images,[19,38,41-44] and these were excluded from this meta-analysis, which is limited to real-time studies evaluating polyps in situ. Six studies, which included 5 published studies[45-49] and 1 abstract,[50] reported real-time classification of CLE images in situ. Two of these studies compared offline image assessment with real-time diagnosis.[47,49] Half of the studies used endoscopy-based CLE,[45,46,48] and half used probe-based CLE.[47,49,50] Two studies included chromoendoscopy as a means to target areas for inspection with CLE.[45,48] One study[45] reported the correlation of CLE with all histology including both polypoid lesions and random sites assessed every 10 cm throughout the colon, whereas other studies specifically targeted polypoid lesions encountered during standard colonoscopy to assess the correlation of CLE with histology.[46,47,49,50] This difference in the denominator where 1 study includes endoscopically apparent normal areas can

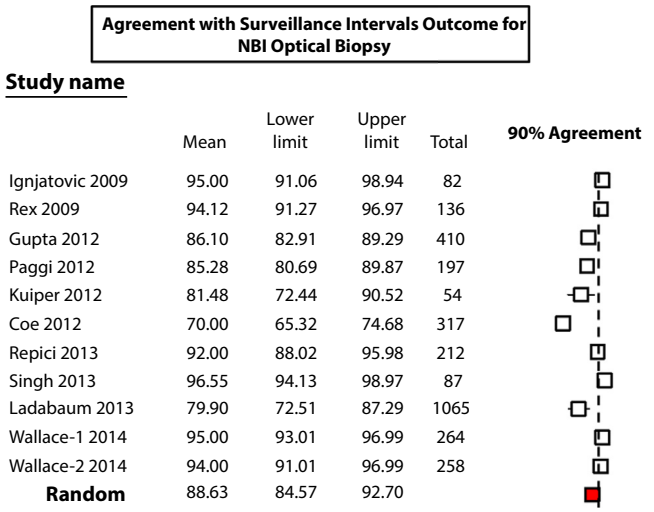

Figure 6. Forest plot of narrow-band imaging (NBI) studies depicting the pooled percentage of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time optical biopsy of colorectal polyps 5 mm or smaller, with histopathologic assessment of polyps larger than 5 mm.

greatly affect the performance of the diagnostic parameters, including NPV. Although most studies used fluorescein sodium as the primary fluorophore, 2 studies also used acriflavin, a contrast agent that also stains the nucleus.[45,48] One study compared the images of fluorescein sodium versus acriflavin.[45] The other study[48] used acriflavin for nuclear staining, in conjunction with fluorescein sodium; this study attempted to classify the difference between low-grade and high-grade dysplasia in suspect

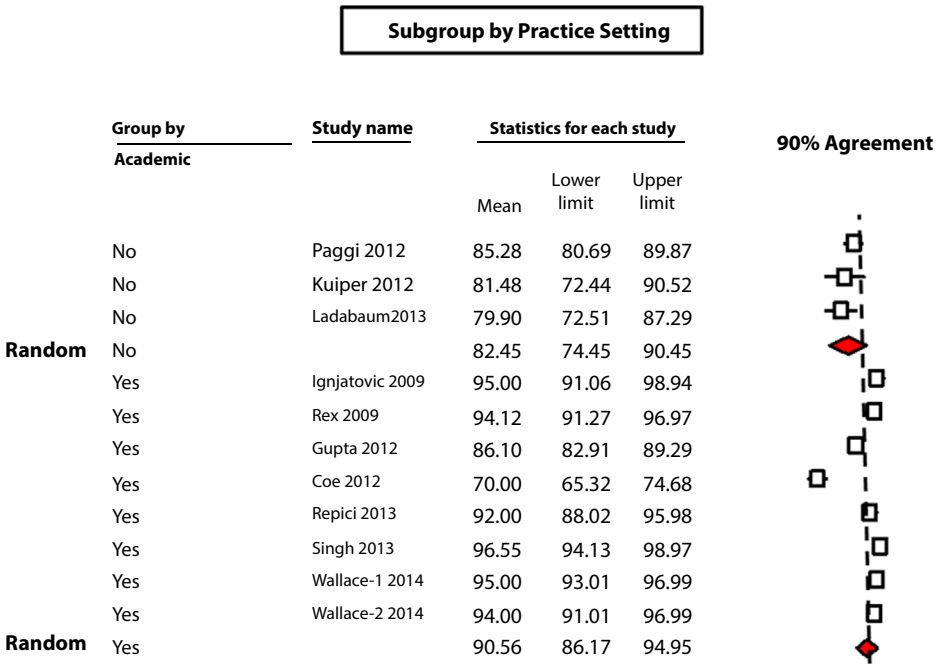

Figure 7. Forest plot of narrow-band imaging studies depicting the pooled percentage of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm stratified by practice setting (academic vs community).

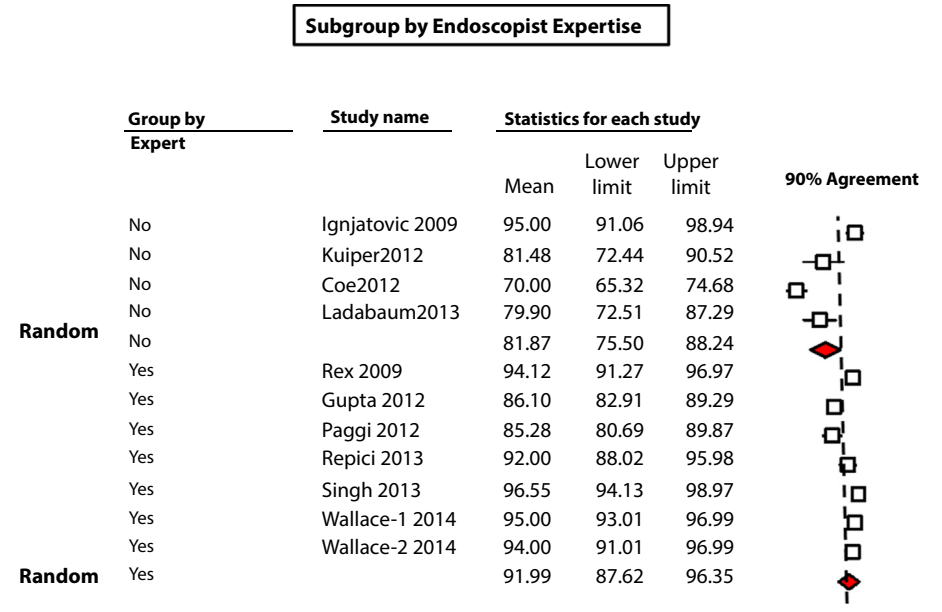

Figure 8. Forest plot of narrow-band imaging studies depicting the pooled percentage of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm stratified by operator expertise (expert vs novice).

lesions compared with histopathology. Among the CLE studies that classified polyps as adenomatous polyps in real time, the NPVs for determining adenomatous histology were 79% (154 polyps),[49] 88% (107 polyps),[50] 92% (115 polyps),[46] and 100% (32 polyps).[47] Notably, the smallest study yielded the highest NPV, whereas the larger studies had more modest NPV values. Given the variability present among these few studies with real-time polyp characterization with CLE, a meta-analysis was not performed.

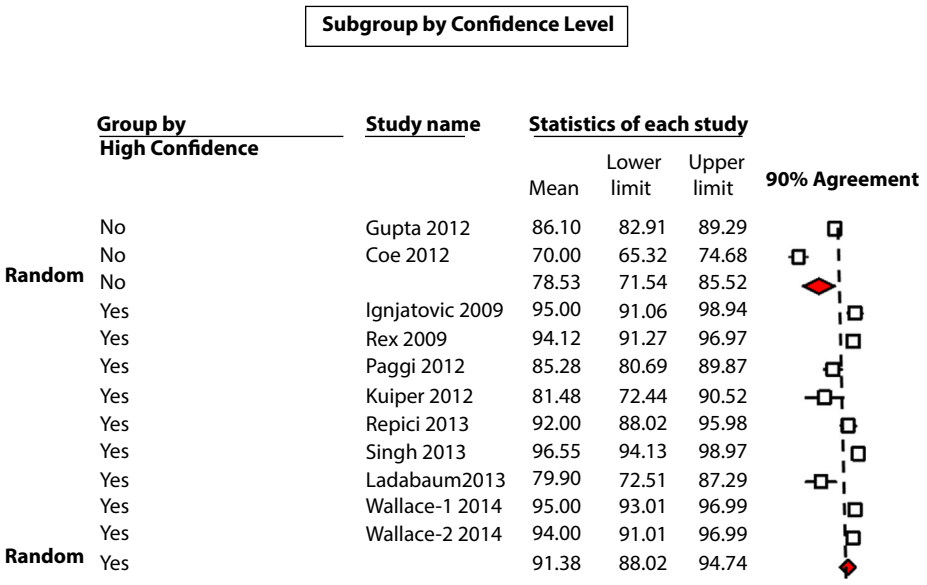

Figure 9. Forest plot of narrow-band imaging studies depicting the pooled percentage of agreement with histopathology when assigning postpolypectomy surveillance intervals based on combining real-time optical biopsy of colorectal polyps 5 mm or smaller with histopathologic assessment of polyps larger than 5 mm stratified by high confidence interpretation of the optical biopsy.

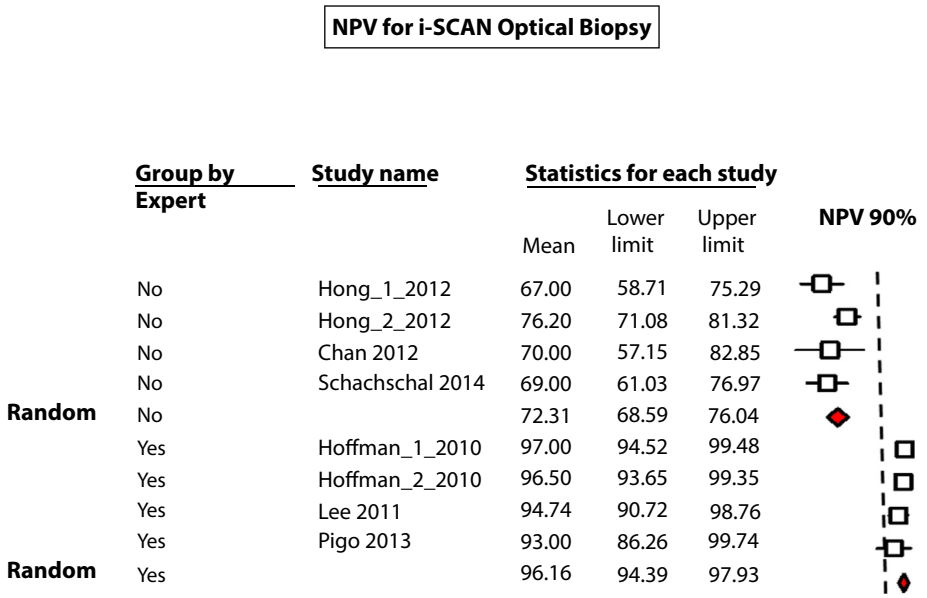

Figure 10. Forest plot of studies evaluating the narrow-band imaging (NBI) for i-SCAN–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps stratified by operator expertise (expert vs novice).

DISCUSSION

The PIVI document on real-time endoscopic assessment of the histology of diminutive colorectal polyps[5] was created by the ASGE to promote and facilitate a potential paradigm shift in the management of diminutive colorectal polyps by using optical biopsy with endoscopic technologies rather than histopathology for polyp characterization and for decision making regarding polyp management as well as assigning surveillance intervals. The PIVI document established performance thresholds that needed to be met before widespread adoption of such technologies to minimize the risks of misclassification of polyps. If and when feasible, based on evolving endoscopic technology and increasing endoscopist experience with these technologies, such an approach would be more cost-effective because of the cost savings associated with avoiding resection of diminutive rectosigmoid hyperplastic polyps and pathology evaluation of resected diminutive adenomatous polyps.

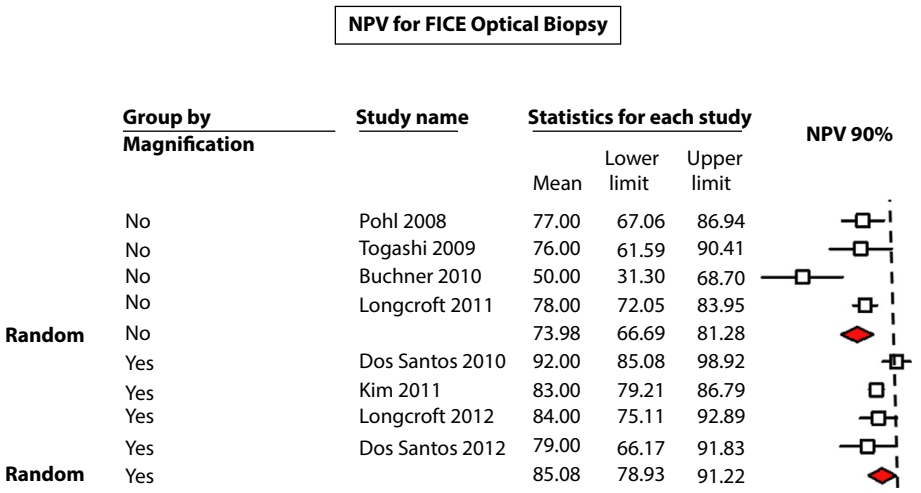

Figure 11. Forest plot of studies evaluating the negative predictive value (NPV) for Fujinon Intelligent Color Enhancement (FICE)–assisted optical biopsy for predicting adenomatous polyp histology of small/diminutive colorectal polyps stratified by concurrent use of magnification.

Simulation Markov modeling has shown that a "resect-and-discard" strategy for diminutive polyps detected by screening colonoscopy resulted in a substantial economic benefit with a cost savings of $25 per person screened, which, projected to the U.S. population, would result in undiscounted annual savings of $33 million.[51] Adding the cost savings from a "diagnose-and-leave" strategy, in which the cost of an endoscopic polypectomy is approximately $179 per person, would translate to a huge cost savings to the U.S. health care system, estimated at more than $1 billion per year, without much impact on colonoscopy efficacy. In addition to the cost savings, such an approach would avoid potential adverse events associated with unnecessary polypectomy of diminutive hyperplastic rectosigmoid polyps and would also be more efficient because in many cases it would allow for immediate postprocedure assignment and communication of colonoscopy surveillance intervals to patients and referring physicians.

For a "diagnose-and-leave" strategy for diminutive rectosigmoid polyps predicted to be nonneoplastic based on optical biopsy, the PIVI recommends that endoscopic diagnosis should provide a 90% or higher NPV for adenomatous histology when used with high confidence. For NBI, our meta-analysis indicated a pooled NPV of 91% using the random-effects model. Subgroup analyses indicated that NPVs were marginally higher in academic settings compared with community settings, although this was not statistically significant. In addition, assessments made by endoscopists experienced in optical biopsy polyp characterization, as well as optical biopsy assessments made with high confidence, were associated with higher NPVs (93%). Our meta-analysis therefore indicates that optical biopsy technology by using NBI can meet this PIVI threshold and supports a "diagnose-and-leave" strategy for diminutive predicted nonneoplastic polyps in the rectosigmoid colon.

For a "resect-and-discard" (without pathology assessment) strategy for adenomas 5 mm or smaller, the PIVI recommends that endoscopic characterization of polyp histology by optical biopsy (when used with high confidence), when combined with the histopathologic assessment of polyps larger than 5 mm, should provide a 90% or higher agreement in assignment of postpolypectomy surveillance intervals compared with decisions based on pathology assessment of all identified polyps. Subgroup analyses of NBI studies indicated that the agreement in assignment of postpolypectomy surveillance intervals exceeded 90% or higher in academic settings (90%), with experienced endoscopists (92%) and when optical biopsy assessments were made with high confidence (91%). The highest agreement in assignment of postpolypectomy surveillance intervals was achieved with experienced endoscopists making optical biopsy assessments with high confidence (93%). Our meta-analysis therefore indicates that optical biopsy technology by using NBI can meet this PIVI threshold and supports a "resect-and-discard" strategy for colorectal adenomas 5 mm or smaller.

In addition to NBI, our study included meta-analyses of additional advanced imaging technologies including i-SCAN and FICE. Although our analyses indicate that, as with NBI, the PIVI thresholds can potentially be met by these technologies, in particular with expert operators, these technologies have not been as frequently studied as NBI, and further studies need to be performed evaluating their use in characterizing diminutive colorectal polyps. Studies using CLE demonstrate potential in the characterization of polyps. However, the majority of these studies were performed with postprocedure offline assessments. Additional CLE studies with real-time use of this technology will be beneficial in evaluating the ability of this technology to meet thresholds set by the PIVI document.

This meta-analysis was conducted only of studies with real-time endoscopic assessment of polyps. Previous meta-analyses, such as the study by Wanders et al,[52] included real-time as well as postprocedure offline analyses to provide an overview of the potential of advanced imaging technology. However, because we were evaluating a paradigm that supports real-time decision making, we limited our analysis to studies performing real-time in situ evaluation.

The PIVI document also specifies that assessments of polyp histology using endoscopic technology be made with high confidence. Not all studies have reported high confidence assessments, but in subgroup analyses of those that did, we were able to demonstrate improved prediction of histology and reinforce the specification detailed in the PIVI that actionable assessments should be made with high confidence. Our findings are also congruent with another recent meta-analysis which indicated that when endoscopic assessments of polyp histology are made with high confidence, the NPV for adenomatous histology and agreement with surveillance intervals based on histopathology alone exceed 90%.[53]

One limitation of our meta-analyses is the high degree of heterogeneity among included studies. We corrected for this by performing subgroup analyses to adjust for some of the confounders contributing to this heterogeneity. Another limitation is the lack of differentiation between small and diminutive polyps in some of the included studies. Finally, this meta-analysis was limited to real-time polyp assessments and therefore excluded studies with postprocedure analyses.

As confirmed by our meta-analyses, expertise in interpreting optical biopsies is a critical factor in optimizing their performance and meeting PIVI thresholds. This underscores the crucial need to train endoscopists in using advanced imaging technologies. Studies indicate that accurate interpretation of optical biopsies follows a learning curve, and this learning curve can be achieved rapidly in both academic and community practice settings.[54-59]

This ASGE Technology Committee systematic review and meta-analysis therefore confirms that the thresholds established by the ASGE PIVI for the real-time endoscopic assessment of the histology of diminutive polyps have been met, at least for NBI, with endoscopists who are experts in using these advanced imaging technologies and when assessments are made with high confidence. The ASGE Technology Committee therefore endorses the use of NBI for both the "diagnose-and-leave" strategy for diminutive rectosigmoid hyperplastic polyps and the "resect-and-discard" strategy for diminutive adenomatous polyps by endoscopists trained in using this technology for polyp characterization, making assessments with high confidence.

Our analyses indicate that the PIVI thresholds can potentially also be met by other advanced imaging technologies including i-SCAN, FICE, and CLE. However, given the limited data on the use of these technologies in the characterization of diminutive colorectal polyps, further studies need to be performed.

Both of the PIVI-defined strategies for endoscopic assessment of the histology of diminutive colorectal polyps perturb the status quo and are likely to cause some trepidation among stakeholders including patients, endoscopists, and pathologists. The "diagnose-and-leave" strategy can be expected to cause more concern than the "resect-and-discard" strategy for both endoscopists and patients. Patients may have concerns regarding the accuracy of polyp characterization, particularly if polyps have been left unresected. Some endoscopists may have concerns regarding the increased unreimbursed work and responsibility, together with litigation risks they may face while taking on a role traditionally performed by pathologists. Finally, some pathologists may be concerned regarding disruptive endoscopic imaging technologies that may affect the scope of their work.

Future challenges therefore remain before the widespread implementation of these strategies in clinical practice, including standardization of polyp classification systems based on advanced endoscopic imaging endoscopic technologies, establishing standards of practice for the use of these technologies in performing optical biopsy, developing training and credentialing programs, and establishing quality metrics to help develop quality assurance programs. 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 and implementation of these PIVI strategies.

DISCLOSURES

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; CLE, confocal laser endoscopy; FICE, Fujinon Intelligent Color Enhancement; MSTF, Multi-Society Task Force; NBI, narrow-band imaging; NPV, negative predictive value; PIVI, Preservation and Incorporation of Valuable endoscopic Innovations.

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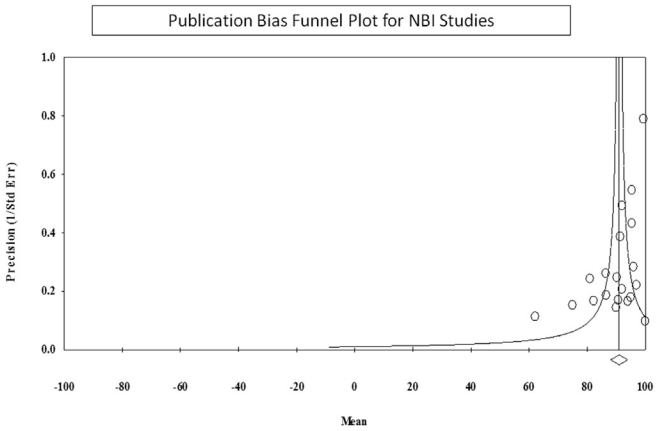
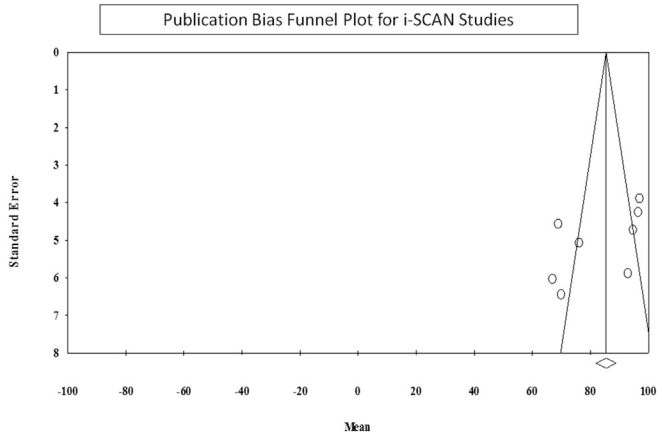
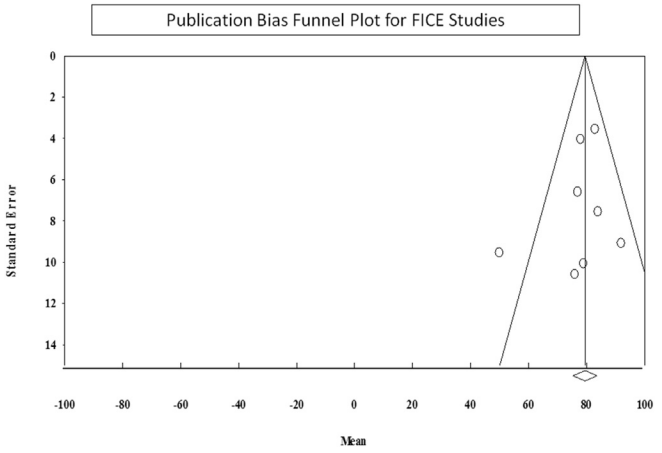


Appendix 1. Publication bias funnel plot for narrow-band imaging studies



Appendix 2. Publication bias funnel plot for i-SCAN studies



Appendix 3. Publication bias funnel plot for FICE studies