

Development of Advanced Imaging Criteria for the Endoscopic Identification of Inflammatory Polyps

Daniel A. Sussman, MD, MSPH^{1,5}, Jodie A. Barkin, MD^{1,5}, Aileen M. Martin¹, Tanya Varma, MD², Jennifer Clarke, PhD³, Maria A. Quintero, MD¹, Heather B. Barkin, MD⁴, Amar R. Deshpande, MD¹, Jamie S. Barkin, MD¹ and Maria T. Abreu, MD¹

OBJECTIVES: Inflammatory polyps (IPs) are frequently encountered at colonoscopy in inflammatory bowel disease (IBD) patients and are associated with an increased risk of colon cancer. The aim of this prospective endoscopic image review and analysis was to describe endoscopic features of IPs in IBD patients at surveillance colonoscopy and determine the ability to endoscopically discern IPs from other colon polyps using high-definition white light (WL), narrow band imaging with magnification (NBI), and chromoendoscopy (CE).

METHODS: Digital images of IPs using WL, NBI, and CE were reviewed by four attending gastroenterologists using a two-round modified Delphi method. The ability to endoscopically discern IPs from other colon polyps was determined among groups of gastroenterology fellows and attendings. IPs were classified by gross appearance, contour, surface pattern, pit pattern, and appearance of surrounding mucosa in IPs, as well as accuracy of diagnosis.

RESULTS: Features characteristic of IPs included a fibrinous cap, surface friability and ulceration, an appendage-like appearance, the halo sign with CE, and a clustering of a multiplicity of IPs. The overall diagnostic accuracy for IP identification was 63% for WL, 42% for NBI, and 64% for CE. High degrees of histologic inflammation significantly improved the accuracy of diagnosis of IP with WL and CE, whereas the use of NBI significantly impaired IP accuracy.

CONCLUSIONS: The overall diagnostic accuracy when applying these criteria to clinical images was modest, with incremental benefit with addition of CE to WL. CE showed promise predicting IP histology in actively inflamed tissue. Institutional Review Board approval was obtained. ClinicalTrials.gov Identifier: NCT01557387.

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INTRODUCTION

Colorectal cancer is one of the most sinister consequences of chronic inflammation in inflammatory bowel disease (IBD). Surveillance colonoscopies in IBD patients aim to detect dysplastic changes at early stages.^{1,2} Narrow band imaging (NBI) and chromoendoscopy (CE) have demonstrated benefit in improving dysplasia detection during IBD surveillance colonoscopy,^{3,4} and have been useful in distinguishing polyp histology in non-IBD patients.^{5–9} These technologies have not been evaluated in their ability to distinguish inflammatory polyps (IPs), also known as “pseudopolyps,” from other polyps. IPs occur in up to 17% of IBD surveillance colonoscopies, and many are large in size.¹⁰ The histologic sampling or removal of polypoid lesions in IBD patients has been recommended only for “suspicious” lesions whose histology cannot be determined endoscopically.^{2,11} However, the twofold increased risk for colorectal cancer in UC patients with multiple IPs suggests the difficulty for endoscopists to appropriately identify these lesions.^{12–14}

This increased risk for colorectal cancer in patients with IPs, and the impractical task of sampling all IPs with associated

cost, heighten the importance of endoscopically differentiating IPs from other polyps. Endoscopic features of IP using white light (WL) were proposed by Rubin *et al.* in 1999,¹⁵ but these descriptors have not been subsequently assessed. There are no data regarding the ability of endoscopists to accurately predict IP histology, nor comprehensive endoscopic criteria to identify IPs using high-definition WL, NBI, and CE. The aim of this study was to define endoscopic features of IPs and determine the ability to endoscopically identify IPs from other colon polyps using WL, NBI, and CE.

METHODS

Study design. This prospective, observational study evaluated different endoscopic methods to identify IPs. Patients with IBD consented to the Institutional Review Board-approved protocol. Inclusion criterion was all patients with IBD undergoing colonoscopy for dysplasia surveillance at the University of Miami (Miami, FL) between September 2011 and September 2012.^{12,16,17} Using the endoscopic images and histologic review of the polyps, we created and validated

¹Department of Medicine, Division of Gastroenterology, University of Miami, Leonard M. Miller School of Medicine, Miami, Florida, USA; ²Department of Pathology, University of Miami, Leonard M. Miller School of Medicine, Miami, Florida, USA; ³Department of Food Science and Technology, Department of Statistics, University of Nebraska-Lincoln, Lincoln, Nebraska, USA and ⁴University of Miami, Leonard M. Miller School of Medicine, Miami, Florida, USA

Correspondence: Jodie A. Barkin, MD, Department of Medicine, Division of Gastroenterology, University of Miami, Leonard M. Miller School of Medicine, 1120 NW 14th Street, Clinical Research Building, Room 1116 (D-49), Miami, Florida 33136, USA. E-mail: jabarkin@med.miami.edu

⁵Co-first authors.

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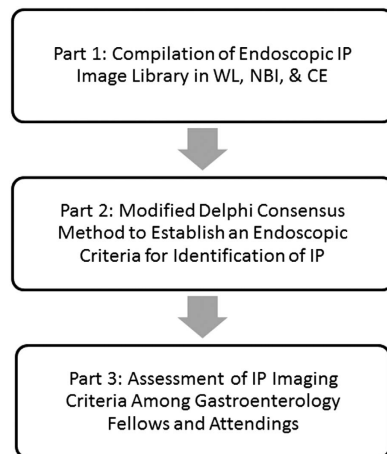


Figure 1 Study design. CE, chromoendoscopy; IP, inflammatory polyp; NBI, narrow band imaging; WL, white light.

a classification scheme for IPs in three phases, adapted from a previously used study design using NBI to predict colon polyp histology⁵ (**Figure 1**).

IP image library. Part 1 accumulated an endoscopic image library of IPs derived from study colonoscopies on 154 IBD patients. Twenty-nine of 154 (18.8%) patients had one or more polyps. Olympus adult CF-180 and pediatric PCF-180 colonoscopes (Olympus Corporation, Shinjuku, Japan) were used. High resolution static images were stored for all polypoid colonic lesions (ProVation MD 2012, Minneapolis, MN). Images were sequentially captured for each polyp using WL, NBI, and CE. CE was performed following SURFACE guidelines.¹⁸ Indigo carmine dye 0.2% was applied using an endoscopic flushing pump (Olympus AFU-100, Olympus Corporation). All polyps that were included in the image library were biopsied and confirmed to be IP by histology. Histologic reading and the degree of inflammation was determined by gastrointestinal pathologists masked to the endoscopic findings.

Delphi consensus of IP characteristics. Investigators reviewed all images in the image library ($n=29$ patients). The highest quality images were determined by complete visualization with best clarity, excellent bowel preparation, polypoid lesion unobscured, and with sharp borders (DAS, JAB). The 25 best IP images were then selected from the image library to generate a list of common endoscopic features using WL, NBI, and CE. Four attending gastroenterologists, with specialty training in IBD and who use NBI and CE in their clinical practices, participated (MTA, JSB, ARD, and DAS), using a PowerPoint slideshow format and a monitor with resolution >720 pixels. These physicians received a teaching session of popular validated classification systems for adenomas (AD) and hyperplastic polyps (HP) using NBI and/or CE, in order to establish a framework of categories to examine in order to determine histology, presented by JAB.^{5,6,8,9} Reviewers were asked to identify endoscopic features suggestive of IP histology using a

two-round modified Delphi method to build a consensus prediction system for IPs. This method compiles the anonymous input of experts, who receive cumulative feedback with group responses. This process is repeated to reduce the range of responses and devise a consensus.^{19,20} In our two-round modified Delphi method, after the initial teaching session, observation on common features of IPs was sought during an individual one-on-one image review by author JAB with each of the four reviewers. Following this, responses were summarized by JAB and presented to the group as feedback in order to move toward a consensus criteria. Subsequently, a second round of individualized image review was performed and responses recorded by JAB. The responses were again summarized, and common features were presented and refined resulting in the comprehensive consensus criteria for identification of IP. Only images of histologically confirmed IPs were included for review in the modified Delphi method. Characteristics of IPs in each image were systematically classified by imaging modality, according to five categories, adapted from one prior study of IP and four prior studies of AD and HP including gross appearance, contour, surface pattern, pit pattern, and appearance of surrounding mucosa.^{5,6,8,9,15}

Assessment of IP features among gastroenterologists.

The findings characteristic of IPs with WL, NBI, and CE were incorporated into a teaching session with previously validated classification systems for AD and HP using NBI and CE to present classification systems for all three polyp types (AD, HP, and IP) to respondents.^{5,6,8,9} Author JAB presented these findings to two groups with endoscopic experience; 12 gastroenterology fellows and 12 gastroenterology attendings (mean 18.4 years of clinical experience). An approximately 1-hour-long verbal education session with accompanying slideshow of 50 slides was presented on a large-screen, high-definition monitor, followed by an opportunity for questions, and then subsequently followed by an image quiz consisting of 25 polyps of AD, HP, and IP histologies, with images presented sequentially in WL, then NBI, and then CE. Respondents identified polyp histology (AD, HP, or IP) on the basis of static endoscopic images with corresponding level of confidence (low, medium, or high), and made an assessment of mucosal inflammation (none, mild, moderate, severe). Gastroenterology attendings were also asked whether they would have biopsied the polyps if encountered at endoscopy. Accuracy was determined using the number of correct responses for the identification of polyp histology on the image quiz for each polyp subtype (AD, HP, or IP), using histology as the gold standard. Given the sequential nature of the image presentation, when comparing accuracy between imaging modalities, WL was truly compared with WL with the addition of NBI and with WL with the addition of CE.

Statistical analyses. Comparisons between imaging modalities were made using McNemar's Chi-squared test for dependent variables. The non-parametric Wilcoxon rank-sum test was performed for non-normal distributions to determine differences in the level of confidence with responses. Analysis of variance (ANOVA) testing was performed and logistic regression models were constructed from

Table 1 Characteristic endoscopic findings of inflammatory polyps classified by imaging modality

	Inflammatory polyps			Surrounding mucosa
	White light	NBI (×1.5 magnification)	Chromoendoscopy	White light
Gross appearance	Mucosal appendage		Pooling of dye in stalk	Clustering or “family” of polyps
Polyp contour	Irregular, elongated contour			
Surface pattern and pit pattern	Hyperemia and surface ulceration Engorged surface	Mild surface heterogeneity Absent vascular or pit pattern	Smooth polyp tip Lack of pit pattern in tip	Inflamed or ulcerated Absent vascular or pit pattern
Polyp tip	White fibrinous cap		“Halo” or “Target” sign Pooling of dye at tip Lack of dye uptake surrounding tip	

NBI, narrow band imaging.

accuracy tables to compare results by group. Spearman correlation was used to determine the accuracy of inflammation scores. Significance was defined as a P -value < 0.05 .

Institutional Review Board approval was obtained on 19 September 2011. ClinicalTrials.gov Identifier:NCT01557387.

RESULTS

The 25 best IP images from the library were reviewed using the modified Delphi method. Nine of these images (36%) were collected from patients without endoscopic evidence of active inflammation, 6 (24%) had mildly active endoscopic inflammation, and 10 (40%) had severe endoscopic inflammation (on a scale of none, mild, moderate, and severe as determined by an attending gastroenterologist during the procedure).

Endoscopic criteria for IP from modified delphi method.

We first sought to establish the endoscopic imaging criteria to define the entity of IPs. Endoscopic findings of IPs were classified by imaging modality (Table 1). Using WL, hyperemia with friability and ulceration of the mucosal surface were frequently described (Figure 2a, b and d). An irregular and elongated contour and engorged surface were noted (Figure 2a). The “stuck-on” appearance of an IP as a mucosal appendage was described (Figure 2a, c and d). A white cap was often present at the luminal tip of the polyp (Figure 2a, b and d).

When NBI was added, mild surface heterogeneity was described, without any clear pattern of vascular markings or pit patterns (Figure 2e and f). Lastly, using CE, heterogeneous pooling of dye was noted in the polyp stalks (Figure 2g and h). A smooth appearance and absence of dye pattern in the polyp tip was common, preventing the description of pit architecture in this region (Figure 2g and h). In many IPs, pooling of dye at the tip with surrounding lack of uptake (pink appearance of mucosa) created a “halo” sign resembling a target (Figure 2g and h). Next, the surrounding mucosa was examined. With WL and CE, the surface of the neighboring mucosa was often inflamed or ulcerated (Figure 2i). Clustering of grossly similar polyps in a “family” was visualized (Figure 2c, j and k). A lack of discernable vascular and pit patterns was also noted in the mucosa surrounding IPs (Figure 2i).

Validation of IP criteria in gastroenterologists

Accuracy of polyp diagnosis. When combining all respondents, the overall accuracy for IP identification was 63% for WL, 42% for NBI, and 64% for CE. Gastroenterology fellows’ accuracy was 63% for WL, 44% for NBI, and 64% for CE, with similar accuracy for gastroenterology attendings (63% for WL, 39% for NBI, and 62% for CE) (Figure 3). The most common error encountered in all groups and all imaging modalities was misclassification of IPs as AD.

Adding CE to WL showed no significant improvement in the accuracy of classification of IP (McNemar’s Chi-squared = 0; $df = 1$; $P = 1$). When NBI was added to WL for IP diagnosis, accuracy was significantly decreased (McNemar’s Chi-squared = 83.10; $df = 1$; $P < 2.2e-16$). Accuracy was also significantly decreased when the addition of NBI to WL was compared with the addition of CE to WL for IP diagnosis (McNemar’s Chi-squared = 64.14; $df = 1$; $P = 1.156e-15$). Accurate prediction of AD was comparable among all three modalities (WL vs. NBI McNemar’s Chi-squared = 0.8; $df = 1$; $P = 0.37$; WL vs. CE McNemar’s Chi-squared = 0; $df = 1$; $P = 1$; NBI vs. CE McNemar’s Chi-squared = 0.8; $df = 1$; $P = 0.37$). For classification of HP, the addition of NBI had slightly increased accuracy compared with both WL and CE, while WL and CE were comparable (NBI vs. WL McNemar’s Chi-squared = 2.4; $df = 1$; $P = 0.12$; NBI vs. CE McNemar’s Chi-squared = 2.77; $df = 1$; $P = 0.096$; WL vs. CE McNemar’s Chi-squared = 0; $df = 1$; $P = 1$).

A high degree of confidence among respondents correlated strongly with an accurate diagnosis (Wilcoxon rank-sum: WL $W = 31738$; $P = 1.9e-06$; 95% confidence interval $-3.48821e-05$ to $-5.34610e-05$; estimate of difference in location $-1.469821e-05$. NBI $W = 33076$; $P = 0.08$; 95% confidence interval $-1.442223e-05$ to $5.925471e-05$; estimate of difference in location $-7.337373e-06$. CE $W = 29505$; $P = 4.93e-09$; 95% confidence interval $-2.507477e-05$ to $-5.993037e-05$; estimate of difference in location $-1.239826e-05$). This was true in both groups of gastroenterologists.

Relationship between years of practice and ability to identify IPs. Increased years of practice in the attending group had no significant impact on accuracy for WL (ANOVA: $F = 1.033$;

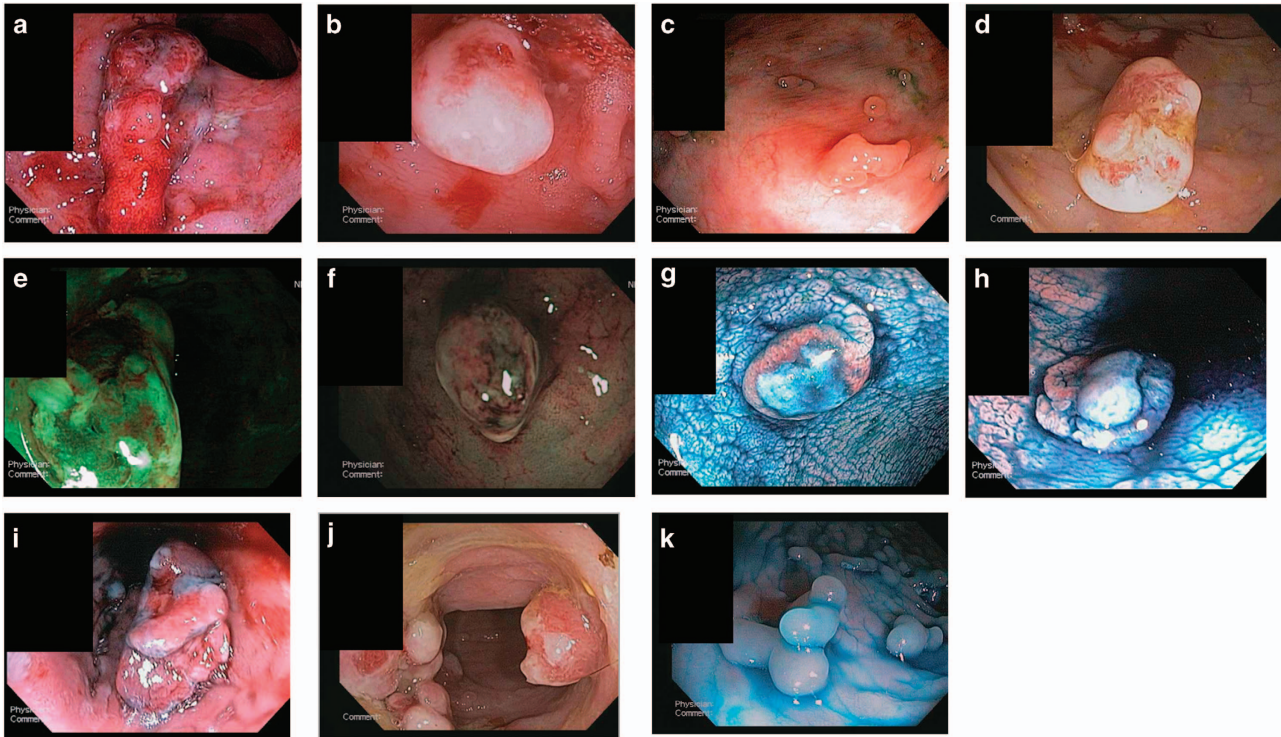


Figure 2 Characteristic endoscopic findings for inflammatory polyps (IPs). (a) IP in WL with hyperemia and surface ulceration, irregular and elongated contour with engorged surface, appearance of a mucosal appendage, and white cap at the polyp tip. (b) IP in WL with a hyperemic and friable surface with a white cap. (c) IPs in WL with appearance of a mucosal appendage, and a clustering of polyps. (d) IP in WL with a hyperemic and friable surface, appearance of a mucosal appendage, and a white cap. (e) IP in NBI with mild surface heterogeneity and lack of pit pattern. (f) IP in NBI with mild surface heterogeneity and lack of pit pattern. (g) IP in CE with pooling of dye around the base of the polyp, smooth polyp tip, and "halo" sign. (h) IP in CE with pooling of dye around the base of the polyp, smooth polyp tip, and "halo" sign. (i) IP in WL with inflamed and ulcerated surrounding mucosa, and lack of surrounding pit pattern. (j) IPs in WL with a clustering of polyps. (k) IPs in CE with a clustering of polyps. CE, chromoendoscopy; NBI, narrow band imaging; WL, white light.

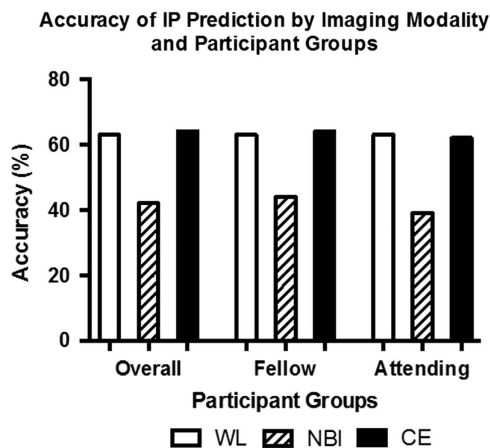


Figure 3 Accuracy of IP prediction by imaging modality and participant groups. CE, chromoendoscopy; IP, inflammatory polyp; NBI, narrow band imaging; WL, white light.

df = 7; $P = 0.41$), NBI (ANOVA: $F = 0.291$; df = 7; $P = 0.96$), or CE (ANOVA: $F = 1.26$; df = 7; $P = 0.27$). Next, we evaluated the relationship between years of GI fellowship training and accuracy for the fellow group. Increased years of training

significantly improved the accurate prediction in all modalities (WL ANOVA: $F = 2.243$; df = 3; $P = 0.083$; NBI ANOVA: $F = 2.114$; df = 3; $P = 0.098$; CE ANOVA: $F = 2.633$; df = 3; $P = 0.05$).

Degree of inflammation and accuracy of IP diagnosis by endoscopy. High degrees of histologic inflammation significantly improved the accuracy of diagnosis of IP with WL (estimate = 0.16; standard error = 0.059; $z = 2.76$; $P = 0.0057$) and CE (estimate = 0.17; standard error = 0.059; $z = 2.89$; $P = 0.0038$). However, high degrees of histologic inflammation had no significant impact on the accuracy of diagnosis of IP for NBI (estimate = 0.01; standard error = 0.056; $z = 0.18$; $P = 0.86$). The endoscopic level of inflammation of IPs assessed by reviewers correlated well with the true histologic inflammation as determined by the pathologist for WL and CE, but not for NBI (**Figure 4**).

Endoscopic appearance of polyps and the decision to biopsy. Addition of imaging modalities was evaluated to determine influence on the choice to biopsy a polyp. Fewer respondents would have biopsied when viewing with NBI after WL (McNemar's Chi-squared = 7.56; df = 1; $P = 0.06$), whereas CE had no impact.

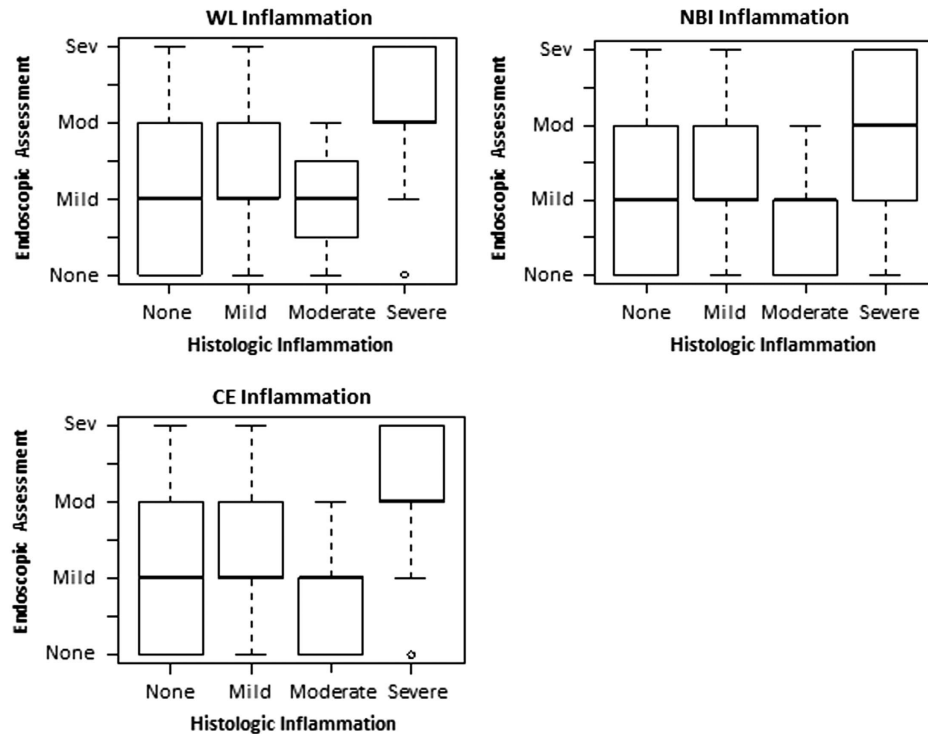


Figure 4 Histologic scoring of inflammation vs. the endoscopic predicted level of inflammation. CE, chromoendoscopy; NBI, narrow band imaging; WL, white light.

DISCUSSION

This study is the first to propose comprehensive criteria for the endoscopic diagnosis of IPs using CE and NBI in addition to WL. Several features were characteristic of IPs including a fibrinous cap, surface friability and ulceration, an appendage-like appearance, the halo sign with CE, and a clustering of a multiplicity of IPs. Our criteria using the Delphi method was similar to an initial IP criteria using WL, which proposed that IPs have a white exudate on a smooth surface with sharp borders, and are encountered in groups.¹⁵ The overall diagnostic accuracy when applying these criteria to clinical images was modest, with minimal incremental benefit with the addition of CE to WL. When respondents were confident they had identified these characteristic features, their diagnostic accuracy was tremendously improved.

IPs occur in a colon with features associated with risk for dysplasia, including severe, extensive disease, and longer duration of inflammation.^{21,22} Although IPs are a common colonoscopic finding, their presence is important given a twofold increased risk for colorectal cancer.¹² It is unclear why colon cancer appears more frequently in colons with IPs. This may be because of the limited efficacy of surveillance in the setting of multiple polypoid lesions.¹² In addition, IPs may be causally associated with a dysplastic environment and a sign of a more severe inflammatory insult. IPs, especially large ones, may harbor dysplastic changes.²³ Furthermore, abnormal cells in the colonic stroma of IPs that mimic pre-malignant changes have been observed.²⁴ These possibilities underlie the importance of correctly identifying IPs during colonoscopy.

Endoscopic classification systems for the determination of dysplastic polyps with NBI and CE have largely focused on mucosal pit patterns and differential uptake of contrast. In Kudo's classification, smaller papillary pits were indicative of HP, with the loss of traditional pit architecture seen in AD and carcinomas.⁹ East *et al.*⁷ proposed that an increased vascular pattern intensity using NBI was more associated with AD than HP. Rastogi *et al.*⁶ described a similar system using NBI in which a fine capillary network was indicative of HP. Most recently, the NBI International Colorectal Endoscopic (NICE) Classification differentiated AD and HP on the basis of color, vascular pattern, and surface features.⁵

Pit patterns are useful for the identification of sporadic HP and AD; however, they were noticeably absent or unhelpful among our collection of IPs. Murata *et al.*²⁵ utilized magnified WL to differentiate IPs from AD and carcinomas in IBD patients on the basis of a differential appearance of the foveolar pit patterns. Our study did not use magnification for WL images, which may have impaired the visualization of pits, but our team observed a smooth appearance of the mucosal surface with all imaging techniques, implying that adequate polyp visualization was achieved and lack of traditional pit appearance was most likely due to truly distorted or edematous surface architecture. Other investigators have described a "neoplastic appearance" to IPs on the basis of distortion of the crypt openings with NBI, but this does not aid with distinguishing IPs from AD, which was the focus of the diagnostic accuracy portion of our study.²⁶ The classic pit-marked tissue cap of AD and HP was not seen in

our IPs, and was instead often replaced with an edematous, white muco-fibrinous cap, visible with WL, and enhanced by CE. This confirms the findings of Rubin *et al.* and East *et al.*^{15,26}

NBI was unhelpful in the identification of IPs. NBI has been shown to be useful in examining the vascular patterns of AD and HP; however, its dysplasia detection is markedly decreased when there is mucosal inflammation as seen in patients with chronic colitis, especially with IPs.⁴ Given this known decrease in dysplasia detection by NBI, perhaps the presence of inflammation impairs visualization if traditional NBI light processing darkens images when there is blood or significant inflammation thereby obscuring subtleties of IP diagnosis. This impaired diagnostic ability of NBI in our study may explain why less respondents chose to biopsy under NBI if they had misclassified an IP as AD or HP. CE was increasingly beneficial especially with higher degrees of histologic inflammation, giving CE a distinct advantage over NBI in imaging IBD patients. Further, CE increases dysplasia detection in IBD patients.^{27–30}

Ultimately, the value of improved endoscopic visualization techniques lies in more efficient biopsying; i.e., providing benefit to the patient by removing dysplastic polyps while giving the endoscopist the confidence to leave other benign lesions *in situ*. In practical terms, it is generally not feasible to sample all of the IPs in a patient at risk for dysplasia. Therefore, it would be ideal to correctly identify IPs to enable focusing on raised lesions that are not IPs. Ignjatovic *et al.*³¹ postulated an approximately 77% savings in cost with the use of CE for optical diagnosis of small colorectal polyps in non-IBD patients compared with traditional biopsy with histopathologic evaluation. Any non-invasive endoscopic technique that decreases the quantity of biopsies in IBD patients and therefore decreases cost would be welcome as gastroenterologists prepare for the era of bundled payments for colonoscopy and pathology services.³²

Our study limitations are that the Delphi method limits findings to that of the selected reviewers. We attempted to minimize this influence by selecting experts in IBD and colonoscopic surveillance with NBI and CE. One author (DAS) was involved in both the selection of the highest quality images for review and then the review itself, which may introduce a degree of bias; however, initial image selection was only based on markers of endoscopic image quality (i.e., best clarity, excellent bowel preparation, and polypoid lesion unobscured and with sharp borders) and not based on features of the polyp itself. The Delphi method makes it challenging to objectively quantify inter-observer agreement, as traditional statistics for inter-observer agreement are unable to be performed. Some images were from the same patients, leading to non-independence, but image reviewers were masked as to this observation. A portion of the terms used to describe IP were subjective in nature, which may limit the repeated implementation of the diagnostic criteria. Final accuracy levels were suboptimal, suggesting that respondents may have needed more extensive training. Digital static endoscopic images were used. Finally, the size of the groups used to validate the proposed classification was relatively small, and minor differences between groups may have been

missed or obscured; however, this is to be expected in a pilot investigation.

In the future, larger studies should be undertaken to further assess the validity of the more salient portions of this classification system, and to potentially identify additional features of IPs using advanced imaging modalities to improve accuracy. The impact, feasibility, and utility of the criteria remain to be seen in the real-time, *in vivo*, endoscopic classification of IPs.

CONCLUSION

We identified many WL and CE features common to histologically confirmed IPs in IBD patients undergoing surveillance colonoscopy. CE added accuracy in the setting of inflammation. NBI was unhelpful in distinguishing features of IPs, potentially related to the presence of significant mucosal inflammation. The overall diagnostic accuracy when applying these criteria to clinical images was modest, suggesting that the identification of additional features to build on our findings is warranted, particularly given the risk for dysplasia among patients with IPs.

CONFLICT OF INTEREST

Guarantor of the article: Daniel A. Sussman, MD, MSPH.

Specific author contributions: Daniel A. Sussman participated in study design, image review and data analysis, manuscript preparation, editing, and review. Jodie A. Barkin participated in data collection, image review, teaching sessions, data analysis, and manuscript preparation. Aileen M. Martin participated in data collection and entry. Tanya Varma participated in data analysis via review of pathology slides to classify polyp histology. Jennifer Clarke participated in performing all statistical analyses. Maria A. Quintero participated in subject enrollment and data collection. Heather B. Barkin participated in data collection and entry. Amar R. Deshpande participated in image review, editing and review. Jamie S. Barkin participated in image review, manuscript preparation, editing, and review. Maria T. Abreu participated in study design, image review, manuscript preparation, editing, and review. All authors read and approved the final manuscript.

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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Inflammatory polyps (“pseudopolyps”) are common in inflammatory bowel disease.
- ✓ The presence of inflammatory polyps is associated with an increased risk of colorectal cancer.
- ✓ It is difficult to endoscopically discern inflammatory polyps from other polyp subtypes.

WHAT IS NEW HERE

- ✓ Multiple characteristic endoscopic features of inflammatory polyps were defined.
- ✓ The overall diagnostic accuracy of these criteria was modest.

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