Preface

This volume was about one year in the planning, and was inspired by the realization that capsule endoscopy and double-balloon endoscopy frequently reveal findings that nevertheless do not result in diagnosis. Another reason was our recognition of the difficulty in distinguishing findings of ulcerative colitis from those of Crohn's disease and other disorders in small intestinal endoscopy. Of course, we have seen numerous case presentations at academic conferences and have also read several books on small intestinal endoscopy. However, these frequently do nothing more than list a large number of disorders without providing a detailed analysis of findings. European and American reference works also seem to fail to address issues such as radiographic comparisons. When endoscopic findings were discussed at an international conference on double-balloon endoscopy held in Japan a few years ago, a leading Western researcher was unaware of such basic observations as the fact that ulcers of the small intestine present on the side of mesenteric attachment in Crohn's disease and on the opposite side in tuberculosis. Probably this lack of awareness was mainly because the researcher had never seen an accurate macroscopic depiction of a resected specimen. Although the United States and European nations are advanced in terms of capsule endoscopy, Americans and Europeans still face many problems in diagnostic imaging for this very reason. We therefore decided to put together a large number of carefully selected Japanese examples of small intestinal lesions, in an effort to compare and contrast small intestinal lesions that exhibit consistent findings and morphologies.

The basic premise of this book is differential diagnosis on the basis of endoscopic findings, and readers should start by taking a close look at the individual endoscopic findings illustrated on the left side of each full-page spread. We have then added an explanation of each finding on the right side, together with radiographic images and macroscopic depictions of resected specimens for comparison. This layout was designed with everyday clinical practice in mind, and we hope that readers will interpret the elements that compose each of these endoscopic findings with the aim of understanding the pathology and distinguishing features of each condition. Radiographic comparisons comprise another important element of the findings. There are limitations to endoscopic observations when it comes to long or large lesions of the small intestine, with its many curves. Therefore, we have also emphasized radiographic findings in this volume. In Japan, many institutions still practice double-contrast imaging, providing beautiful results, and we believe this point will resonate with many readers. Since a single disorder may exhibit great variety, this volume includes multiple depictions of the same disorders. We have also included lesions in both active and inactive phases. This is because both appearances are highly likely to be encountered simultaneously in actual clinical practice. Presenting a good overall balance of these cases would require a huge page area. We therefore decided to limit the number of findings depicted and to put together only carefully selected cases. In producing a work such as this, we thought it important to reflect the underlying concept in the title. After consulting among all the editors, we decided on *Endoscopy in the Diagnosis of Small Intestine Diseases*.

Because we wanted this book to be published before the Japan Digestive Disease Week (JDDW) held in Fukuoka in the fall of 2011, we had only about six months to spend on production. The editors were in communication with one another on a daily basis and brought in colleagues to share diagnostic knowledge. The cases presented in this volume were assembled jointly from three institutions: the Department of Gastroenterology at Kyushu University, the Department of Gastroenterology at Fukuoka University, and the Department of Gastroenterology at Fukuoka University Chikushi Hospital. A number of cases were requested from leading researchers at external institutions in the event that no suitable case was available from any of these three institutions. Within our group, we regularly hold joint seminars and undertake joint clinical trials. As we were already using the same methods for diagnosing small intestinal disease and applying radiographic procedures and treatment methods, we could assemble cases at the same pace. This meant that each institution ultimately held responsibility for a very similar number of cases.

As members of our group have some predecessors in common, we have a long history of joint research into disorders of the small intestine, such as Crohn's disease. We have also treated and accumulated a large number of cases. *Shōchō shikkan no rinshō* (Clinical Treatment of Small Intestinal Disease), edited by Tsuneyoshi Yao and Mitsuo Iida, was a major compilation of a large number of disorders published by Igaku Shoin in 2004. Since then, dramatic advances have been made in the field of small intestinal endoscopy. The simplicity of diagnostic operations has also meant that an increased number of images are now shared among multiple institutions. However, the inadequacy of a number of aspects has also become evident, including comparisons with radiography, pathological diagnosis, and handling of cases. We therefore regarded as a matter of great importance the publication of this volume focusing on accurate diagnosis and procedures for differentiating between conditions on the basis of endoscopic findings.

We are grateful for the assistance of Mr. Shingo Ano from the Medical Publications Department of Igaku Shoin in the production of this book. He established the original plan, provided swift editing, and overcame numerous problems in assembling the manuscript. We would also like to express our warm thanks to the pathologists who provide everyday diagnostic support for our clinical work. We are profoundly grateful to Dr. Akinori Iwashita (Department of Pathology, Fukuoka University Chikushi Hospital), Dr. Minako Hirahashi (Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University), Dr. Satoshi Nimura (Department of Pathology, Fukuoka University Faculty of Medicine), and Dr. Takashi Yao (Department of Human Pathology, Juntendo University School of Medicine; formerly of the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University), who not only were involved in diagnosing the cases presented in this volume, but also have been passionately dedicated to the macroscopic and histological diagnosis of small intestinal disease for many years. It is thanks to their efforts that we were able to compile this volume. If our purpose in proposing this book is widely understood and arouses interest in the interpretation of findings rather than being viewed solely as a collection of rare cases, we will have succeeded beyond our expectations.

Chikushino, Japan

Toshiyuki Matsui
On behalf of the editors

The purpose of this book is to improve diagnostic yields of capsule endoscopy and double-balloon endoscopy, because those procedures can depict nonspecific findings that may not lead to a proper diagnosis. Another reason for the publication was recognition of the difficulty in distinguishing enteroscopic findings of ulcerative colitis from those of Crohn's disease.

From a practical point of view, it is important to observe endoscopic pictures first, then to compare the images of other modalities, and finally to compare macroscopic pictures of resected specimens. For that reason, a large number of well-depicted examples of small intestinal lesions were assembled to clarify differences among small intestinal lesions that appear to exhibit similar findings and morphologies.

Comparisons with radiographic findings comprise another important element in diagnosis. There are limitations in endoscopic observations of gross lesions of the small intestine, with its many convolutions. In Japan, many institutions still practice double-contrast imaging, which provides beautiful results. Because a single disorder may exhibit variations, this volume includes multiple depictions of the same disorders. Also included are lesions in active and inactive phases, as both appearances are highly likely to be encountered simultaneously in clinical practice. The number of illustrated findings therefore has been limited to strictly selected cases.

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CONSENSUS STATEMENT

SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease

INTRODUCTION

Patients with ulcerative colitis or Crohn's colitis have an increased risk of colorectal cancer (CRC). Most cases are believed to arise from dysplasia, and surveillance colonoscopy therefore is recommended to detect dysplasia. Detection of dysplasia traditionally has relied on both examination of the mucosa with targeted biopsies of visible lesions and extensive random biopsies to identify invisible dysplasia. Current U.S. guidelines recommend obtaining at least 32 random biopsy specimens from all segments of the colon as the foundation of endoscopic surveillance.[1-4]

However, much of the evidence that provides a basis for these recommendations is from older literature, when most dysplasia was diagnosed on random biopsies of colon mucosa.[5] With the advent of video endoscopy and newer endoscopic technologies, investigators now report that most dysplasia discovered in patients with inflammatory bowel disease (IBD) is visible.[6,7] Such a paradigm shift may have important implications for the surveillance and management of dysplasia.

The evolving evidence regarding newer endoscopic methods to detect dysplasia has resulted in variation among guideline recommendations from organizations around the world.[1-4,8-10] We therefore sought to develop unifying consensus recommendations addressing 2 issues: (1) How should surveillance colonoscopy for detection of dysplasia be performed? (2) How should dysplasia identified at colonoscopy be managed?

DEVELOPMENT PROCESS

An international multidisciplinary group representing a wide spectrum of stakeholders and attitudes regarding IBD surveillance (Appendix 1, available online at www.giejournal.org) developed these recommendations following a process that adhered to suggested standards for guideline development from the Institute of Medicine and others and that incorporated the GRADE methodology.[11-14] Details regarding the development process are provided in Figure 1 and Appendix 2. A systematic review was performed for each focused clinical question. The search strategy is shown in Appendix 3, and the full synthesis of evidence reviewed by panelists is presented in Appendix 4. All appendices are available online at www.giejournal.org.

The strength of recommendation, provided for each recommendation, reflects the level of confidence that desirable effects of an intervention outweigh undesirable effects. Strong recommendations mean panelists are confident that the desirable effects outweigh the undesirable effects; therefore, most informed patients would choose the recommended management, and clinicians would provide the intervention to most patients. Conditional recommendations mean the desirable and undesirable effects of the intervention are closely balanced or appreciable uncertainty exists regarding the balance; therefore, informed patients' choices will vary according to their values and preferences, with many not wanting the intervention, and clinicians must ensure that patients' care is in keeping with their values and preferences.[13]

TERMINOLOGY

A subgroup of panelists developed a set of terms for colonoscopic findings in IBD surveillance to establish uniformity in communication. Descriptive phrases, modified from the Paris Classification,[15] were recommended for adoption (Table 1). Modifications included the addition of terms for ulceration and border of the lesion. It was agreed that the terms *dysplasia-associated lesion or mass (DALM), adenoma-like,* and *non-adenoma-like* should be abandoned. The term *endoscopically resectable* indicates that (1) distinct margins of the lesion could be identified, (2) the lesion appears to be completely removed on visual inspection after endoscopic resection, (3) histologic examination of the resected specimen is consistent with complete removal, and (4) biopsy specimens taken from mucosa immediately adjacent to the resection site are free of dysplasia on histologic examination.

CONSENSUS RECOMMENDATIONS AND SUMMARY OF SUPPORTING EVIDENCE

Detection of dysplasia on surveillance colonoscopy

The goal of this section is to define the optimal method(s) of detecting colon dysplasia in patients

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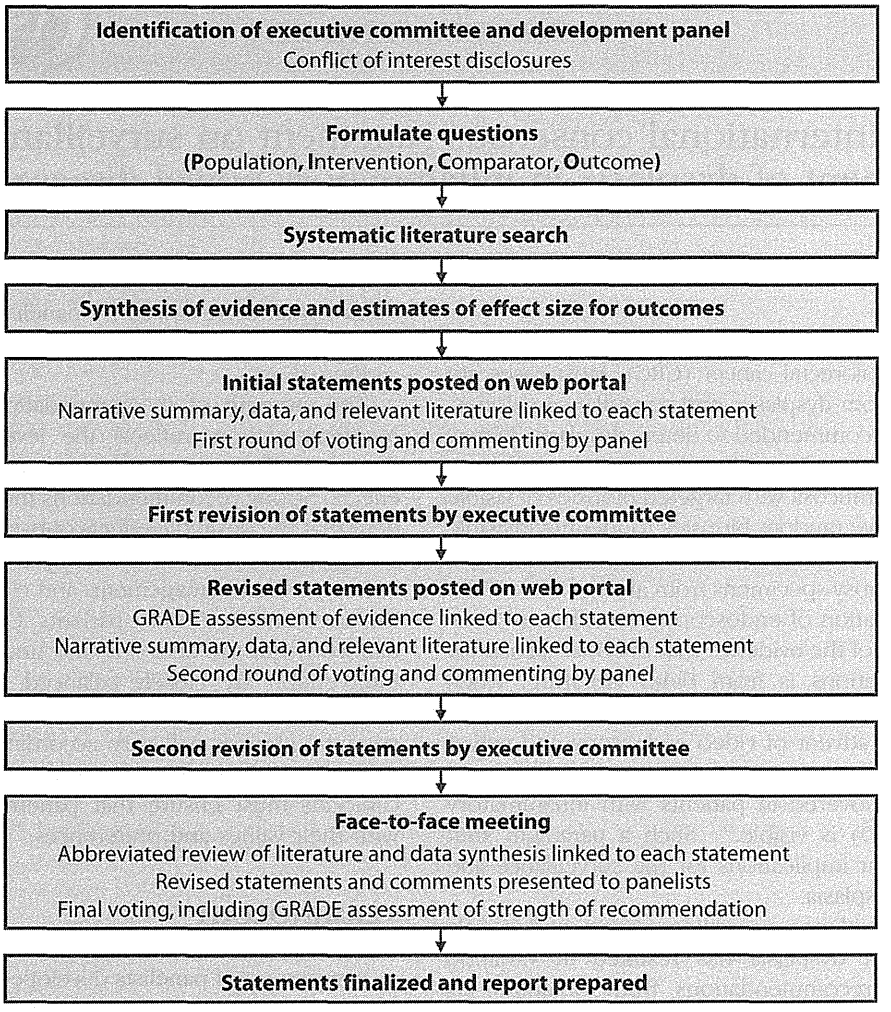

Figure 1. Development process.

with IBD. Detection of dysplasia, which is the immediate goal of surveillance colonoscopy, was chosen as the primary endpoint, with the understanding that detection of dysplasia is not clearly documented to improve clinical outcomes such as CRC incidence or mortality. Only histologic diagnoses of low-grade or high-grade dysplasia were considered; diagnoses of indefinite for dysplasia were excluded. Current guideline recommendations regarding the need for serial surveillance colonoscopy in patients with IBD were accepted, and other issues such as the appropriate surveillance interval or risk stratification[1-4,8-10] were not addressed.

Recommendations are listed in Table 2 and appear individually hereafter with the proportion of panelists in agreement, the strength of the recommendation, and the quality of evidence. A summary of the evidence and discussion regarding the recommendation follows each statement.

Statement 1: When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition.

(80% agreement; strong recommendation; low quality evidence)

Summary of evidence and discussion. High definition (1080 system) endoscopy provides image signal of higher pixel density than standard definition (480 system), with faster line scanning on high-definition monitors leading to sharper images with fewer artifacts.[16] A high definition system includes a high-definition endoscope processor, cabling, and monitor. A retrospective observational study found that dysplasia was discovered in approximately twice as many patients undergoing high-definition colonoscopy (n = 203) compared with a cohort undergoing standard-definition colonoscopy (n = 154): adjusted prevalence ratio = 2.2 (95% confidence interval [CI] 1.1-4.5).[17]

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TABLE 1. Terminology for reporting findings on colonoscopic surveillance of patients with inflammatory bowel disease (modified from Paris Classification[15])

Term	Definition
Visible dysplasia	Dysplasia identified on targeted biopsies from a lesion visualized at colonoscopy
Polypoid	Lesion protruding from the mucosa into the lumen ≥2.5 mm
Pedunculated	Lesion attached to the mucosa by a stalk
Sessile	Lesion not attached to the mucosa by a stalk: entire base is contiguous with the mucosa
Nonpolypoid	Lesion with little (<2.5 mm) or no protrusion above the mucosa
Superficial elevated	Lesion with protrusion but <2.5 mm above the lumen (less than the height of the closed cup of a biopsy forceps)
Flat	Lesion without protrusion above the mucosa
Depressed	Lesion with at least a portion depressed below the level of the mucosa
General descriptors	
Ulcerated	Ulceration (fibrinous-appearing base with depth) within the lesion
Border	
Distinct border	Lesion's border is discrete and can be distinguished from surrounding mucosa
Indistinct border	Lesion's border is not discrete and cannot be distinguished from surrounding mucosa
Invisible dysplasia	Dysplasia identified on random (non-targeted) biopsies of colon mucosa without a visible lesion

Given that most dysplastic lesions are visible,[6,7] the improved visualization and lack of negative effects with high-definition endoscopy justified a strong recommendation for its use. In addition, patients likely would strongly desire high-definition colonoscopy because of the belief that visualization and examination are improved. The cost of purchasing new high-definition endoscopic equipment is a consideration. However, high-definition colonoscopy already is widely used in endoscopic units.

Statement 2: When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy.

(85% agreement; strong recommendation; moderate-quality evidence)

Summary of evidence and discussion. Chromoendoscopy involves the application of dye to the colon mucosa, thereby providing contrast enhancement to improve visualization of epithelial surface detail. Methylene blue and indigo carmine, the agents most commonly used, are applied to the colon mucosa via a catheter or the colonoscope biopsy or water jet channel,[18] and accentuate the changes in epithelial surface topography.[19]

We identified 8 trials that used standard-definition colonoscopy and compared chromoendoscopy with white-light colonoscopy alone (Table 3).[20-27] The proportion of patients with dysplasia was 0% to 10% greater with chromoendoscopy in the individual studies, but the difference was not significant in any study. Meta-analysis revealed a significantly greater proportion of patients with dysplasia by using chromoendoscopy (relative risk [RR] = 1.8 [1.2-2.6] and absolute risk increase = 6% [3%-9%]). Meta-analysis of the 2 randomized, parallel-group trials also confirmed a significant increase with chromoendoscopy in the proportion of patients with dysplasia (RR = 2.3 [1.1-4.6], absolute increase = 8% [2%-15%]). The number of dysplastic lesions identified was greater with chromoendoscopy in all studies (Table 3), and in the 4 tandem studies in which all patients had both chromoendoscopy and white-light examination, the number of dysplastic areas discovered increased almost 2-fold (RR = 1.9, 1.4-2.7) with chromoendoscopy. Chromoendoscopy significantly increased the duration of colonoscopy by a mean of 11 minutes (range 9-12 minutes).

An economic analysis concluded that chromoendoscopy with targeted biopsies was less costly and more effective than white-light colonoscopy with random biopsies,[28] suggesting that chromoendoscopy should be used in place of white-light endoscopy when surveillance colonoscopy is performed. The cost-effectiveness of chromoendoscopy increased with increasing surveillance interval, suggesting that varying the surveillance interval based on the risk of CRC may be appropriate and could increase the cost effectiveness of surveillance colonoscopy. However, when surveillance is performed, even if performed less frequently than currently recommended in lower-risk patients, the best technique should be used.

Although chromoendoscopy increases the yield of dysplasia compared with standard-definition white-light colonoscopy, whether the additional lesions identified with chromoendoscopy are associated with the same increased risk for CRC as the visible and invisible dysplasia identified in older studies is not known. Data from the Surveillance, Epidemiology and End-Results Medicare-linked database of patients ≥67 years old revealed that interval cancers 6 to 36 months after colonoscopy occurred in a

TABLE 2. Summary of recommendations for surveillance and management of dysplasia in patients with inflammatory bowel disease

Detection of dysplasia on surveillance colonoscopy
1. When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition recommendation, low-quality evidence).
2. When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colo (*strong recommendation, moderate-quality evidence*).
3. When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy (cor recommendation, low-quality evidence).
4. When performing surveillance with standard-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colo (conditional recommendation, low-quality evidence).
5. When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colo (conditional recommendation, moderate-quality evidence).
6. When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in p chromoendoscopy (conditional recommendation, moderate-quality evidence).
Management of dysplasia discovered on surveillance colonoscopy
7. After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than co (strong recommendation, very low-quality evidence).
8. After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than co (conditional recommendation, very low-quality evidence).
9. For patients with endoscopically invisible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertis surveillance using chromoendoscopy with high-definition colonoscopy (conditional recommendation, very low-quality evidence).

much higher proportion of patients with IBD (15.1% with Crohn's disease and 15.8% with ulcerative colitis) than patients without IBD (5.8%),[29] suggesting that clinically relevant areas of neoplasia may be missed with current colonoscopic surveillance.

Potential barriers to use of chromoendoscopy also were considered. These include the additional preparation and time required for chromoendoscopy, need to train endoscopists in this technique, need to develop quality measures and assess performance after training, procedure-related costs, and barriers to reimbursement (eg, lack of procedure code for chromoendoscopy in the United States). These issues were discussed in detail by a subgroup of the panel, and their report will appear in a separate publication.

Statement 3: When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy.

(84% agreement; conditional recommendation; low-quality evidence)

Summary of evidence and discussion. A prospective, tandem study that used high-definition colonoscopy in 75 patients with IBD found that dysplasia was identified in significantly more patients undergoing chromoendoscopy than white-light colonoscopy alone: 16 (21%) versus 7 (9%); $P = .007$.[30] Ten dysplastic lesions were identified on the initial white-light examination, and an additional 12 were discovered on the subsequent chromoendoscopic examination. Despite the significant difference in favor of chromoendoscopy, the strength of this recommendation is conditional because of its reliance on only one relatively small observational study whose primary aim was to assess chromoendoscopy training and performance.

Statement 4: When performing surveillance with standard-definition colonoscopy, narrow-band imaging (NBI) is not suggested in place of white-light colonoscopy.

(84% agreement; conditional recommend low-quality evidence)

Summary of evidence and discussion. Cu available endoscope-based image-enhancement tec gies include NBI (Olympus, Tokyo, Japan), *i*-scan (F Tokyo, Japan), and Fuji Intelligent Chromo Endoscop jinon, Tokyo, Japan).[16] NBI, which uses filters to p narrow bands of blue and green light wavelength the only one of these technologies that has been s in IBD surveillance and thus the only one conside this recommendation.

A randomized, crossover study of 42 patients fou significant difference between NBI and standard-def white-light colonoscopy in the proportion of patient dysplasia (8 [19%] vs 7 [17%]).[31] Fewer total lesion found with NBI than with white-light colonoscopy 12 lesions).

Given the absence of any evidence of a benefi cannot be suggested in place of standard-def white-light colonoscopy alone. Furthermore, i absence of evidence for *i*-scan or Fuji Intelligent Cl Endoscopy, neither can be recommended for use i surveillance.

Statement 5: When performing surveillanc high-definition colonoscopy, narrow-band im is not suggested in place of white-light colono

(80% agreement; conditional recommend moderate-quality evidence)

Summary of evidence and discussion. Two s comparing NBI to high-definition white-light colon were identified—a randomized, parallel-group trial in 1 tients and a randomized, crossover trial in 48 patien

TABLE 3. Proportion of patients with dysplasia and number of visible dysplastic lesions identified in studies comparing chromoendoscopy versus white-light colonoscopy

Study	Study type	Patients with dysplasia/all patients		RR (95% CI)	Absolute risk increase (95% CI)	No. of visible dysplastic lesions	
		Chromoendoscopy	White-light			Chromoendoscopy	White-light
Kiesslich[20]	Randomized parallel-group	13/84	6/81	2.1 (0.8-5.2)	8% (-2% to 18%)	32	10
Kiesslich[21]	Randomized parallel-group	11/80	4/73	2.5 (0.8-7.5)	8% (-1% to 17%)	19	2
Marion[24]	Prospective tandem	22/102	12/102	1.8 (0.96-3.5)	10% (0% to 20%)	35	13
Rutter[23]	Prospective tandem	7/100	2/100	3.5 (0.8-16.4)	5% (-1% to 11%)	9	2
Matsumoto[25]	Prospective tandem	12/57	12/57	1.0 (0.5-2.0)	0% (-2% to 2%)	18	8
Hlvaty[26]	Prospective tandem and additional cohort	4/30	2/45	3.0 (0.6-15.4)	9% (-5% to 23%)	6	2
Gunther[27]	Retrospective two-group	2/50	0/50	5.0 (0.3-101.6)	4% (-3% to 11%)	2	0
Chiorean[22]	Prospective tandem	No per-patient data given (N = 63)				41	18
SCENIC meta-analysis				1.8 (1.2-2.6)	6% (3%-9%)		

RR, Relative risk; *CI,* confidence interval; *SCENIC,* Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations.

Neither study suggested a benefit for NBI, with the proportion of patients having dysplasia identified with NBI versus white-light colonoscopy of 5 of 56 (9%) versus 5 of 56 (9%) and 9 of 48 (19%) versus 13 of 48 (27%). In addition, NBI identified slightly fewer dysplastic lesions than white-light colonoscopy (5 vs 7 and 14 vs 16). Again, in the absence of any evidence of a benefit, NBI cannot be suggested in place of high-definition white-light colonoscopy alone.

Statement 6: When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy.

(90% agreement; conditional recommendation; moderate-quality evidence)

Summary of evidence and discussion. Four studies were identified comparing chromoendoscopy with NBI: two randomized, parallel-group trials; a randomized crossover trial; and a prospective, tandem study.[34-37] The proportion of patients with dysplasia was 0.1% to 22% greater with chromoendoscopy than with NBI in the individual studies, but none of the differences were significant. Meta-analysis also failed to show a significant difference: RR = 1.3 (0.8-2.1) and absolute risk difference = 6% (-1% to 14%). The mean withdrawal times were identical in one study,[36] whereas the mean procedure or withdrawal times in the other studies were 11 to 12 minutes longer with chromoendoscopy.

The results of the studies indicate that a meaningful benefit of NBI over chromoendoscopy is unlikely. Nonetheless, they do not document a benefit of chromoendoscopy over NBI.

Additional topics considered for detection of dysplasia

Random biopsies with high-definition white-light colonoscopy or chromoendoscopy. Given that high-definition white-light colonoscopy and chromoendoscopy were considered superior to standard-definition white-light colonoscopy, the panelists considered the question of whether random biopsies should be performed when endoscopists use high-definition white-light colonoscopy or chromoendoscopy. Table 4 shows the yield of targeted and random biopsies for dysplasia from pooled analyses; the evidence was graded as low quality.

Among patients with dysplasia undergoing high-definition white-light colonoscopy[17,30,32,33,36] or chromoendoscopy,[20-27,36,38] dysplasia is detected only on random biopsies in approximately 10% of patients and on targeted biopsies in the other 90%. About 1% to 1.5% of all patients undergoing surveillance would not have dysplasia detected if random biopsies were not performed. Only about one in a thousand random biopsies reveals dysplasia. Pooled results also were determined for detection of dysplasia by using standard-definition white-light colonoscopy.[6,17,20-27,31,33,39-41] The proportion of patients

TABLE 4. Pooled analyses of detection of dysplasia with targeted biopsies and with random biopsies alone in studies of high-definition white-light colonoscopy, chromoendoscopy, and standard-definition white-light colonoscopy

		High definition[17,30,32,33,36]	Chromoendoscopy[20-27,36,38]	Standard definition[6,17,20-27,31,33,39-41]
Proportion of all patients with IBD surveyed and found to have dysplasia by each modality	No. of studies (no. of patients)	4 (382)	7 (1289)	11 (1735)
	Identified on targeted biopsies	15.4% (9.3%-24.5%)*	12.4% (8.3%-18.3%)*	11.8% (8.6%-16.1%)*
	Identified on random biopsies only	1.6% (0.7%-3.6%)	1.2% (0.8%-2.0%)	2.6% (1.1%-6.0%)*
Proportion of patients with dysplasia identified by each modality	No. of studies (no. of patients)	4 (59)	7 (158)	12 (270)
	Identified on targeted biopsies	90.6% (80.1%-95.9%)	90.2% (85%-94%)	80.4% (85%-94%)*
	Identified on random biopsies only	9.4% (4.1%-19.9%)	9.8% (6%-15%)	19.6% (11.5%-31.2%)*
Proportion of all random biopsy specimens positive for dysplasia	No. of studies (no. of biopsies)	5 (8739)	11 (48,522)	11 (25,238)
	Proportion positive for dysplasia	0.2% (0.0%-1.2%)*	0.1% (0.0%-0.3%)*	0.1% (0.1%-0.3%)*

*Statistical heterogeneity with Cochran Q; $P \leq .02$ and I^2 statistic $\geq 65\%$.

with dysplasia identified only on random biopsies was approximately 20% with standard-definition colonoscopy.

Panelists did not reach consensus regarding random biopsies: 45% agreed and 30% disagreed with performing random biopsies when using high-definition white-light colonoscopy, whereas 25% agreed and 60% disagreed with performing random biopsies when using chromoendoscopy. Judgments varied regarding the importance of missing dysplasia in a small proportion of patients, and potential benefits of foregoing biopsies were considered, including a decrease in procedure time (which may offset some of the increased time required for chromoendoscopy) and a reduction in cost related to a decrease in the number of biopsy specimens submitted for histologic examination. Other recent guidelines suggest use of multiple random biopsies when using high-definition white-light colonoscopy but only targeted biopsies of visible lesions when using chromoendoscopy for detection of dysplasia.[2,8]

Other image-enhancement modalities. Autofluorescence, a technique that uses differences in emission spectra of neoplastic and nonneoplastic tissue after exposure of colon mucosa to short wavelength light,[42] has been studied in surveillance colonoscopy for patients with IBD. A tandem study found that a nonsignificantly higher proportion of patients had dysplasia detected with autofluorescence as compared with white-light colonoscopy (8/50 [16%] vs 2/50 [4%]; $P = .09$), and more dysplastic lesions were identified with autofluorescence (13 vs 3 lesions).[39] The evidence was graded low quality, and the statement "when performing surveillance with high-definition colonoscopy, autofluorescence imaging is preferred to white-light colonoscopy" was not endorsed.

Confocal laser endomicroscopy, a technique allowing real-time histologic examination of colon mucosa during endoscopy that has been studied in IBD surveillance,[21,27,42] was not included in the focused questions for guideline development because it cannot practically be used for primary examination of the entire surface area of the colon as required for IBD surveillance. Rather, its potential role would be in characterization of lesions identified during surveillance.

Management of dysplasia discovered on surveillance colonoscopy

The goal of this section is to define the optimal management of patients with IBD in whom dysplasia is identified on endoscopic surveillance. Management of endoscopically nonresectable visible lesions is not included, because such patients generally would undergo surgery.

Endoscopically resectable polypoid and nonpolypoid lesions are considered separately in these guidelines for several reasons. First, it is not clear that the risk of CRC is the same for polypoid and nonpolypoid dysplastic lesions in patients with IBD. Only recently, because of improvements in endoscopic imaging, have nonpolypoid lesions been identified regularly in patients with IBD. Consequently, little is known about the natural history of nonpolypoid lesions, although studies in patients without IBD suggest that the molecular biology of nonpolypoid

colorectal neoplasms may differ from that of polypoid colorectal neoplasms.[43] Second, the methods for endoscopic resection of polypoid and nonpolypoid lesions differ, with endoscopic resection of nonpolypoid lesions typically more difficult and often requiring advanced endoscopic skills that many endoscopists may lack. Third, confidence that the lesion has been completely removed may be lower for nonpolypoid than for polypoid lesions.

Statement 7: After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy.

(100% agreement; strong recommendation; very low-quality evidence)

Summary of evidence and discussion. No study comparing surveillance colonoscopy and colectomy after endoscopic resection of dysplastic lesions was identified. However, 6 studies from the video-endoscopic era (1990 onward) were identified that reported CRC incidence after endoscopic removal of polypoid dysplastic lesions in >15 patients with IBD.[6,44-48] Among studies that reported the proportion of patients with low-grade versus high-grade dysplasia, most patients had low-grade dysplasia. Over mean follow-up periods of 36 to 82 months, the incidence of CRC in these studies was 19 of 311 (6%, range 2%-13%). A single study focused only on polypoid lesions with high-grade dysplasia[49] found that 0 of 9 patients followed for a mean of 76.5 months (range 52-99 months) after endoscopic resection developed CRC or flat dysplasia.

A recent systematic review of 10 studies, which followed 376 patients with IBD with resected polypoid dysplasia for a mean of 54 months, reported an annualized incidence for CRC of 0.5%.[50] The definition of an "acceptable" incidence of synchronous and metachronous CRC for physicians—and, more importantly, for patients—needs to be considered when determining management strategies.

The strength of this recommendation was considered strong despite the lack of evidence comparing the management strategies, largely based on views regarding patient preference. Stakeholders indicated that patients diagnosed with dysplasia were much more likely to refuse or delay colectomy and choose surveillance colonoscopy. They suggested that patients might accept colectomy at a later date, depending on results of subsequent surveillance procedures and further information and education about colectomy and CRC risk provided by physicians, nurses, other patients, and patient advocacy groups. These views were supported by a survey that assessed the management preferences of 199 patients with ulcerative colitis who were told that dysplasia was detected.[51] On average, patients would agree to immediate colectomy only when the risk of synchronous CRC rose to ≥73%.[51]

More intensive surveillance for patients with endoscopically resectable dysplasia than for those without dysplasia seems reasonable, and subsequent surveillance may vary based on the size and appearance of the dysplastic lesion. For example, current multi-society guidelines on colorectal polyps in patients without IBD suggest a short interval of < 1 year for flat and sessile adenomatous and serrated polyps >15 mm that are removed by using injection-assisted polypectomy and piecemeal resection if there is any question about completeness of resection.[52] Thus, patients with IBD who have larger sessile lesions removed in piecemeal fashion or via endoscopic mucosal resection or endoscopic submucosal dissection probably should return at approximately 3 to 6 months, with longer subsequent intervals (eg, yearly) if the initial repeat colonoscopy result is negative. Patients with smaller polypoid lesions resected en bloc may return at 1-year intervals.

Statement 8: After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy.

(80% agreement; conditional recommendation; very low-quality evidence)

Summary of evidence and discussion. No study comparing surveillance colonoscopy to colectomy or providing the natural history for nonpolypoid dysplastic lesions after endoscopic resection was identified.

Analogous to the polypoid lesion discussed previously, if a nonpolypoid lesion is removed completely at endoscopy, it is acceptable to follow the patient with regular surveillance colonoscopy, because most dysplasia is visible, and careful follow-up with high-definition chromoendoscopy likely would identify new or recurrent dysplastic lesions. Nonetheless, this recommendation is conditional, given the possibility that nonpolypoid lesions could confer a higher CRC risk and the greater endoscopic difficulty in assuring complete removal of these lesions. In addition, because many of the larger nonpolypoid lesions must be removed with endoscopic mucosal resection or endoscopic submucosal dissection and/or in piecemeal fashion, patients with such lesions should undergo initial follow-up surveillance colonoscopy in approximately 3 to 6 months as outlined previously for larger sessile polypoid lesions.

In contrast to the recommendation from this and other publications,[10] some recent guidelines have suggested colectomy for nonpolypoid dysplastic lesions because they considered such lesions generally not amenable to endoscopic resection.[2,8] However, variation in terminology for dysplastic lesions across publications makes comparisons difficult.

Statement 9: For patients with endoscopically-invisible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy.

(100% agreement; conditional recommendation; very-low-quality evidence)

Summary of evidence and discussion. No study comparing surveillance colonoscopy and colectomy for endoscopically invisible dysplasia was identified. However, 4 studies from the video-endoscopic era reported CRC incidence

after invisible dysplasia was diagnosed in >15 patients with IBD.[45,48,53,54] Over a mean follow-up of 15 to 50 months, CRC developed in 7 of 122 patients (6%, range 3%-9%).

The proportion of patients with synchronous CRC at the time invisible dysplasia is detected also is important when considering management strategies. A systematic review[55] of 20 surveillance studies and 477 patients with invisible low-grade dysplasia (which included patients from before the video-endoscope era) found that 18 of 81 patients (22%) with invisible low-grade dysplasia who had colectomy had CRC. It is uncertain what characteristics led the minority of patients with low-grade dysplasia to undergo colectomy—other unknown or unreported factors that increase the risk of CRC may have been present in some of these patients.

Colectomy has been performed more commonly when invisible high-grade dysplasia is discovered because of the reported higher risk of CRC. A 1994 systematic review found that 10 of 24 patients (42%) with non-DALM high-grade dysplasia had CRC on colectomy, whereas 15 of 47 patients (32%) who had high-grade dysplasia on subsequent surveillance examinations developed CRC.[5] Other individual studies of patients with invisible high-grade dysplasia undergoing colectomy reported since 1994 show rates of CRC ranging from 45% to 67%.[56-59]

The findings reported in older studies may be of limited relevance in the current video-endoscopic era. A 1994 review of 10 prospective studies with 1225 patients undergoing surveillance colonoscopy found that dysplasia that is not associated with a lesion accounted for 272 of 312 patients (87%) found to have dysplasia.[5] In contrast, more recent studies of chromoendoscopy or high-definition white-light colonoscopy report that invisible dysplasia accounts for about 10% of patients with dysplasia (Table 4). Thus, random biopsy specimens showing invisible dysplasia in older studies may have been taken from previously unrecognizable lesions that can now be visualized with modern endoscopic techniques.

Based on this information, general statements that the initial management step for patients with invisible low-grade or high-grade dysplasia be surveillance colonoscopy or colectomy[2,8] were not endorsed. Rather, referral to an endoscopist with expertise in IBD surveillance and image-enhanced examination using chromoendoscopy with high-definition endoscopy was considered an appropriate next step to better inform subsequent decisions regarding surveillance colonoscopy versus colectomy. If a visible dysplastic lesion is identified in the same region of the colon as the invisible dysplasia, and the lesion can be resected endoscopically, then such patients may remain in a surveillance program, as recommended previously in statements 7 and 8. Alternatively, if dysplasia is not discovered, management of such patients would be individualized after discussion of the risks and benefits of surveillance colonoscopy and colectomy. Continued intensive surveillance is an acceptable strategy if, after careful discussion, patients prefer this course.

Histologic distinctions may play a role in management decisions for patients with invisible dysplasia and no visible lesions on follow-up chromoendoscopy. Physicians may be comfortable having patients with invisible low-grade dysplasia remain in intensive surveillance while more strongly suggesting colectomy for those with invisible high-grade dysplasia. In addition, some physicians believe that multifocal invisible low-grade dysplasia is associated with higher CRC risk than unifocal low-grade dysplasia, leading to a greater likelihood of recommending colectomy, although a single study assessing this issue[54] failed to show an increased risk.

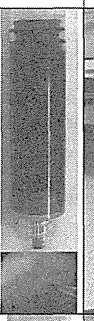
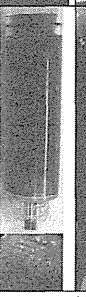
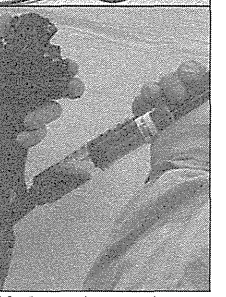
Confirmation of dysplasia by a pathologist with expertise in IBD is suggested before making management decisions. Even expert GI pathologists show no better than fair or moderate interobserver agreement on the histologic diagnosis of dysplasia, low-grade dysplasia, or high-grade dysplasia.[60-62] Diagnosis of low-grade dysplasia in Barrett's esophagus by one pathologist does not predict progression to high-grade dysplasia or cancer, but agreement among 2 or 3 pathologists significantly increases the risk of progression.[63] Similar studies are not available for IBD, but confirmation of dysplasia by a second pathologist seems appropriate before embarking on major diagnostic and therapeutic interventions.

IMPLEMENTATION OF HIGH-QUALITY ENDOSCOPIC SURVEILLANCE

Widespread implementation of high-quality endoscopic surveillance in patients with IBD will require a variety of initiatives, which will be discussed in a separate publication. Resources will be needed to train endoscopists in endoscopic surveillance and recognition of visible dysplasia with both white-light endoscopy and chromoendoscopy. These may include training courses, photographic atlases,[64-66] and video repositories.[67] Quality metrics and methods to document acceptable performance quality also should be developed. In addition, techniques such as chromoendoscopy should be standardized to allow implementation in endoscopy units, and endoscopic resection techniques for nonpolypoid lesions should be taught and disseminated.[68-70] Development of a procedure code for chromoendoscopy and reimbursement for the increased time and intensity required for chromoendoscopy would increase implementation, at least in the United States.

Performance of chromoendoscopy for surveillance of patients with IBD

Description of the technique. Surveillance colonoscopy should be performed when the disease is in remission in order to minimize potential misdiagnosis between inflammatory changes and dysplasia.[18,71,72] Clean bowel preparation is a prerequisite—the entire mucosa should be free from pus, mucus, blood, or stool. Small amounts

Purpose	Technique	Method	Dilution*	Color	
Lesion detection	Pan chromo-endoscopy	Water jet channel using auxillary foot pump or biopsy channel using spray catheter	Indigo carmine (0.8%, 5ml ampule): 2 ampules + 250ml water (0.03%) Methylene blue (1%,10ml ampule): 1 ampule + 240ml water (0.04%)		
Lesion characterization and delineation of borders	Targeted chromo-endoscopy	Syringe spray through biopsy channel	Indigo carmine (0.8%, 5ml ampule): 1 ampule + 25ml water (0.13%) Methylene blue (1%,10ml ampule): 1 ampule + 40ml water (0.2%)		

*Various dilutions ranging from 0.03-0.2% of indigo carmine and methylene blue have been reported for for panchromoendoscopy.

Figure 2. Chromoendoscopy technique.

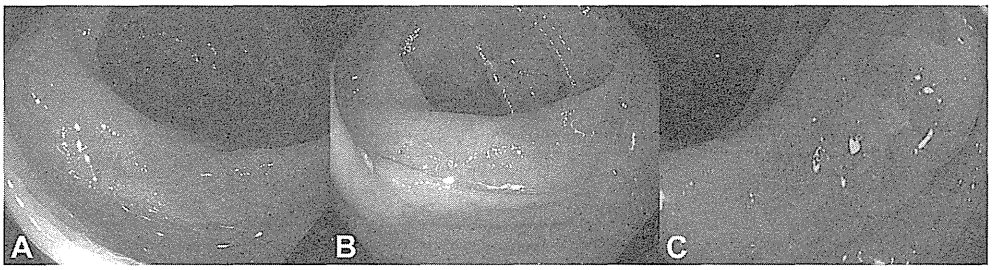


Figure 3. A, 3-cm, nonpolypoid, superficial, elevated lesion after indigo carmine chromoendoscopy. **B,** The area of the lesion before dye spray. **C,** Th same lesion had likely been photographed approximately a year earlier (on fold to left of ulcer), but it was not recognized to be dysplastic. Histologi examination showed low-grade dysplasia.

of debris or fluid are washed and suctioned during insertion. Once the cecum is reached and the mucosa is cleaned, the application of either diluted indigo carmine or methylene blue dyes is initiated. We spray a total of approximately 250 mL of diluted dye (indigo carmine 0.03% to 0.1% or methylene blue 0.04 to 0.1%) circumferentially throughout the colon either through the water jet channel by using a pump or through the biopsy channel by using a spray catheter (Fig. 2). Efficient spraying of the dye through the water jet channel is typically performed by directing the stream of dye to the antigravity side of the colon.[18] When a spray catheter is used, the spray catheter is inserted through the biopsy channel until its tip protrudes 2 to 3 cm, and dye is sprayed throughout the mucosa while the colonoscope is being withdrawn.[71]

During inspection, by using the pan-chromoendoscopy technique, the endoscopist looks for areas that appear to be different from the surrounding background in color, pattern, or level. Nonpolypoid le sions may appear discolored (uneven redness), nodula or villous, slightly elevated or depressed, friable, o have an obscure vascular pattern. Polypoid lesions ar easier to detect, but the dye can help delineate the le sion's border. Once a suspicious lesion is identified, w selectively spray approximately 30 mL of a more concen trated dye (indigo carmine 0.13% or methylene blu 0.2%) directly from a 60-mL syringe through the biops channel. With targeted chromoendoscopy, the darke blue dye can be helpful to further enhance the borde and surface topography of a lesion (Fig. 3).[18] These area should be photographed. Endoscopically resectable sus picious lesions may be removed by using polypectom or endoscopic mucosal resection. Biopsy specimens ar taken from lesions that are deemed to be unresectable A biopsy specimen is taken from the flat area surround ing the lesion to detect dysplasia. A tattoo may b

TABLE 5. Suggested steps for implementation of chromoendoscopy into endoscopic practice

Equipment	
Colonoscope	High-definition colonoscope, monitor, and cables
Accessories	Apply dye via: Water jet channel by using water pump attached to the endoscope activated via foot pedal or Spray catheter: length 240 cm, endoscope accessory channel 2.8 mm
Contrast agent	Indigo carmine, 5-mL ampule (0.8%) Methylene blue, 10-mL ampule (1%)
Procedure and protocol	
Time allotment	Consider doubling colonoscopy time slot initially during the learning curve period.
Standard operating procedure	Complete colonoscopy to cecum. Lavage with water and suction during intubation.
	Prepare dye solution during insertion for application via the foot pump or spray. Indigo carmine (0.03%): mix 2 5-mL ampules of 0.8% indigo carmine with 250 mL water. Methylene blue (0.04%): mix one 10-mL ampule of 1% methylene blue with 240 mL water.
	If using a foot pump: once the cecum is intubated, the water irrigation can be exchanged with the contrast solution. Apply the dye solution in a circumferential technique while withdrawing the colonoscope. Direct spray to the anti-gravity side.
	If using a spray catheter: the dye spray catheter is inserted into the biopsy channel; the catheter tip should protrude 2-3 cm from the endoscope. Apply dye solution segmentally by using a rotational technique while withdrawing the colonoscope to cover the surface mucosa with dye.
	Suction any excess solution after approximately 1 minute to aid mucosal visualization.
	Focus on 20-30–cm segments sequentially with reinsertion of the endoscope to the proximal extent of each segment before slow withdrawal and mucosal visualization.
	Targeted dye spray for suspicious lesions: Prepare more concentrated dye solution for application. Indigo carmine (0.13%): mix one 5-mL ampule of 0.8% indigo carmine with 25 mL water. Methylene blue (0.2%): mix one 10-mL ampule of 1% methylene blue with 40 mL water. Spray about 30 mL directly from a 60-mL syringe through the biopsy channel.
	Remove endoscopically resectable suspicious lesions by using polypectomy or endoscopic mucosal resection.
	Do targeted biopsies of any unresectable abnormality visualized through chromoendoscopy to diagnose dysplasia.
	Do biopsies of flat area surrounding lesions to assess for dysplasia.
	Consider tattoo of suspicious dysplastic lesions arising from flat mucosa or not amenable to complete removal.
	Recommendations regarding the need to perform random, non-targeted biopsies for detection of dysplasia vary.
	If biopsies for dysplasia are not done, 2 random biopsies in every bowel segment are commonly recommended to document microscopic disease activity.

necessary to mark the location of resection or suspicious lesion. Biopsies to document disease activity may be performed during the procedure.

Available resources for self-learning. Descriptions of a systematic approach to performance of pancolonic chromoendoscopy by using either indigo carmine or methylene blue dyes with targeted biopsy for surveillance of patients with IBD are available.[18,71] In addition, endoscopic videos,[18,67] atlases,[64-66] and books[73,74] have been published recently to provide readers with information on the techniques and findings related to endoscopy in IBD. Open access of several of the materials serves to facilitate learning (http://www.youtube.com/watch?v=OARkbgwlObI, http://www.giendo.theclinics.com/issues/?elsca1=etoc&elsca2=email&elsca3=1052-5157_201407_24_3&elsca4=gastroenterology&issue_key=S1052-5157%2814%29X0003-6). Key steps for the implementation of chromoendoscopy technique into endoscopic practice are provided in Table 5.

FUTURE RESEARCH

The evidence currently available to inform decisions on appropriate colonoscopic surveillance methods to detect and manage dysplasia in patients with IBD is limited. Thus, further research would be of value for most of the issues addressed in this guideline. Suggested research includes the following: larger trials of chromoendoscopy using high-definition colonoscopy, comparison of different chromoendoscopy techniques (eg, indigo carmine vs methylene blue, concentration of dye, delivery of dye via spray catheter vs endoscopy water jet channel), a registry of endoscopists performing chromoendoscopy to

determine detection rates and learning curves, evaluation of new generations of equipment-based modalities, determination of appropriate surveillance intervals with high-definition chromoendoscopy, the natural history of visible dysplastic lesions after endoscopic resection (especially nonpolypoid lesions), and the natural history of patients with endoscopically invisible dysplasia, even after expert chromoendoscopy.

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*Abbreviations: CRC, colorectal cancer; IBD, inflammatory bowel disease; NBI, narrow-band imaging; SCENIC, **S**urveillance for **C**olorectal **E**ndoscopic **N**eoplasia Detection and Management in Inflammatory Bowel Disease Patients: **I**nternational **C**onsensus Recommendations.*

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The SCENIC international consensus statement also was reviewed and endorsed by the Asian Pacific Association of Gastroenterology, British Society of Gastroenterology, Canadian Association of Gastroenterology, European Society of Gastrointestinal Endoscopy, and Japan Gastroenterological Endoscopy Society.

APPENDIX 1. PARTICIPANTS, AFFILIATIONS, ROLES/AREAS OF FOCUS, AND POTENTIAL CONFLICTS

Participant affiliations and roles/areas of focus

Voting chair and co-chair: Loren Laine, United States, and Alan Barkun, Canada

Voting executive committee members:

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Fabrizio Michelassi, Cornell Medical Center, New York, NY, United States. Colorectal surgeon (first vote only; scheduling conflicts prevented subsequent participation)

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Venkataraman Subramanian, University of Leeds, Leeds, United Kingdom. Methodology (systematic review), endoscopic imaging

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Nonvoting ethics expert: Derek J. Jones, Montreal, Quebec, Canada, and Yidan Lu, McGill University, Montreal, Canada.

Nonvoting scribe: Sarah K. McGill, Veterans Affairs Palo Alto Health Care System, Stanford University School of Medicine, Palo Alto, CA, United States.

Participants potential conflicts:

Declaration of personal interests:

The following is a summary of the financial disclosure provided by the following participants: Alan Barkun (AB), James E. East (JE), Francis A. Farraye (FF), Brian Feagan (BF), John Ioannidis (JI), Tonya Kaltenbach (TK), Ralf Kiesslich (RK), Michael Krier (MK), Loren Laine (LL), Takayuki Matsumoto (TM), Robert P. McCabe (RM), Kenneth R. McQuaid (KMc), Fabrizio Michelassi (FM), Klaus Mönkemüller (KM), Robert Odze (RO), Michael Picco (MP), David T. Rubin (DR), Michele Rubin (MR), Carlos A. Rubio (CR), Matt D. Rutter (MRu), Andres Sanchez-Yague (AS-Y), Silvia Sanduleanu (SS), Amandeep Shergill (ASh), Roy Soetikno (RS), Venkataraman Subramanian (VS), Thomas Ullman (TU), Fernando Velayos (FV), Douglas Yakich (DY), Yu-Xiao Yang (Y-XY).

No significant financial interest to report:

JI, RK, MK, LL, TM, RM, KMc, FM, RO, MP, MR, CR, AS-Y, SS, ASh, VS, FV, DY, Y-XY.

Yes, a significant financial interest as follows:

Advisory Board: Abbvie (JE, BF), Amgen (BF), AstraZeneca (BF), Avaxia Biologics (BF), Braintree (FF), Bristol Myers Squibb (BF), Celgene (BF), Centocor (BF), Cosmo Pharmaceuticals (JE), Elan/Biogen (BF), Entera Health (FF), Ferring (BF), Genentech (TU), Janssen (FF, BF), Merck (BF), Novartis (BF), NovoNordisk (BF), Olympus (AB), Pendopharm (AB), Pfizer (BF), Prometheus (BF), Salix Pharmaceuticals (FF, BF), Takeda (BF), Teva Pharmaceuticals (BF), Tillotts Pharmaceuticals (BF), UCB Pharmaceuticals (BF).

Honorarium: Abbvie (JE, BF), Actogenix (BF), Albireo Pharmaceuticals (BF), Amgen (BF), AstraZeneca (AB, BF), Avaxia Biologics (BF), Axcan (BF), Baxter (BF), Boehringer-Ingelheim (BF), Boston Scientific (AB), Bristol Myers Squibb (BF), Calypso Biotech (BF), CDX (TU), Celgene (BF), Centocor (BF), Cook (AB, KM), Cosmo Pharmaceuticals (JE), Elan/Biogen (BF),EnGene (BF), Ferring (BF), Genentech (TU), GiCare Pharmaceuticals (BF), Gilead (BF), Given Imaging (BF), GSK (BF), Ironwood Pharmaceuticals (BF), Janssen Biotech (Centocor) (BF), Janssen (TU, BF), Kyowa Kakko Kirin (BF), Lexicon (BF), Lilly (BF), Merck (BF), Millennium (BF), Nektar (BF), Novartis (BF), NovoNordisk (BF), Olympus, (AB, MRu), Ovesco (KM), Pendopharm (AB), Prometheus Laboratories (BF), Prometheus Therapeutics and Diagnostics (BF), Pfizer (BF, TU), Receptos (BF), Roche/Genentech (BF), Salix Pharmaceuticals (BF), Serono (BF), Shire (BF), Sigmoid Pharmaceuticals (BF), Synergy Pharmaceuticals (BF), Takeda (AB, BF), Teva Pharmaceuticals (BF), Tillotts Pharmaceuticals (BF), UCB Pharmaceuticals (BF), Vertex Pharmaceuticals (BF), Warner-Chilcott (BF), Wyeth (BF), Zealand (BF), Zyngenia (BF).

Research Support: Abbott (BF), Abbvie (BF, DR), Amgen (BF), AstraZeneca (BF), Boston Scientific (AB), Bristol Myers Squibb (BF), Cook (AB), Cosmo Pharmaceuticals (JE), Cubist (FF), Elan Pharmaceuticals (DR), Genentech (BF, TU), Janssen Biotech (Centocor) (BF), Janssen (BF), Millennium (BF), Olympus (JE, RS, TK), Pfizer (BF), Prometheus Pharmaceuticals (FF, DR), Receptos (BF), Santarus (BF), Sanofi (BF), Shire (DR), Tillotts (BF), UCB Pharmaceuticals (BF), Warner Chilcott (DR).

Speaker's Bureau: Abbvie (JE, BF), AstraZeneca (AB), Cook (AB, KM), Cosmo Pharmaceuticals (JE), Janssen (BF, TU), Ovesco (KM), Olympus (RS, MRu), Pendopharm (AB), Takeda (AB, BF), UCB Pharmaceuticals (BF), Warner-Chilcott (BF).

Consultant: Abbvie (BF, DR), Actogenix (BF), Albireo Pharmaceuticals (BF), Amgen (BF), AstraZeneca (BF), Avaxia Biologics (BF), Axcan (BF), Baxter (BF), Boehringer-Ingelheim (BF), Bristol Myers Squibb (BF, DR), Calypso Biotech (BF), CDX (TU), Celgene (BF), Cook (AB), Elan/Biogen (BF, DR), EnGene (BF), Emmi (DR), Ferring (BF), Genentech (BF, TU), GiCare Pharmaceuticals (BF), Gilead (BF), Given Imaging (BF, DR), GSK (BF), Ironwood Pharmaceuticals (BF, DR), Janssen Biotech (Centocor) (FF, BF, DR, TU), Janssen (BF), Kyowa Kakko Kirin (BF), Lexicon (BF), Lifecore Biomedical (DR), Lilly (BF), Merck (BF), Nektar (BF), NovoNordisk (BF), Olympus (TK), Olympus (RS), Pfizer (BF, TU), Prometheus Pharmaceuticals (DR), Prometheus Therapeutics and Diagnostics (BF), Receptos (BF), Roche/Genentech (BF), Salix Pharmaceuticals (BF), Santarus (FF, DR), Serono (BF), Shire (BF), Sigmoid Pharmaceuticals (BF), Synergy Pharmaceuticals (BF), Takeda (BF), Teva Pharmaceuticals (BF), Tillotts (BF), Takeda-Millennium (BF, DR), Telsar Pharmaceuticals (DR), UCB Pharmaceuticals (BF, DR), Vertex Pharmaceuticals (BF, DR), Warner-Chilcott (BF), Wyeth (BF), Zealand (BF), Zyngenia (BF).

Investor: Genentech (TU)

Equipment loan: Olympus (JE), Pentax (JE).

Other:

Celgene (FF) Data Safety Monitoring Committee

Cornerstones Health, Inc (DR) Co-founder, non-profit medical education entity

Genentech (TU) investigator

Identified potential companies with interests:

1. When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition.

EndoChoice, Fujifilm, Fujinon, Olympus, Pentax

2. When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy.

EndoChoice, Fujifilm, Fujinon, Mauna Kea Technology—Cellvizio, Medivator, Olympus, Pentax, Akorn, Amend Chemical Company, American Regent, Baker JT, Lex Pharmaceuticals, Medsica, Professional Compounding Centers, Akorn, Amend Chemical Company, American Regent, Baker JT, Lex Pharmaceuticals, Medsica, Professional Compounding Centers

3. When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy.

EndoChoice, Fujifilm, Fujinon, Mauna Kea Technology—Cellvizio, Medivator, Olympus, Pentax, Akorn, Amend Chemical Company, American Regent, Baker JT, Lex Pharmaceuticals, Medsica, Professional Compounding Centers, Akorn, Amend Chemical Company, American Regent, Baker JT, Lex Pharmaceuticals, Medsica, Professional Compounding Centers

4. When performing surveillance with standard-definition colonoscopy, narrow band imaging is not suggested in place of white-light colonoscopy.

EndoChoice, Fujifilm, Fujinon, Mauna Kea Technology—Cellvizio, Olympus, Pentax

5. When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy.

EndoChoice, Fujifilm, Fujinon, Mauna Kea Technology—Cellvizio, Olympus, Pentax

6. When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy.

EndoChoice, Fujifilm, Fujinon, Mauna Kea Technology—Cellvizio, Olympus, Pentax

7. After complete removal of endoscopically-resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy.

Boston Scientific, Conmed, Cook, Covidien, EndoChoice, Erbe, Johnson and Johnson, LifeCore Biomedical, Medivators, Fuji, Olympus, Pentax, Seikakagu Co, TOP, US Endoscopy, Valley Lab

8. After removal of endoscopically-resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is preferred to colectomy.

Boston Scientific, Conmed, Cook, Covidien, EndoChoice, Erbe, Johnson and Johnson, LifeCore Biomedical, Medivators, Fuji, Olympus, Pentax, Seikakagu Co, TOP, US Endoscopy, Valley Lab

9. For patients with endoscopically-invisible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy.

Boston Scientific, Conmed, Cook, Covidien, EndoChoice, Erbe, Johnson and Johnson, LifeCore Biomedical, Medivators, Fuji, Olympus, Pentax, Seikakagu Co, TOP, US Endoscopy, Valley Lab

APPENDIX 2. DEVELOPMENT PROCESS

Development panel

A 5-member executive committee of content experts, general gastroenterologists, and methodologists oversaw the development process. The executive committee selected a multidisciplinary panel to represent a wide spectrum of stakeholders in the diagnosis and management of dysplasia in patients with inflammatory bowel disease (IBD) and to provide international viewpoints. This 21-member panel included IBD experts, general gastroenterologists, advanced endoscopists, methodologists, pathologists, a surgeon, an advanced practice IBD nurse, and a patient representative from an IBD non-profit organization. We emphasized representation from a wide spectrum of stakeholders and attitudes toward the detection and management of dysplasia in IBD. An additional 8 non-voting physicians, chosen for their expertise in areas such as endoscopic techniques or guideline dissemination/implementation, attended the meeting to provide information as requested by voting panelists. The list of participants is provided in Appendix 1.

Formulation of focused clinical questions

The participants formulated clinically pertinent focused statements related to the detection and management of dysplasia in IBD and framed each statement in terms of population, intervention, comparator, and outcome (PICO).

Systematic literature search and meta-analyses

A systematic literature search of multiple bibliographic databases (EMBASE 1980 to 2013 Week 38; Cochrane Central Register of Controlled Trials 1898 to August 2013; Ovid MEDLINE, 1946 to present, in-process and other non-indexed citations, and daily update September 24, 2013) was performed for each focused statement by the Cochrane Upper Gastrointestinal Pancreatic Diseases Review Group. Additional searches from major gastroenterology scientific meetings (eg, Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week) for 2009-2013 and of reference lists from selected articles were also performed (Figure). The search strategy keywords were framed for the PICO-formatted focused clinical statements (Appendix 3). The search was limited to human studies without any language restriction. Two reviewers (T.K., V.S.) performed the initial title and abstract review, review of full-text articles for inclusion, and data extraction independently. Following full text review and article selection, a third person (L.L.) adjudicated any discrepancies.

By using pre-specified criteria, we excluded abstracts/articles when (1) the population did not include colonic inflammatory bowel disease; (2) the intervention or comparator did not include sigmoidoscopy or colonoscopy for the detection, diagnosis or management of colorectal neoplasia, dysplasia or early cancer; (3) the outcome did not include colorectal neoplasia, dysplasia or cancer-related detection, incidence or mortality; (4) the article type was a case report or series; (5) the article contained duplicate data; (6) the article had relevant missing data that could not be obtained despite attempts to contact corresponding authors; (7) the author had articles on the topic retracted from the literature; and (8) the studies included data from the fiberoptic endoscope era (predating 1990).

Risk of bias for individual studies was assessed independently by two reviewers (T.K., V.S.) with the QUADAS-2 tool for observational diagnostic studies and a modified Jadad score (one point added if allocation was concealed) for randomized trials; a third person (L.L.) adjudicated any discrepancies. The quality of the evidence for each statement was rated by two reviewers (L.L., A.B.) independently as very low quality, low quality, moderate quality, and high quality based on the GRADE methodology; disagreements were resolved by discussion. Quality of evidence definitions were: (1) very low quality—any estimate of effect is very uncertain; (2) low quality—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; (3) moderate quality—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; and (4)

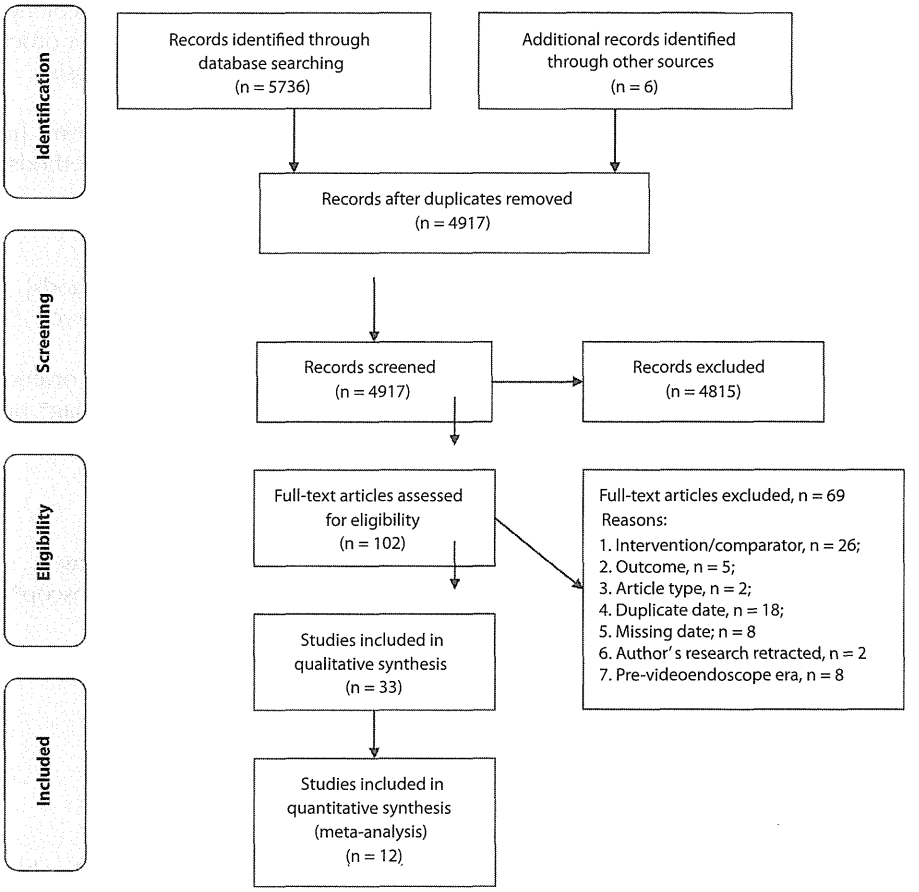

Figure. Flow diagram for systematic review and meta-analysis

high quality—further research is very unlikely to change our confidence in the estimate of effect.

Meta-analyses were performed when multiple studies relevant to a focused question were found and could be appropriately pooled. We used a fixed effect model, except in cases of significant heterogeneity when we used a DerSimonian-Laird random effects model. We used the Cochran Q test and I^2 statistic to assess heterogeneity. Significant heterogeneity was defined as a $P < .10$ for the Cochran Q test or I^2 statistic $>50\%$. We performed the data analysis by using the Comprehensive Meta Analysis version 2.2 (Biostat, Englewood, NJ) statistical package.

We identified 4917 abstracts and selected 102 for full article retrieval based on the pre-defined inclusion criteria. We ultimately included 33 articles for qualitative synthesis for the statements (see flow diagram). We performed meta-analysis of articles for statements 2 and 6.

Consensus process for development of recommendations

We deployed an online consensus platform to facilitate most aspects of the consensus process. The panel received evidence reports for each statement. Two rounds of votin on level of agreement with the statements were conducte by using the online platform prior to a face-to-face meetin of all participants to determine consensus on the recom mendations. Modifications to the wording of the state ments were made as needed in response to th participants' comments after each round of voting.

We held a one and a half–day consensus conference i March 2014, where data were presented, wording of th statements was discussed and finalized, and participant voted on their level of agreement by using a 5-point scal (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). We defined the criterion for ac cepting a statement as a recommendation as $\geq 80\%$ of par ticipants voting 4 (agree) or 5 (strongly agree). If a pane member was absent or did not vote at the time of vote, the denominator of panelists who were present an voted was used. Once a recommendation was accepted panelists voted on whether to label the recommendatio as strong or conditional according to GRADE criteria Wording of recommendations was based on the strengt of recommendation: *recommend* was used for strong rec ommendations, and *suggest* was used for conditiona

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