

# Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline



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## Institutions

Institutions are listed at the end of article.

## Bibliography

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This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It addresses the role of advanced endoscopic imaging for the detection and differentiation of colorectal neoplasia.

## Main recommendations

**1** ESGE suggests the routine use of high definition white-light endoscopy systems for detecting colorectal neoplasia in average risk populations (weak recommendation, moderate quality evidence).

**2** ESGE recommends the routine use of high definition systems and pancolonial conventional or virtual (narrow band imaging [NBI], i-SCAN) chromoendoscopy in patients with known or suspected Lynch syndrome (strong recommendation, low quality evidence).

**2b** ESGE recommends the routine use of high definition systems and pancolonial conventional or virtual (NBI) chromoendoscopy in patients with known or suspected serrated polyposis syndrome (strong recommendation, low quality evidence).

**3** ESGE recommends the routine use of 0.1% methylene blue or 0.1%–0.5% indigo carmine pancolonial chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing colitis. In appropriately trained hands, in the situation of quiescent disease activity and adequate bowel preparation, nontargeted, four-quadrant biopsies can be abandoned (strong recommendation, high quality evidence).

**4** ESGE suggests that virtual chromoendoscopy (NBI, FICE, i-SCAN) and conventional chromoendoscopy can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive ( $\leq 5$  mm) colorectal polyps to replace histopathological diagnosis. The optical diagnosis has to be reported using validated scales, must be adequately photodocumented, and can be performed only by experienced endoscopists who are adequately trained and audited (weak recommendation, high quality evidence).

**5** ESGE suggests the use of conventional or virtual (NBI) magnified chromoendoscopy to predict the risk of invasive cancer and deep submucosal invasion in lesions such as those with a depressed component (0-IIc according to the Paris classification) or nongranular or mixed-type laterally spreading tumors (weak recommendation, moderate quality evidence).

## Conclusion

Advanced imaging techniques will need to be applied in specific patient groups in routine clinical practice and to be taught in endoscopic training programs.

## Abbreviations

|        |                                                                              |
|--------|------------------------------------------------------------------------------|
| ▼      |                                                                              |
| CAC    | cap-assisted colonoscopy                                                     |
| CRC    | colorectal cancer                                                            |
| EMR    | endoscopic mucosal resection                                                 |
| ESGE   | European Society of Gastrointestinal Endoscopy                               |
| FAP    | familial adenomatous polyposis                                               |
| FICE   | Fujinon intelligent color enhancement, flexible spectral imaging enhancement |
| FAP    | familial adenomatous polyposis                                               |
| GRADE  | grading of recommendations assessment, development and evaluation            |
| HD-WLE | high definition white-light endoscopy                                        |
| i-SCAN | Pentax virtual chromoendoscopy system                                        |
| MAP    | <i>MUTYH</i> -associated polyposis                                           |
| NBI    | narrow band imaging                                                          |
| PICO   | population, intervention, comparator, outcome                                |
| PIVI   | preservation and incorporation of valuable endoscopic innovations            |
| RCT    | randomized controlled trial                                                  |
| SD-WLE | standard definition white-light endoscopy                                    |
| TER    | third eye retroscope                                                         |
| WLE    | white-light endoscopy                                                        |

## Introduction

Colonoscopy is widely used for colorectal cancer (CRC) detection and prevention [1, 2]. Its efficacy depends on the ability to detect colorectal neoplasia [3, 4]. In order to maximize the detection of colorectal neoplasia we may not only need to improve the examination technique and quality of bowel preparation but also to engage advanced imaging technologies such as high definition endoscopy, conventional or virtual chromoendoscopy, autofluorescence imaging (AFI) or add-on devices [5]. Some of these technologies may in addition help to characterize detected lesions and thereby guide decisions about endoscopic resection or enable real-time endoscopic diagnosis. Despite being readily available, most technologies have been little adopted into clinical practice outside academic settings [6], mostly because they are perceived as cumbersome, time-consuming and requiring special training. In our view, however, an important barrier to widespread adoption is the lack of a clear guideline on which technology is worth using in which clinical scenario. This Guideline aims to provide endoscopists with a comprehensive review of advanced imaging techniques available for the detection and differentiation of colorectal neoplasia. We also make recommendations about the circumstances under which those techniques warrant introduction into routine clinical practice.

## Methods

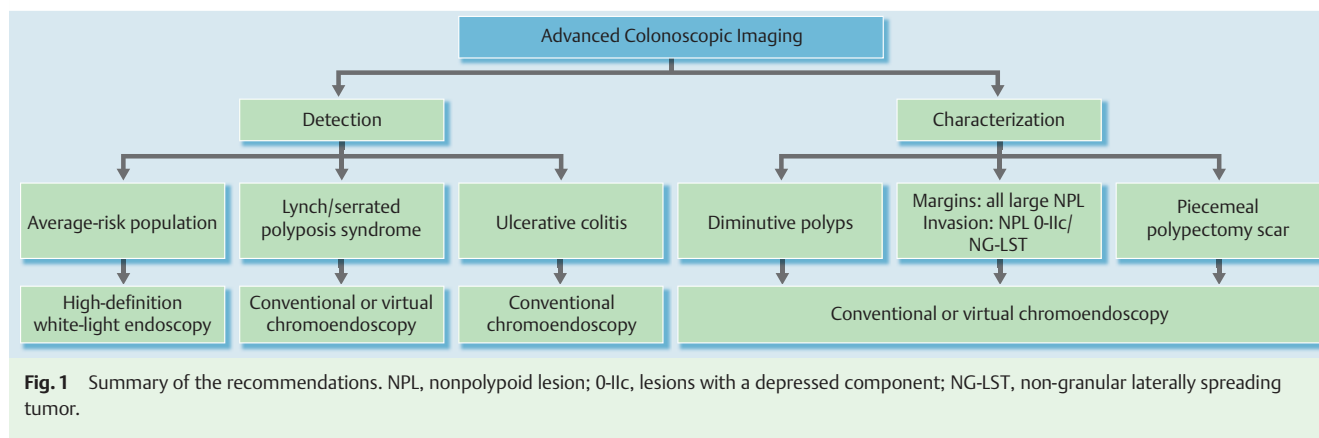
The European Society of Gastrointestinal Endoscopy (ESGE) commissioned this Guideline. The guideline development process included meetings and online discussions among members of the guideline committee during December 2012 and February 2013. Subgroups were formed, each in charge of a series of clearly defined key questions (► **Appendix e1**, available online). The guideline committee chairs (C.H., J.M.D.) worked with the subgroup leaders (J.P., M.P., R.B., J.E., M.F.K.) to identify pertinent search terms that included: high definition endoscopy, chromoendos-

copy, virtual chromoendoscopy (always including additional separate searches for NBI, FICE, and i-SCAN), autofluorescence endoscopy, and add-on devices (cap-assisted colonoscopy, Third Eye Retroscope [TER]), as well as terms pertinent to specific key questions. Techniques still under development, such as confocal laser endomicroscopy, endocytoscopy, and optical coherence tomography, were not included in this Guideline. Technical aspects of advanced imaging technologies will be described in a separate technology review; they are summarized in ► **Table 1**. For ease of literature searching, key questions were formulated using PICO methodology [7].

Searches were performed on Medline (via Pubmed) and the Cochrane Central Register of Controlled Trials up to October 2012; additionally abstracts from the 2012 United European Gastroenterology Week and the 2012 Digestive Disease Week were searched. Articles were first selected by title; their relevance was then assessed by reviewing full-text articles, and publications with content that was considered irrelevant were excluded. Evidence tables were generated for each key question, summarizing the level of evidence of the available studies. For important outcomes, articles were individually assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence levels and recommendation strengths [8]. The GRADE system is clinically orientated as the grading of recommendations depends on the balance be-

**Table 1** Summary of characteristics of advanced imaging techniques.

- High definition white-light endoscopy (HD-WLE) systems use a charge-coupled device with up to a million pixels and high definition monitors (1080 lines of vertical resolution) to provide images of higher resolution than standard definition white-light endoscopy (SD-WLE) systems.
- Conventional chromoendoscopy uses contrast dyes to enhance the visualization of colonic mucosa and to highlight surface contours. In conventional pancolonic chromoendoscopy, dye, usually indigo carmine or methylene blue, is sprayed with a catheter or is applied directly through the working channel of the endoscope in a segmental fashion onto the entire colorectal mucosa.
- Virtual chromoendoscopy refers to the use of image enhancement technologies built into the colonoscope system to alter the white-light image to enhance visualization of mucosal surface architecture and capillary pattern. All three of the key endoscope manufacturers (Olympus Medical Systems, Fujinon Endoscopy, and Pentax Medical) have introduced proprietary technologies to achieve this, with narrow band imaging (NBI), Fujinon Intelligent Color Enhancement (FICE) and i-SCAN, respectively. These systems all work differently, but have a key aim of reducing the amount of red light in the image and of narrowing the bandwidth of blue and green light.
- Autofluorescence imaging (AFI) endoscopy is based on real-time detection of natural tissue fluorescence emitted by endogenous molecules. Differences in fluorescence emission between neoplastic and non-neoplastic tissues are captured during endoscopy and visualized as magenta or green color, respectively. The device is activated by a push-button on the handle of the endoscope. AFI mode is commercially available only in the United Kingdom and Asia with EVIS Lucera Spectrum endoscopes (Olympus Medical Systems).
- Add-on devices described in this guideline (cap and third eye retro-scope [TER]) were designed to increase the area of mucosal surface inspected. Endoscopic caps are transparent, single-use devices mounted on the tip of the endoscope to maintain a distance between the mucosa and the optics, and to facilitate deflection of mucosal folds. TER is a single-use, through-the-scope, retrograde viewing device, connected with a dedicated video processor to provide a retrograde view on the same monitor as the standard colonoscopy forward view.



tween benefits and risks or burden of any health intervention (Appendix e2a, b, available online). In order to answer the question on accuracy of virtual chromoendoscopy systems and AFI in differentiating between small neoplastic and non-neoplastic colorectal polyps, one of the subgroups performed a bivariate meta-analysis using a linear mixed model approach [9].

Each subgroup developed draft proposals that were presented to the entire group for general discussion during a meeting held in February 2013 (Düsseldorf, Germany). Based on evidence tables and draft proposals, key topics for further research were formulated. Further details on the methodology of ESGE guidelines have been reported elsewhere [10].

In October 2013, a draft prepared by M.F.K. and C.H. was sent to all group members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. The journal subjected the manuscript to peer review, and the manuscript was amended to take into account the reviewers' comments. The final revised manuscript was agreed upon by all the authors.

This Guideline was issued in 2014 and will be considered for update in 2017. Any interim updates will be noted on the ESGE website: <http://www.esge.com/esge-guidelines.html>.

## Recommendations and statements

Evidence statements and recommendations are stated in italics, key evidence statements and recommendations are in bold. For ease of clinical use, recommendations and statements were grouped into five categories defined by target population and/or the role of advanced imaging for detection and/or differentiation of colorectal neoplasia. Statements on the use of virtual chromoendoscopy mention in parentheses the type of technology (NBI, FICE or i-SCAN), which was proven to be effective. The summary of the recommendations is presented in Fig. 1.

### Detection of colorectal neoplasia in average risk populations

The term "average risk population" is most widely used in the setting of CRC screening [11, 12]. For the purpose of this Guideline, this term applies to all patients outside the setting of colitis or hereditary syndromes. As a large number of colonoscopies are performed in average risk populations [13], even minor increases in neoplasia detection rates achieved in this population may

translate into a large effect on absolute numbers of CRC prevented. On the other hand, an advanced imaging technology should be very practical and cost-effective in order not to overload already stressed health care systems if it is to be recommended for average risk populations.

***ESGE suggests the routine use of high definition white-light endoscopy systems for detecting colorectal neoplasia in average risk populations (weak recommendation, moderate quality evidence).***

A meta-analysis of five studies that included 4422 average risk patients showed a 3.5% (95% confidence interval [95%CI] 0.9%–6.1%) incremental yield from high definition white-light endoscopy (HD-WLE) over standard definition white-light endoscopy (SD-WLE) for the detection of patients with at least one adenoma [14]. There were no differences between HD-WLE and SD-WLE for high risk adenomas. We postulate that the difference in the fields of view of the endoscopes that were used is unlikely to account for the increased yield observed with HD-WLE because three randomized controlled trials (RCTs), from two centers, found no significant difference in polyp detection rates between SD-WLE with 140° and 170° fields of view [15–17]. In a two-center RCT published after the meta-analysis [18], the proportion of participants in whom adenomas were detected was higher with HD-WLE compared with SD-WLE (45.7% vs. 38.6%;  $P=0.166$ ) and the difference was significant in the proportions of patients with flat adenomas (9.5% vs. 2.4%;  $P=0.003$ ) and with right-sided adenomas (34.0% vs. 19.0%;  $P=0.001$ ). The cost-effectiveness of adopting HD-WLE in routine practice was not studied. High definition colonoscopes are available from all major manufacturers. *ESGE does not suggest routine use of conventional pancolonic chromoendoscopy in average risk populations, despite its proven benefit, for practical reasons (weak recommendation, high quality evidence).*

A recent Cochrane systematic review [19] analyzed five RCTs (total 1059 patients) that assessed the role of conventional chromoendoscopy in detecting colorectal lesions outside the setting of polyposis or colitis. Pancolonic chromoendoscopy significantly increased the number of patients with at least one polyp detected (odds ratio [OR] 2.22, 95%CI 1.55–3.16) and of those with at least one dysplastic lesion detected (OR 1.67, 95%CI 1.29–2.15). A limitation of the systematic review was the significant heterogeneity observed between the studies.

Since the publication of this Cochrane systematic review, four RCTs have compared HD-WLE with conventional chromoendoscopy for detecting neoplastic lesions [20–23]. Only one of them

[22] did not find that conventional chromoendoscopy detects significantly more adenomas than HD-WLE (32.7% vs. 26.9%;  $P=0.47$ ). However this study only evaluated the detection of adenomas located in the distal colon and in the rectum. The other three studies [20, 21, 23] showed that chromoendoscopy increased the overall detection of adenomas, including flat and small adenomas. None of the studies showed an increased detection rate for advanced neoplastic lesions but none of them was sufficiently powered for this aim.

In expert hands, additional procedure duration associated with pancolonoscopic chromoendoscopy was 4–10 minutes in all studies that reported this item, i.e., a 30%–40% increase in total procedure duration [20, 23]. Additional costs associated with dyes, removal, and histopathological evaluation of additional non-neoplastic lesions and the increase in total procedure duration, coupled with the absence of evidence supporting an increased detection rate of advanced neoplasia, call against the routine use of pancolonoscopic chromoendoscopy in average risk populations.

*ESGE does not recommend routine use of virtual pancolonoscopic chromoendoscopy, AFI, or add-on devices for detecting colorectal neoplasia in average risk populations (strong recommendation, high quality evidence).*

### Virtual chromoendoscopy

Two recent meta-analyses of RCTs compared detection [24, 25] and miss rates [25] of colonic lesions in average risk populations using white-light endoscopy (WLE) and NBI. In the meta-analysis [24], of 7 RCTs, that included a total of 2936 patients, there was no significant difference in adenoma detection rate between NBI and WLE (36% vs. 34%,  $P=0.413$ ; relative risk [RR] 1.06, 95%CI 0.97–1.16). The other meta-analysis [25], included 9 RCTs [26–34] (3 studies published in abstracts only), and a total of 3059 patients. This meta-analysis also showed no difference between HD-NBI and HD-WLE for the detection of adenomas (OR 1.01, 95%CI 0.74–1.37), of patients with adenomas (OR 1.0, 95%CI 0.83–1.20), of flat adenomas (OR 1.26, 95%CI 0.62–2.57), nor in the miss rate of adenomas (OR 0.65, 95%CI 0.40–1.06). Two recent large, multicenter RCTs [18, 35] further corroborated the results of these meta-analyses.

Data on the use of FICE or i-SCAN for detection of colonic neoplasia during colonoscopy are scarce. Two RCTs [36, 37] did not find any difference between HD-FICE and HD-WLE concerning adenoma detection [36] or adenoma miss rate [37] in screening or surveillance colonoscopies. The single RCT that compared HD-i-SCAN with HD-WLE for screening colonoscopy showed no significant difference either in adenoma detection or in the adenoma miss rates [38].

NBI and FICE are often criticized for darkening the endoscopy image and in turn hampering the wider view of the colon [24]. Whether newer-generation, brighter systems make a difference in adenoma detection remains to be evaluated.

### Autofluorescence endoscopy

Five RCTs evaluating AFI for the detection of colorectal neoplasia in average risk patients have produced conflicting results [39–43]. Details of these studies are summarized in **Appendix e3** (available online). A tandem study of AFI vs. HD-WLE [41] showed significantly lower proximal adenoma miss rates with AFI. Another RCT, from Japan [42], that allocated patients to four groups: HD-WLE alone, HD-WLE+cap-assisted colonoscopy [CAC], AFI alone, AFI+CAC, found a significantly higher number of adenomas per patient in the AFI+CAC group compared with

the HD-WLE alone group. In contrast, all three tandem RCTs that were conducted in Europe have not demonstrated differences in colorectal adenoma miss rates between AFI and HD-WLE in academic settings [40, 43] or between AFI and SD-WLE in a nonacademic setting [39].

### Add-on devices

Four meta-analyses, published in 2011 and 2012, have compared the efficacy of CAC with that of regular colonoscopy [44–47]. Three of them [44–46] included between 7 and 14 RCTs for the analysis of detection of colorectal lesions; one considered available data regarding polyp detection not adequate for meta-analysis [47]. All three meta-analyses demonstrated a significantly higher polyp detection rate (by 8%–13%) but no difference in the adenoma detection rate between CAC and regular colonoscopy. Therefore, the role of CAC for the detection of colorectal neoplasia is limited.

One multicenter, tandem colonoscopy RCT compared the detection of adenomas using the “third eye” retro-scope (TER) with regular colonoscopy in an average risk population [48]. The per-protocol analysis showed that more adenomas were missed with regular colonoscopy compared with the TER (RR 1.92; 95%CI 1.07–3.44) but the difference was not statistically significant in the intention-to-treat analysis (RR 1.46,  $P=0.185$ ). The total procedure and withdrawal times were 4 and 2 minutes longer with TER, respectively, because of device manipulation and additional polypectomies. The utility of TER in routine practice is further limited by technical difficulties with the use of the device in 5% of patients [48], impaired ability to aspirate luminal contents, relatively high cost [49], and limited availability.

### Detection of colorectal neoplasia in hereditary syndromes



Advanced imaging, compared with regular colonoscopy, can potentially help in hereditary syndromes in two principal ways. First, it can assist in making a diagnosis by revealing additional lesions required to meet diagnostic criteria for sessile serrated and adenomatous polyposis syndromes [50, 51]. Second, when a hereditary CRC syndrome is diagnosed and surveillance is undertaken, advanced imaging may lead to better lesion detection thereby reducing the risk of interval cancer [52] or allowing the safe extension of surveillance intervals.

*ESGE recommends the routine use of high definition pancolonoscopic chromoendoscopy in patients with known or suspected Lynch syndrome (conventional chromoendoscopy, NBI, i-SCAN) or serrated polyposis syndrome (conventional chromoendoscopy, NBI) (strong recommendation, low quality evidence).*

Patients and family members with Lynch syndrome or serrated polyposis syndrome are recommended frequent, usually annual to biennial colonoscopy surveillance [53, 54] in order to minimize the risk of developing interval cancer [55, 56]. In both syndromes, precursor lesions are more likely to be nonpolypoid, located proximally, and difficult to recognize [54, 57, 58]. Four small tandem colonoscopy studies [59–62], showed higher detection rates of adenomas [59–61] or polyps [62] with conventional chromoendoscopy compared with SD-WLE or HD-WLE in patients with Lynch syndrome, at the cost of additional time (range 1.8 to 17

minutes per case) (the studies are summarized in [Appendix e4](#), available online).

The role of virtual chromoendoscopy in patients with Lynch syndrome was assessed in two prospective cohort studies [61, 63] and one RCT [64]. In the first cohort study [63] an additional pass with NBI significantly increased the proportion of patients detected with adenomas (absolute difference 15%, 95%CI 4%–25%) compared to a single pass with HD-WLE. In the other cohort study [61] the total numbers of adenomas and flat adenomas detected by a second pass with conventional chromoendoscopy were significantly higher than with a first pass using HD-NBI. In a tandem RCT [64] the miss rate of polyps was significantly lower with i-SCAN compared with HD-WLE (16% vs. 52%, respectively;  $P < 0.01$ ).

A tandem RCT compared specifically AFI (Xillix Technologies Corporation) with HD-WLE in patients with Lynch syndrome or familial CRC [65]. The sensitivity for the detection of adenomas was significantly higher with AFI compared with HD-WLE (92% vs. 68%,  $P = 0.01$ ). The AFI system used in this study is not widely commercially available. Although there are no studies that have assessed conventional chromoendoscopy in sessile serrated polyposis, a review that summarized serrated lesion detection in an average risk population suggested that conventional chromoendoscopy doubled the detection rate of serrated lesions, overall and in the proximal colon (no differentiation between hyperplastic and sessile serrated polyps was made) [51]. One tandem colonoscopy RCT in patients with sessile serrated polyposis [66] showed significantly lower polyp miss rates with HD-NBI compared with HD-WLE (OR 0.21; 95%CI 0.09–0.45). One pilot study showed suboptimal diagnostic accuracy of AFI in differentiation between sessile serrated polyps, hyperplastic polyps, and adenomas [67].

*ESGE does not make any recommendation for the use of advanced endoscopic imaging in patients with suspected or known familial adenomatous polyposis (FAP) including attenuated and MUTYH-associated polyposis (insufficient evidence to make a recommendation).*

Patients with classical FAP have hundreds of adenomas uniformly distributed in the colorectum while those with attenuated FAP and *MUTYH*-associated polyposis (MAP) have much fewer, more proximally distributed, adenomas. For surveillance, sigmoidoscopy is recommended in patients with classical FAP and colonoscopy in those with attenuated FAP or with MAP [68, 69]. In patients with classical FAP, conventional and virtual chromoendoscopy increase the detection rate of adenomas compared with HD-WLE [70]; however the clinical usefulness of these techniques is limited, because of the recommendation for proctocolectomy early in the course of the disease. In the context of attenuated FAP and of MAP, the usefulness of these techniques during surveillance is unknown.

Following proctocolectomy for FAP, small adenomas are better detected in the ileal pouch with conventional chromoendoscopy [71, 72] but the clinical significance of this finding is unclear.

### Detection and differentiation of colorectal neoplasia in long-standing inflammatory bowel disease

Patients with long-standing left-sided or extensive ulcerative colitis or extensive Crohn's colitis are recommended to have intensive colonoscopic surveillance because of an increased risk of CRC compared with the average risk population [53, 73]. Advanced

imaging may be of benefit by: (i) increasing the detection of dysplasia [74]; (ii) improving the differentiation of lesions (colitis associated neoplasia, sporadic neoplasia [75, 76], and non-neoplastic lesions); and (iii) reducing the number of unnecessary biopsies.

***ESGE recommends the routine use of 0.1% methylene blue or 0.1%–0.5% indigo carmine pancolonic chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing colitis. In appropriately trained hands, in the situation of quiescent disease activity and adequate bowel preparation, nontargeted four-quadrant biopsies can be abandoned (strong recommendation, high-quality evidence).***

Two sufficiently powered RCTs compared the diagnostic yield of conventional chromoendoscopy and SD-WLE [77, 78]. Additionally, one high quality meta-analysis [79] including these two RCTs and four cohort studies confirmed the overall findings in 1277 patients from a well-defined target population (disease duration > 8 years). In the meta-analysis the pooled incremental yield of conventional chromoendoscopy with random biopsies over SD-WLE with random biopsies for the detection of patients with neoplasia was 7% (95%CI 3.2%–11.3%). Moreover, the difference in proportion of lesions detected by targeted biopsies only was 44% (95%CI 28.6%–59.1%) in favor of conventional chromoendoscopy. Two prospective cohort studies [80, 81] published after the meta-analysis further corroborated the results. Overall, in 8 prospective studies comparing conventional chromoendoscopy with SD-WLE, the former consistently increased the proportion of patients found with dysplasia with a factor 2.08–3.26 [77–81].

Although in all the abovementioned studies [77–81] random four-quadrant biopsies were taken as a back-up method in conjunction with chromoendoscopy-targeted biopsies, the diagnostic yield of those back-up biopsies was rather limited. The pooled sensitivity for the detection of neoplasia with chromoendoscopy-targeted biopsies only was 86% (range 71%–100%) for all studies that reported this data and 95% (range 87%–100%) after exclusion of one study [82] in which targeted rather than pancolonic chromoendoscopy was used ([Appendix e5](#), available online; [77, 78, 80–82, 83, 84, 85]). The median number of targeted biopsies sampled per procedure was 1.3 (range 0.28–14.2) and the median number of targeted plus random biopsies per procedure was 34.3 (range 7.0–42.2).

The number of biopsies needed during conventional chromoendoscopy surveillance of long-standing colitis can therefore be significantly reduced if only targeted biopsies are taken. The case for abandoning random biopsies is further supported by evidence of poor adherence to endoscopic protocols for random biopsies in clinical practice [86]. There is however no evidence to show what the process of pancolonic chromoendoscopy training and abandoning random biopsies should look like. It has been suggested during expert discussion at the Disease Digestive Week 2009 (T.A. Ullman and R. Kiesslich) that the following logical steps should be undertaken: (i) chromoendoscopy training with an expert on at least 30 colonoscopies; (ii) chromoendoscopy with targeted and random biopsies; (iii) chromoendoscopy with random biopsies in special situations only (multiple post-inflammatory polyps, neoplasia on previous colonoscopy, etc); and (iv) chromoendoscopy with targeted biopsies only.

In studies summarized in the meta-analysis cited above [79], the duration of surveillance colonoscopy in long-standing colitis was

longer with pancolonoscopic chromoendoscopy plus random biopsies compared with SD-WLE with random biopsies, by an average 11 minutes (95%CI 10 min 15 s to 11 min 43 s). It is likely, however, that the duration of pancolonoscopic chromoendoscopy with only targeted biopsies is comparable to or shorter than that of WLE with random biopsies [84, 85].

In all prospective studies [77–81] 0.1% methylene blue or 0.1–0.5% indigo carmine solutions were used for chromoendoscopy, with no evidence for difference in their efficacy. Some concern was raised by a report on oxidative DNA damage in Barrett's epithelium caused by methylene blue in combination with photosensitization by WLE [87], but there is no clinical evidence indicating an increased risk in patients with long-standing colitis.

Limitations of conventional chromoendoscopy in the context of long-standing colitis surveillance needs to be mentioned. There is no proof that better detection of neoplasia by conventional chromoendoscopy translates into reduced CRC mortality or decreased risk of interval CRC. Cost-effectiveness is also unclear for chromoendoscopy compared to WLE plus random biopsies, although it may be cheaper when combined with risk stratification thereby entailing fewer colonoscopies and fewer histological samples [88]. It is unknown whether there would be any benefits of conventional chromoendoscopy over WLE with newer-generation HD-WLE colonoscopes. Several prerequisites are listed in the SURFACE guidelines [89], such as quiescent disease and excellent bowel preparation, which must be met in the performance of pancolonoscopic chromoendoscopy surveillance. Nevertheless the use of pancolonoscopic chromoendoscopy with only targeted biopsies for dysplasia detection in colitis is now strongly endorsed by the British Society of Gastroenterology [90], and the European Crohn's and Colitis Organization [91].

*ESGE found insufficient evidence to recommend for or against the use of virtual chromoendoscopy or autofluorescence imaging (AFI) for the detection of colorectal neoplasia in inflammatory bowel disease (insufficient evidence to make a recommendation).*

Three RCTs compared virtual chromoendoscopy (NBI in all cases) with WLE for the detection of neoplasia in long-standing inflammatory bowel disease [92–94]. Regardless of generation of NBI and the level of definition of colonoscopes used, virtual chromoendoscopy did not significantly increase the detection rate of neoplastic lesions compared with WLE [92–94]. However, in all three RCTs, virtual chromoendoscopy with targeted biopsies alone yielded neoplasia detection rates comparable to WLE with targeted and nontargeted four-quadrant biopsies [92–94]. Mean number of biopsies per patient was 0.5 to 3.5 in NBI with targeted biopsies only and 24.6 to 38.3 in WLE with targeted and random quadrant biopsies [92, 94].

Two RCTs compared an HD-NBI system with high definition conventional chromoendoscopy, both without nontargeted biopsies, for the detection of neoplasia in long-standing inflammatory bowel disease [95, 96]. The first study was a single-center, crossover RCT aimed at comparing neoplasia miss rates with HD-NBI and high definition conventional chromoendoscopy [95]. The miss rate of neoplastic lesions was considerably higher with HD-NBI compared with high-definition conventional chromoendoscopy (31.8% and 13.6%, respectively) but the study was not powered enough to test the observed difference for statistical significance. The second study was a multicenter, parallel group RCT aimed at comparing neoplasia detection rates with HD-NBI and high definition conventional chromoendoscopy [96]. Preliminary results (108 of 134 planned patients have been included) showed similar neoplasia detection rates for NBI and conventional chro-

moendoscopy, per lesion (24.0% and 17.2%, respectively;  $P=0.385$ ) and per patient (18.5% and 16.7%, respectively). Median withdrawal time was significantly shorter in the NBI group compared to the chromoendoscopy group (21 vs. 27 minutes, respectively;  $P=0.003$ ).

There were only two studies, of which one was an RCT, comparing HD-WLE with AFI for the detection of colorectal neoplasia in inflammatory bowel disease [94, 97]. A pilot study [97] showed that protruding lesions with a low autofluorescence signal were significantly more likely to be neoplastic than lesions with a high autofluorescence signal (45.0% vs. 13.3%, respectively,  $P=0.043$ ). In the RCT, the miss rate for neoplastic lesions was statistically significantly lower with AFI compared with HD-WLE (0% vs. 50%,  $P=0.036$ ). It should be noted that inadequate bowel preparation and active inflammation interrupt tissue autofluorescence, resulting in discoloration on AFI and resembling neoplasia [97]. Further studies including comparison with conventional chromoendoscopy are needed.

*ESGE recommends taking biopsies from flat mucosa surrounding neoplastic lesions and taking biopsies from or resecting all suspicious lesions identified at neoplasia surveillance in long-standing colitis, because there is no evidence that nonmagnified conventional or virtual chromoendoscopy can reliably differentiate between colitis-associated and sporadic neoplasia or between neoplastic and non-neoplastic lesions (strong recommendation, low to moderate quality evidence).*

### Neoplastic vs. non-neoplastic lesions

A modified pit pattern classification has been used in three conventional chromoendoscopy studies to differentiate between neoplastic and non-neoplastic lesions in long-standing inflammatory bowel disease [77, 80, 82]. The surface staining pattern allowed differentiation between neoplastic and non-neoplastic lesions with high sensitivity and specificity (93%–100% and 88%–97%, respectively) [77, 80, 82]. However, in the reported studies magnifying endoscopes, which are not widely available, were used for lesion characterization and total procedure times were on average 9–11 minutes longer. No studies report on differentiation between neoplastic and non-neoplastic lesions in inflammatory bowel disease using nonmagnifying colonoscopes with conventional chromoendoscopy.

Four studies evaluated the role of non-magnified NBI in differentiating neoplastic and non-neoplastic lesions in patients with long-standing colitis [94, 98–100]. One case report [100] and one pilot study [99] showed that a tortuous pit pattern and a high vascular pattern intensity may help to distinguish neoplastic and non-neoplastic lesions in long-standing colitis. In two small RCTs [94, 98] the sensitivity and specificity of NBI in predicting histology were unsatisfactory. In one of these RCTs [94] combining AFI with NBI increased sensitivity for predicting histology from 75% to 100% without a major drop in specificity. No other virtual chromoendoscopy systems were assessed for differentiation of lesions in the setting of colitis.

### Colitis-associated vs. sporadic neoplasia

Current guidelines suggest taking biopsies from the flat mucosa surrounding neoplastic lesions in long-standing colitis, because differentiation between colitis-associated and sporadic neoplasia is crucial in determining their optimal management [73, 90]. Although it has been suggested that conventional chromoendoscopy cannot distinguish these two entities because of a similar staining pattern [89], it has recently been shown that magnifying

conventional chromoendoscopy combined with NBI can be useful for this purpose if the borders of the circumscribed lesion are thoroughly assessed [75]. This finding has to be confirmed by larger and more robust studies.

### Differentiation between neoplastic and non-neoplastic diminutive colorectal polyps

It is current practice to resect all colorectal polyps and to send them for histological analysis. This is expensive and generates a large burden of work for histopathology departments. In considering diminutive polyps ( $\leq 5$  mm in size), which represent approximately 60% of all polyps detected at primary screening colonoscopy [101, 102], the main goal of histological examination is to differentiate between neoplastic and non-neoplastic lesions in order to determine the need and timing for surveillance colonoscopy. Techniques for optical diagnosis using advanced imaging have been developed which have the potential to supplement or replace formal histological diagnosis with in vivo optical diagnosis [103–105]. A “resect and discard” policy has been proposed which suggests making a real-time optical diagnosis of diminutive colorectal polyps using advanced imaging, photodocumenting them, and resecting and discarding them without histological assessment [103]. This could not only reduce costs for histological assessment but also allow an immediate recommendation regarding the interval to the next colonoscopy [106]. It was further proposed to photodocument and leave in situ diminutive polyps in the rectosigmoid region considered to be non-neoplastic at optical diagnosis [106]. A recent statement from the American Society for Gastrointestinal Endoscopy [106] (Preservation and Incorporation of Valuable endoscopic Innovations [PIVI] statement) has attempted to set standards against which a technology should be assessed in order to be deemed suitable for applying a policy of resect and discard ( $\geq 90\%$  agreement in assignment of post-polypectomy surveillance intervals when compared with decisions based on pathology assessment) or a policy of leaving suspected non-neoplastic polyps in place ( $\geq 90\%$  negative predictive value, when used with high confidence).

**ESGE suggests that virtual chromoendoscopy (NBI, FICE, i-SCAN) and conventional chromoendoscopy can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive ( $\leq 5$  mm) colorectal polyps to replace histopathological diagnosis. The optical diagnosis has to be reported using validated scales, must be adequately photodocumented, and can be performed only by experienced endoscopists who are adequately trained and audited (weak recommendation, high quality evidence).**

Major concerns regarding the use of optical diagnosis techniques are that advanced pathology (i.e. high grade dysplasia, tubulovillous or villous morphology) and cancers might be missed, leading to setting of inappropriate surveillance intervals or suboptimal treatment. However, the risk estimates for advanced pathology are low for polyps  $\leq 5$  mm in size (ranging from 0.1% to 26%, with most estimates tending towards the lower end of this range; [Appendix e6](#), available online; [102, 105, 107–132]). Moreover, data are limited on the importance of advanced pathology in small and diminutive polyps in terms of the future risk of advanced pathology or cancer. This is further confounded by the poor agreement between even expert pathologists for the diagnosis of villosity or high grade dysplasia, with 10-fold variation

in rates [133–135]. Given this variability, British guidelines have chosen to ignore these characteristics and use size only as a criterion, and United European guidelines have chosen to add them as accessory criteria, whereas the ESGE and American guidelines use these features to determine surveillance intervals [90, 136–138]. A second concern is the rate of carcinoma in diminutive polyps which is very low but not negligible (the risk estimate for lesions  $\leq 5$  mm ranges from 0% to 0.6%, again with most estimates at the lower end of the range; see the summary of evidence in [Appendix e6](#)). Although it is unknown whether diminutive cancer polyps harbor the same characteristics as larger cancer polyps at endoscopic examination, it is generally recommended that optical biopsy be avoided in suspicious lesions (e.g. depressed lesions, Paris classification 0-IIc) [139], which might further reduce the risk of missing a cancer.

A meta-analysis that included 56 studies [9] showed that the overall sensitivity and specificity of NBI for differentiation between neoplastic and non-neoplastic colorectal polyps were 91.0% (95%CI 88.6%–93.0%) and 85.6% (95%CI 81.3%–89.0%), respectively. In a subset of real-time assessment studies, the negative predictive value (NPV) was 82.5% (95%CI 75.4%–87.9%). For FICE, this meta-analysis included 14 studies; the corresponding overall sensitivity, specificity and NPV were 91.8% (95%CI 87.1%–94.9%), 83.5% (95%CI 77.2%–88.3%), and 83.7% (95%CI 77.5%–88.4%). For i-SCAN this meta-analysis included 10 studies; the corresponding overall sensitivity, specificity and NPV were 89.3% (95%CI 83.3%–93.3%), 88.2% (95%CI 80.3%–93.2%), and 86.5% (95%CI 78.0%–92.1%). For AFI this meta-analysis included 11 studies; the corresponding overall sensitivity, specificity and NPV were 86.7% (95%CI 79.5%–91.6%), 65.9% (95%CI 50.9%–78.2%), and 81.5% (95%CI 54.0%–94.3%). There were no significant differences between real-time versus post-procedure studies [9]. The effect of high definition on diagnostic performance of real-time assessments remains uncertain [9, 140]. The abovementioned results for NBI are in accordance with those reported in another recent meta-analysis [141]. The diagnostic performance of optical diagnosis for NBI, FICE and i-SCAN (not AFI) would be acceptable for clinical use according to PIVI requirements and it should be possible to estimate surveillance intervals with NBI, FICE or i-SCAN with at least 90% accuracy [106]. Although NPVs did not quite meet the 90% standard set in the PIVI, most studies looked at polyps throughout the colon and not just rectosigmoid diminutive lesions. Conventional chromoendoscopy shows similar accuracy in differentiating between neoplastic and non-neoplastic polyps [36, 142], but because of inconvenience and costs associated with the use of dyes it is unlikely to be adopted in routine clinical practice.

Although there is now significant evidence for using virtual chromoendoscopy-based optical diagnosis, most data come from enthusiasts or experts and may not represent the actual performance by community gastroenterologists [143–145]. Indeed available data suggest a significant interobserver variability ([Appendix e7](#), available online; [104, 121, 122, 124, 146–152]) and learning curve [153, 154], which can to some extent be rapidly surmounted with training [155–158], but achievement of the performance reported by experts may take longer [143]. No universal training system for differentiation between neoplastic and non-neoplastic colorectal polyps has yet been established, but all of three computer-based training modules using still photographs [155, 156, 158] achieved significant improvement in accuracy, and one using videos resulted in improvements both in accuracy and in the number of “high confidence” assessments

[157]. With the use of validated scales, such as the NBI International Colorectal Endoscopic (NICE) classification [159], diagnostic accuracy of in vivo optical diagnosis will likely improve, and interobserver variability decrease. However, it has to be emphasized that new or updated scales should incorporate sessile serrated polyps/adenomas in their classification systems [160].

Computer algorithms that analyze the polyp image may be able to support clinician decision making at optical biopsy and help community-based gastroenterologists to meet the required standards. Four studies reported on the diagnostic performance of computer-aided classification systems for NBI images, showing 82%–98% sensitivity and 61%–98% specificity for differentiation between neoplastic and non-neoplastic colorectal polyps [161–164]. Computer-aided diagnostic performance appears to be improving with two recent large NBI studies reporting diagnostic accuracy equivalent to expert readers [163, 164]; however magnifying endoscopes were used in these studies, making use in the community challenging.

There are currently no data to suggest what kind of documentation is needed for the resect and discard policy. The PIVI document [106] stated that, as an endoscopic photograph rather than a histology slide becomes the record of a small polyp, photographs must be stored to be used not only as evidence of adenoma detection but also of accuracy of optical diagnosis. This poses significant challenges at present, especially with regard to recording in high definition and the available disk space on servers in endoscopy units.

There is moderate quality evidence from several large and well conducted studies that in vivo optical diagnosis using NBI or FICE would be a cost-effective alternative to histology especially for diminutive polyps [103, 165–167] (► **Appendix e8**, available online). No studies to date have looked at i-SCAN for this purpose, although it shows a similar degree of accuracy as NBI and hence the findings on cost-effectiveness would be transferable. Two British prospective cohort studies [103, 166] and one American retrospective multicenter cohort study [165] showed a simple reduction in costs of histopathology of €62–€210 per colonoscopy associated with the use of a resect and discard policy. A Markov modelling study showed that a resect and discard policy applied to a US screening population [167] would allow for annual undiscounted savings of \$33 million/year (\$25 [€20]/person) with negligible impact on surveillance intervals or screening efficacy. Concerns associated with the data used for model analysis include: (i) the use of US and UK models of screening for CRC, which may not be simply transferred to the various screening programs in use in Europe; (ii) the use of assumptions derived from studies performed by experts; and (iii) the exclusion of costs associated with implementation of the resect and discard policy (training for and photodocumentation of real-time diagnosis).

### Advanced endoscopic imaging in the treatment of neoplasia

Advanced endoscopic imaging techniques can be particularly suited for optimizing the endoscopic resection of large sessile or nonpolypoid colorectal lesions and for post-resection surveillance. Such lesions scheduled for endoscopic resection require adequate delineation of margins, prediction of the risk of invasive cancer and deep submucosal invasion, and thorough post-resection surveillance for residual neoplasia. These lesions should be removed by level 4 competent endoscopists [168], who usually

work at tertiary referral centers, where advanced endoscopic imaging is often readily available.

**ESGE suggests the use of conventional or virtual (NBI) magnified chromoendoscopy to predict the risk of invasive cancer and deep submucosal invasion in lesions such as those with a depressed component (0-IIc according to the Paris classification) or nongranular or mixed-type laterally spreading tumors (weak recommendation, moderate quality evidence).**

Superficially invasive submucosal CRCs are amenable to endoscopic resection under strictly controlled criteria [169, 170]. Advanced endoscopic imaging may help to differentiate between noninvasive lesions and superficially invasive submucosal cancers so that the appropriate endoscopic removal technique can be used and the resection site tattooed. In addition, advanced imaging may help to predict the risk of deep submucosal cancer which is associated with increased risk of lymph node metastases and perforation and bleeding, and requires surgical treatment [169–171].

### Risk of submucosal invasion

Certain mucosal and vascular patterns of colorectal lesions have been associated with the risk of submucosal (or deeper) cancer being found at histological examination [172, 173]. At magnifying chromoendoscopy, a Kudo V pit pattern predicted a substantially higher risk of invasive cancer compared with non-V pit patterns (II–IV). In detail, pit pattern V has been associated with a risk of deep submucosal cancer greater than 40%, and it has been further divided in two subtypes, namely Vi (irregular) and Vn (nonstructured), which have been associated with a 20%–30% and >90% risk of submucosal invasion, respectively [172, 174–176]. The sensitivity of pit pattern V for the diagnosis of submucosal (or deeper) cancer was 85% in a large Japanese series and 79% in a European cohort study [176, 177]. A few studies also addressed whether the classification of the vascular pattern or combined vascular–surface pattern of the lesion at magnifying virtual chromoendoscopy was able to predict the risk of underlying malignancy. In Japanese series, an irregular or a sparse vascular pattern on magnified NBI have been associated, with a 50% or >90% risk, respectively, of submucosal (or deeper) cancer, such risk being marginal in those lesions with other vascular patterns [173, 178, 179].

### Depth of submucosal invasion

Several endoscopic studies addressed whether mucosal or vascular patterns at magnifying chromoendoscopy are able to predict the level of submucosal invasion. A Japanese series showed that pit pattern Vn was highly predictive of deep submucosal invasion (100%), whilst such a risk broadly ranged between 17%–85% in those with pit pattern Vi [176]. For this reason, it has been proposed to further subclassify pit pattern Vi, according to the severity of the irregularity in the mucosal pattern. In particular, the risk of deep submucosal invasion has been shown to be very high in those with more severe irregularity [175, 180, 181].

Factors other than pit pattern have also been considered as predictors of deep submucosal invasion at magnifying colonoscopy. Two studies showed that some morphological characteristics at magnifying colonoscopy—including fold convergence, an expansive appearance, an irregular surface contour, a demarcated depressed area, or a >1 cm nodule—predicted deep submucosal invasion with a higher sensitivity and equal specificity compared



with the nonlifting sign [182, 183]. In a recent large prospective analysis, combined mucosal and morphological invasive patterns at magnifying conventional chromoendoscopy have been confirmed to be highly predictive of deep submucosal invasion with a 98.8% overall accuracy [184]. Vascular pattern at magnified NBI has also been associated with the depth of cancer invasion. In particular, an irregular/sparse or severely irregular pattern has been shown to be predictive of deep submucosal invasion with sensitivity and specificity of 83%–100% and 72%–100%, respectively [173, 176].

The predictions of submucosal invasion and depth of invasion at magnified virtual or conventional chromoendoscopy have however never been compared with routine predictions made by endoscopists at nonmagnified WLE, which means that we do not know the added value of advanced imaging over routine practice. Moreover, magnifying colonoscopes are not yet widely available in Europe so the applicability of assessments based on magnified views may be limited.

Recently, an expanded NICE classification for the characterization of deep submucosal cancer has been proposed [185]. Its advantages are the use of nonmagnified views and objective criteria for assessing deep submucosal invasion. On the other hand the overall accuracy of the expanded NICE classification for diagnosing submucosal invasion was relatively low (70% and 50% high confidence predictions, with 84% and 90% accuracy for experts and trained novices, respectively), and the scale was validated using only still images. The ability to predict the risk of submucosal (or deeper) cancer using different virtual chromoendoscopy systems was not assessed.

Irrespective of the accuracy of magnified or nonmagnified virtual or conventional chromoendoscopy in predicting potential submucosal invasion, it is questionable whether such techniques should be applied to all lesions. Their clinical impact would necessarily depend also on the expected prevalence of submucosal (or deeper) invasion. In large Japanese, US, and European series, the risk of submucosal (or deeper) cancer appeared to be low (<2%) in 0-IIa or 0-IIb lesions, as well as in homogeneous granular-type laterally spreading tumors (LSTs) [176, 186–192]. Such a risk appeared to be substantially higher (up to 36%) for nonpolypoid lesions with a depressed component (0-IIc) and nongranular or mixed LSTs [176, 186–192]. The addition of mucosal and vascular pattern stratification, using virtual or conventional chromoendoscopy, to the morphological classification of nonpolypoid lesions and presence or not of the nonlifting sign may be the most informative way to guide decisions on whether to undertake endoscopic or surgical resection.

*ESGE recommends the use of virtual or conventional chromoendoscopy to define the margins of large nonpolypoid or otherwise indistinct lesions before or during endoscopic resection (strong recommendation, very low quality evidence).*

Incomplete resection has been suggested to contribute significantly to the risk of interval or post-polypectomy CRC [193, 194]. Recently it has been shown that incomplete resection of 5–20 mm neoplastic polyps occurs in approximately 10% of cases and that this risk significantly increases with polyp size and sessile serrated histology [195]. Therefore, advanced endoscopic imaging may be particularly useful to assist with endoscopic resection of large nonpolypoid or otherwise indistinct lesions. Despite the fact that many centers commonly use conventional chromoendoscopy to delineate large sessile or nonpolypoid colorectal lesions prior to endoscopic resection (either surface staining [196, 197] or stain solution injection [198, 199]) the evidence

**Table 2** Key topics for further research.

|                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. What are the neoplasia detection rates of conventional chromoendoscopy, virtual chromoendoscopy, and autofluorescence imaging compared with high definition white-light endoscopy (HD-WLE) in patients with Lynch syndrome (tested in a multicenter, parallel group randomized controlled trial [RCT])? Does advanced imaging reduce interval colorectal cancer (CRC) rates or allow extension of colonoscopy surveillance intervals? |
| 2. What is the role of conventional or virtual chromoendoscopy in the diagnosis and surveillance of patients with sessile serrated polyposis?                                                                                                                                                                                                                                                                                            |
| 3. What is the role of advanced imaging in the diagnosis of attenuated familial adenomatous polyposis (FAP) and <i>MUTYH</i> -associated polyposis in patients with multiple adenomas?                                                                                                                                                                                                                                                   |
| 4. What are the neoplasia detection rates of newer-generation narrow band imaging (NBI) and other virtual chromoendoscopy systems in long-standing inflammatory bowel disease?                                                                                                                                                                                                                                                           |
| 5. Does conventional chromoendoscopy allow the lengthening of colonoscopy surveillance intervals in long-standing colitis or reduce interval cancer rates? How should endoscopists be trained in conventional chromoendoscopy, and at what point on the learning curve can we abandon random, four-quadrant biopsies?                                                                                                                    |
| 6. What are the neoplasia detection rates of conventional chromoendoscopy compared with HD-WLE, autofluorescence imaging, and virtual chromoendoscopy in long-standing inflammatory bowel disease?                                                                                                                                                                                                                                       |
| 7. What is the role of advanced imaging in differentiation between colitis-associated neoplasia and sporadic neoplasia in long-standing inflammatory bowel disease?                                                                                                                                                                                                                                                                      |
| 8. What is the role of nonmagnified advanced imaging in differentiation between neoplastic and non-neoplastic lesions in long-standing inflammatory bowel disease?                                                                                                                                                                                                                                                                       |
| 9. What is the diagnostic accuracy of virtual chromoendoscopy for differentiation of diminutive rectosigmoid polyps? What is the performance of community endoscopists when using validated classification scales?                                                                                                                                                                                                                       |
| 10. What is the diagnostic accuracy of virtual chromoendoscopy for differentiation of diminutive sessile serrated lesions from hyperplastic polyps? How should sessile serrated polyps be incorporated into new or updated classification systems?                                                                                                                                                                                       |
| 11. What is the performance of virtual chromoendoscopy for differentiating between neoplastic and non-neoplastic diminutive polyps by community gastroenterologists using validated scales? What is the role of computer-aided diagnosis?                                                                                                                                                                                                |
| 12. What is the diagnostic accuracy of advanced imaging techniques for detection of residual neoplasia at endoscopic mucosal resection (EMR) or piecemeal polypectomy scars?                                                                                                                                                                                                                                                             |
| 13. What is the diagnostic accuracy of advanced imaging techniques for delineation of colorectal neoplasia before endoscopic removal?                                                                                                                                                                                                                                                                                                    |

that this results in more radical resection is very weak. One large prospective, single-center study assessed the usefulness of high magnification conventional chromoendoscopy in predicting completeness of endoscopic mucosal resection (EMR) based on pit pattern analysis of resection margins [196]. High magnification conventional chromoendoscopy yielded 80% sensitivity for predicting remnant neoplastic tissue at resection margins. In another study, high magnification endoscopy alone was used to predict remnant neoplastic tissue at piecemeal polypectomy sites, with 98% sensitivity and 90% specificity [200]. This approach, however, has never been tested against WLE assessment, and requires high magnification endoscopes. The usefulness of submucosal injection using methylene blue solution has been formally assessed only in one pilot study of 25 polyps and using subjective criteria [201].

No studies were found that compared focal, surface application of dyes or virtual chromoendoscopy with WLE for delineation of colorectal neoplasia before endoscopic removal. Despite the lack of evidence, conventional or virtual chromoendoscopy can be advised for delineation of colorectal lesions because it offers potential benefit at relatively low time and cost.

*ESGE recommends the use of virtual or conventional chromoendoscopy in addition to white light endoscopy for the detection of residual neoplasia at a piecemeal polypectomy scar site (strong recommendation, low quality evidence).*

Large sessile or nonpolypoid colon polyps are often removed in a piecemeal fashion which is associated with a mean recurrence rate of 25% [202]. Professional societies recommend endoscopic follow up at 2 to 6 months after piecemeal resection of colorectal polyps to check for residual neoplasia [136, 137]. HD-WLE alone identifies 69% to 83% of recurrences revealed by targeted and random biopsies [202, 203]. One study on high definition virtual chromoendoscopy and one study on high magnification conventional chromoendoscopy showed that advanced imaging identified neoplastic lesions that were not detected using SD-WLE or HD-WLE alone [204, 205]. One prospective study showed that high magnification conventional chromoendoscopy without random biopsies detected all 8 recurrences evidenced over 2 years of endoscopic follow-up in patients who underwent EMR of LSTs [206]. However a recent study [203] showed poor sensitivity and specificity of high definition virtual chromoendoscopy (72% and 78%, respectively) in predicting neoplastic histology of EMR scars as compared with conventional histopathology. Further studies are needed to establish whether the diagnostic accuracies of conventional or virtual chromoendoscopy are high enough to justify abandoning biopsy of macroscopically normal EMR or piecemeal polypectomy scars.

### Key topics for further research

Despite a thorough literature search some of the key questions remained unanswered and other research questions were formulated as a consequence of the analysis of the available evidence.

• **Table 2** summarizes key topics for further research in advanced imaging for the detection and differentiation of colonic neoplasia.

### Use of the guideline

**Caution:** In addition to the legal disclaimer applicable to all ESGE guidelines [10], it is mentioned that methylene blue is contraindicated in individuals with glucose-6-phosphate dehydrogenase deficiency.

ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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## Appendix e1 – e8

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**Appendix e1** Chapter structure, task forces and key questions.

**General remark:** Techniques still under development such as confocal, endocytoscopy, optical coherence tomography are not be included in this Guideline.

| Task force I. Detection of colorectal neoplasia in average risk population                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Task forces (leaders in bold) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| <ul style="list-style-type: none"> <li>– What is the efficacy of conventional chromoendoscopy compared with white-light endoscopy for the detection of colorectal neoplasia in an average-risk population?</li> <li>– What is the additional time and cost associated with the use of conventional chromoendoscopy?</li> <li>– Is this method applicable to an average-risk population?</li> </ul>                                                                                                                                                                                                                                                    | Ana Ignjatovic                |
| <ul style="list-style-type: none"> <li>– What is the efficacy of virtual chromoendoscopy (NBI, FICE, i-SCAN) compared with white-light endoscopy for the detection of colorectal neoplasia in an average-risk population?</li> <li>– What is the additional time and cost associated with the use of virtual chromoendoscopy?</li> </ul>                                                                                                                                                                                                                                                                                                              | <b>Jürgen Pohl</b>            |
| <ul style="list-style-type: none"> <li>– What is the efficacy of autofluorescence imaging compared with white-light endoscopy for the detection of colorectal neoplasia in an average-risk population?</li> <li>– What is the additional time and cost associated with the use of autofluorescence imaging?</li> </ul>                                                                                                                                                                                                                                                                                                                                | Maria Pellisé                 |
| <ul style="list-style-type: none"> <li>– What is the efficacy of high definition white-light endoscopy compared with standard white-light endoscopy for the detection of colorectal neoplasia in an average-risk population?</li> <li>– What is the additional cost associated with the use of high definition endoscopy?</li> </ul>                                                                                                                                                                                                                                                                                                                  | Arthur Hoffman                |
| <ul style="list-style-type: none"> <li>– What is the efficacy of white light endoscopy plus add-on devices (e. g. third eye retroscope [TER], cap-assisted colonoscopy) compared with white-light endoscopy only for the detection of colorectal neoplasia in an average-risk population?</li> <li>– What is the additional time and cost associated with the use of add-on devices?</li> </ul>                                                                                                                                                                                                                                                       | Jean-Marc Dumonceau           |
| <p><b>Task force II.</b> Detection of colorectal neoplasia in hereditary syndromes including Lynch syndrome, familial adenomatous polyposis (FAP), attenuated FAP and <i>MUTYH</i>-associated polyposis (MAP), serrated polyposis and Peutz – Jeghers syndrome</p> <ul style="list-style-type: none"> <li>– What is the efficacy of virtual chromoendoscopy (NBI, FICE, i-SCAN) compared with white-light endoscopy for the detection of colorectal neoplasia in hereditary syndromes?</li> <li>– What is the additional time and cost associated with the use of virtual chromoendoscopy?</li> </ul>                                                 | <b>Maria Pellisé</b>          |
| <ul style="list-style-type: none"> <li>– What is the efficacy of conventional chromoendoscopy compared with white-light endoscopy for the detection of colorectal neoplasia in hereditary syndromes?</li> <li>– What is the additional time and cost associated with the use of conventional chromoendoscopy? Is this method applicable to a high risk population?</li> </ul>                                                                                                                                                                                                                                                                         | Gaius Longcroft-Wheaton       |
| <ul style="list-style-type: none"> <li>– What is the efficacy of other advanced endoscopic techniques for the detection of colorectal neoplasia in hereditary syndromes?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | James East                    |
| <ul style="list-style-type: none"> <li>– What is the efficacy of other advanced endoscopic techniques for the detection of colorectal neoplasia in hereditary syndromes?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Evelien Dekker                |
| <p><b>Task force III.</b> Detection and differentiation of colorectal neoplasia in inflammatory bowel disease (IBD)</p> <ul style="list-style-type: none"> <li>– What is the efficacy of conventional pan-chromoendoscopy compared with four-quadrant random biopsies for the detection of colorectal neoplasia in IBD?</li> <li>– What is the time and number of biopsies needed to perform pan-chromoendoscopy compared with four-quadrant random biopsies? What is the preferable type, amount, and concentration of the stain to be used?</li> <li>– Should it be recommended for surveillance in all patients with long-standing IBD?</li> </ul> | <b>Raf Bisschops</b>          |
| <ul style="list-style-type: none"> <li>– What is the efficacy of virtual chromoendoscopy compared with four-quadrant random biopsies or conventional pan-chromoendoscopy for the detection of colorectal neoplasia in IBD?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                 | Michał F. Kamiński            |
| <ul style="list-style-type: none"> <li>– What is the efficacy of other advanced endoscopic techniques for the detection of colorectal neoplasia in IBD?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>Raf Bisschops</b>          |
| <ul style="list-style-type: none"> <li>– What is the efficacy of pan-chromoendoscopy/virtual chromoendoscopy compared with white-light endoscopy for differentiation of colorectal neoplasia in IBD?</li> <li>– Is there a reduction in the number of biopsies if these techniques are combined?</li> </ul>                                                                                                                                                                                                                                                                                                                                           | Arthur Hoffman                |
| <p><b>Task force IV.</b> Differentiation between neoplastic and non-neoplastic small colorectal polyps</p> <ul style="list-style-type: none"> <li>– What is the efficacy of advanced endoscopic imaging compared with white-light endoscopy for differentiation between neoplastic and non-neoplastic small colorectal polyps?</li> </ul>                                                                                                                                                                                                                                                                                                             | Evelien Dekker                |
| <ul style="list-style-type: none"> <li>– What are the implications of a resect and discard strategy for post-polypectomy follow-up and cost – effectiveness?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Gaius Longcroft-Wheaton       |
| <ul style="list-style-type: none"> <li>– What is the prevalence of advanced colorectal neoplasia in colorectal polyps less than 6 mm (10 mm)?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Denis Heresbach               |
| <ul style="list-style-type: none"> <li>– What is the interobserver variability in differentiation between neoplastic and non-neoplastic colorectal polyps?</li> <li>– Is there a training system for differentiation between neoplastic and non-neoplastic colorectal polyps?</li> </ul>                                                                                                                                                                                                                                                                                                                                                              | Ana Ignjatovic                |
| <ul style="list-style-type: none"> <li>– What kind of documentation is needed for the resected and discarded polyps?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Ana Ignjatovic                |
| <ul style="list-style-type: none"> <li>– Role of computer-aided characterization</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>James East</b>             |
| <p><b>Task force V.</b> Advanced endoscopic imaging aided treatment of neoplasia</p> <ul style="list-style-type: none"> <li>– What is the efficacy of advanced endoscopic imaging for differentiation of malignant and non-malignant colorectal neoplasia?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                 | Cesare Hassan                 |
| <ul style="list-style-type: none"> <li>– What is the efficacy of advanced endoscopic imaging for determining the depth of invasion in early colorectal cancer?</li> <li>– How does it compare with submucosal injection?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                   | Cesare Hassan                 |
| <ul style="list-style-type: none"> <li>– What is the efficacy of advanced endoscopic imaging for demarcating the margins of EMR/ESD?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Ana Ignjatovic                |
| <ul style="list-style-type: none"> <li>– What is the efficacy of advanced endoscopic imaging for the detection of post-polypectomy/post-EMR scars and residual/recurrent colorectal neoplasia?</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>Michał F. Kamiński</b>     |

NBI, narrow band imaging; FICE, Fujinon Intelligent Color Enhancement; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection



**Appendix e2a** Levels of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [8].

| Evidence level                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High quality                  | One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Moderate quality              | RCTs with important limitations (i. e. biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case – control analytic studies, and multiple time series with or without intervention are in this category. It also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate. |
| Low quality                   | Observational studies would typically be rated as low quality because of the risk for bias. <sup>1</sup> It also means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate.                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Very low quality <sup>2</sup> | Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

<sup>1</sup> Quality of evidence based on observational studies may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose – response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

<sup>2</sup> Insufficient evidence to determine for or against routinely providing a service.

**Appendix e2b** Strength of recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [8].

| Strength of recommendation |                                                                                             |
|----------------------------|---------------------------------------------------------------------------------------------|
| Strong                     | Benefits clearly outweigh risks and burden or vice-versa. Usually stated as “we recommend”. |
| Weak                       | Benefits closely balanced with risks and burden. Usually stated as “we suggest”.            |

**Appendix e3** Summary of evidence from randomized controlled trials (RCTs) on the use of autofluorescence (AFI) for the detection of colorectal neoplasia in an average risk population.

| Authors Publication, Year                                  | Study design Study objectives                                                                                                                                                                                                                                     | Intervention                                                        | Participants                                                                                                                                                                                                | Outcomes                                                                              | Results                                                                                                                                                                                                                          | Level of evidence Conclusions                                                              |
|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Matsuda et al. Am J Gastroenterol, 2008 [41]               | Prospective Right colon Tandem colonoscopy Random order Pilot study Academic hospital Evaluate AFI for the detection of polyps in the right colon                                                                                                                 | AFI → HD-WLE<br>HD-WLE → AFI<br>From cecum to splenic flexure       | Average risk<br>No sample size calculation<br>n = 167                                                                                                                                                       | Polyps/adenoma detection<br>Polyps/adenoma miss rate                                  | Polyp miss-rate:<br>AFI 30% vs. HD-WLE 49%<br>( <i>P</i> = 0.01)<br>Adenoma miss-rate:<br>AFI 29% vs. HD-WLE 47%<br>( <i>P</i> = 0.02)<br>AFI detects more flat polyps.                                                          | Moderate quality<br>AFI is useful for the detection of right-sided lesions                 |
| Van den Broek et al. Clin Gastroenterol Hepatol, 2009 [40] | Prospective Segmental tandem Random order Academic hospital Compare AFI with HD-WLE for adenoma detection<br>Compare AFI with NBI for differentiation of adenomas from non neoplastic polyps                                                                      | HD-WLE → AFI<br>AFI → HD-WLE                                        | High risk patients (history of CRC; HNPCC), n = 38<br>Family history of CRC, n = 24<br>Sample size calculation<br>n = 50                                                                                    | Adenoma miss rate                                                                     | Adenoma miss-rate:<br>AFI 20% vs. HD-WLE 29%<br>( <i>P</i> = 0.351)<br>Mean adenoma detection rate per patient:<br>AFI 0.64 vs. HD-WLE 0.70                                                                                      | Moderate quality<br>AFI did not reduce the adenoma miss rate compared with HD-WLE          |
| Takeuchi et al. Gastrointest Endosc., 2010 [42]            | Prospective 2×2 factorial designed Randomized Controlled Tertiary cancer center To evaluate the efficacy of AFI with transparent cap (CAC) for detection of colorectal neoplasms                                                                                  | 4 groups:<br>1. HD-WLE<br>2. HD-WLE + CAC<br>3. AFI<br>4. AFI + CAC | Average risk patients<br>Sample size calculation<br>n = 561                                                                                                                                                 | Colorectal neoplasm detection rate between HD-WLE and AFI + CAC                       | Neoplasm detection rate:<br>AFI + CAC = 1.96 [1.50 – 2.43] vs. HD-WLE = 1.19 [0.93 – 1.44]<br>( <i>P</i> = 0.023)<br>AFI detected more flat lesions than WLE<br>(0.41 vs. 0.31)                                                  | High quality<br>AFI + CAC detected more colorectal neoplasm than HD-WLE                    |
| Kuiper et al. Gastroenterology, 2011 [39]                  | Prospective Segmental tandem Randomized Controlled trial Non academic setting Compare endoscopic trimodal imaging (ETMI; AFI + NBI) with standard white light endoscopy (SD-WLE) in the detection (with AFI) and differentiation (with NBI) of colorectal lesions | HD-WLE → ETMI<br>SD-WLE → SD-WLE                                    | High risk patients (history of CRC; HNPCC), n = 41<br>Family history of CRC and polyps surveillance, n = 203<br>Sample size calculation<br>n = 234 patients<br>ETMI group, n = 118<br>SD-WLE group, n = 116 | Number of adenomas detected in each arm<br>Number of patients with at least 1 adenoma | Adenoma detection rate:<br>ETMI 1.03 vs. SD-WLE 0.97<br>( <i>P</i> = 0.36)<br>Adenoma miss-rate:<br>HD-WLE 29% vs. SD-WLE 28%<br>Inspection time:<br>ETMI group > SD-WLE group<br>(7.06 min vs. 6.18 min)<br>( <i>P</i> = 0.025) | High quality<br>ETMI did not improve the detection rate for adenomas compared with HD-WLE. |

**Appendix e4** Mean withdrawal time, number of polyps per patient and number of adenomas per patient in studies using conventional chromoendoscopy compared with standard definition or high definition white-light endoscopy (WLE) for colonoscopic surveillance in Lynch syndrome.

| Study design                                             | Patients, n     | Mean withdrawal time, min |                 | Mean number of polyps per patient |                 | Mean number of adenomas per patient |                 |
|----------------------------------------------------------|-----------------|---------------------------|-----------------|-----------------------------------|-----------------|-------------------------------------|-----------------|
|                                                          |                 | WLE                       | Chromoendoscopy | WLE                               | Chromoendoscopy | WLE                                 | Chromoendoscopy |
| <i>Tandem, sequential<sup>1</sup></i>                    |                 |                           |                 |                                   |                 |                                     |                 |
| Hurlstone et al. 2005 [59]                               | 25              | 14.8 <sup>2</sup>         | 16              | 0.96                              | 2.08            | 0.44                                | 1.28            |
| Lecomte et al. 2005 [60]                                 | 33              | n/a                       | 17              | 0.69                              | 1.25            | 0.19                                | 0.30            |
| Huneberg et al. 2009 [61]                                | 47 <sup>3</sup> | 7.6                       | 18.0            | 0.53                              | 0.98            | 0.15                                | 0.13            |
| <i>Tandem, randomized second examination<sup>4</sup></i> |                 |                           |                 |                                   |                 |                                     |                 |
| Stoffel et al. 2008 [62]                                 | 52              | 25.3                      | 29.8            | 0.6                               | 0.8             | 0.5                                 | 0.4             |

<sup>1</sup> Note: "chromoendoscopy" detection rates shown here represent the total number of lesions detected by rates WLE plus chromoendoscopy.

<sup>2</sup> Includes time for saline lavage

<sup>3</sup> WLE – chromoendoscopy arm only

<sup>4</sup> Note: WLE rates here reflect standard WLE plus WLE with intensive inspection versus chromoendoscopy rates which are standard WLE plus chromoendoscopy as above

**Appendix e5** Diagnostic yield of targeted and random biopsies in conventional chromoendoscopy surveillance of long-standing colitis.

| Study                                                             | Colonoscopies, n | Biopsies per procedure, n |                      | Neoplasia yield from biopsies |                        |                                        |
|-------------------------------------------------------------------|------------------|---------------------------|----------------------|-------------------------------|------------------------|----------------------------------------|
|                                                                   |                  | Targeted                  | Targeted and random  | Targeted-only, n              | Targeted and random, n | (Targeted-only/Targeted and random), % |
| Kiesslich et al. 2003 [77]                                        | 84               | 14.2                      | 42.2                 | 35                            | 35                     | 100%                                   |
| Matsumoto et al. 2003 [83]                                        | 117              | 1                         | 7                    | 25                            | 28                     | 89%                                    |
| Rutter et al. 2004 [84]                                           | 100              | 1.1                       | 30.1                 | 7                             | 7                      | 100%                                   |
| Hurlstone et al. 2005 <sup>1</sup> [82]                           | 350              | 1.8                       | 38.8                 | 49                            | 69                     | 71%                                    |
| Kiesslich et al. 2007 [78]                                        | 80               | 3.9 <sup>2</sup>          | 21.1                 | 19                            | 19                     | 100%                                   |
| Marion et al. 2008 [85]                                           | 102              | 1.3                       | 33.3                 | 20                            | 23                     | 87%                                    |
| Hlavaty et al. 2011 [80]                                          | 45               | n.a.                      | 35.2                 | 6                             | 6                      | 100%                                   |
| Gunther et al. 2011 [81]                                          | 50               | 0.28                      | 36.2                 | 2                             | 2                      | 100%                                   |
| Pooled                                                            | 928              | 1.3 <sup>3</sup>          | 34.3 <sup>3</sup>    | 163                           | 189                    | 86%                                    |
| (Pancolonic-only chromo-<br>endoscopy values in par-<br>entheses) | (578)            | (1.2 <sup>3</sup> )       | (33.3 <sup>3</sup> ) | (114)                         | (120)                  | (95%)                                  |

n.a., not available

<sup>1</sup> Non-pancolonic chromoendoscopy was used

<sup>2</sup> Suspicious lesions were assessed additionally with endomicroscopy

<sup>3</sup> Median

**Appendix e6** Proportions of adenomas with advanced pathology and with carcinoma, by size.

| First author<br>Year      | Number of patients<br>Baseline risk                                                               | Lesions, number and type                                                   | % Tubulovillous or villous and/or<br>HGD, % |                                        |                                          | Carcinoma <sup>1</sup>   |                          |                         |
|---------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------|----------------------------------------|------------------------------------------|--------------------------|--------------------------|-------------------------|
|                           |                                                                                                   |                                                                            | ≤5 mm                                       | 6–10 mm                                | >10 mm                                   | ≤5 mm                    | 6–9 mm                   | ≥10 mm                  |
| Granqvist<br>1979 [107]   | 114 patients<br>Risk unknown                                                                      | 300 polyps<br>111 adenomas<br>300 polyps ≤4 mm                             | 0.3<br>0.9                                  | n.a.                                   | n.a.                                     | —                        | n.a.                     | n.a.                    |
| Church<br>1988 [108]      | 303 patients<br>Risk increased 73%<br>Retrospective                                               | 766 polyps<br>458 adenomas<br>766 polyps ≤5 mm                             | 0.5<br>0.9                                  | n.a.                                   | n.a.                                     | —                        | n.a.                     | n.a.                    |
| O'Brien<br>1990 [109]     | 2362 patients<br>Risk medium<br>Prospective                                                       | 5066 polyps<br>3371 adenomas                                               | —<br>1.1                                    | —<br>4.6                               | —<br>20.6                                |                          |                          |                         |
| Weston<br>1995 [110]      | 901 patients<br>Risk unknown<br>Prospective                                                       | 1938 polyps ≤5 mm<br>920 adenomas<br>88 adenomas mixed                     | 0.26                                        | n.a.                                   | n.a.                                     | 0                        | n.a.                     | n.a.                    |
| Read<br>1997 [111]        | 768 patients (311 with<br>adenomas)<br>1st sigmoidoscopy<br>Risk medium                           | 203 adenomas distal                                                        | 6                                           | 21                                     | 36                                       | —                        | —                        | —                       |
| Nusko<br>1997 [112]       | 5621 patients<br>Risk unknown                                                                     | 20076 polyps<br>11 188 adenomas                                            | n.a.                                        | —                                      | n.a.                                     | 0                        | 2.2 (6–<br>15 mm)        | n.a.                    |
| Aldridge<br>2001 [113]    | 445 patients<br>Risk unknown<br>Prospective                                                       | 1228 polyps<br>657 adenomas                                                | 1.1                                         | 6.8                                    | 5.8                                      | 0                        | 1.5                      | 10.2                    |
| Gschwantler<br>2002 [102] | 4216 patients<br>Risk unknown<br>Retrospective                                                    | 11 283 polyps<br>9038 adenomas<br>3016 adenomas <5 mm                      | —<br>3.4 <sup>2</sup>                       | —<br>12.5 <sup>2</sup>                 | —<br>29 <sup>2</sup>                     | —<br>0 <sup>2</sup>      | —<br>0.9 <sup>2</sup>    | —<br>8.7 <sup>2</sup>   |
| Pickhardt<br>2003 [114]   | 1233 patients<br>Risk medium<br>Prospective                                                       | 1310 polyps<br>554 adenomas<br>966 polyps <5 mm<br>344 adenomas <5 mm      | 0.1<br>0.3 <sup>2</sup>                     | —<br>—                                 | —<br>—                                   | 0<br>0                   | 0<br>0                   | 2.4<br>4.0 <sup>2</sup> |
| Church<br>2004 [115]      | 5123 patients<br>Risk increased 27%<br>Retrospective                                              | 2980 adenomas<br>5490 polyps<br>4381 polyps ≤5 mm                          | 2.6 <sup>2</sup><br>1.9                     | 12.9 <sup>2</sup><br>3.6               | 47.8 <sup>2</sup><br>24.8                | 0.05 <sup>1,2</sup><br>— | 0.15 <sup>1,2</sup><br>— | 4.2 <sup>1,2</sup><br>— |
| O'Brien<br>2004 [116]     | 938 patients<br>Risk medium<br>Retrospective                                                      | 1750 adenomas                                                              | 0.7                                         | 6.5                                    | 15.5                                     | 0                        | 0.4                      | 0.8                     |
| Souques<br>2006 [117]     | 10 936 patients<br>Risk medium<br>Retrospective                                                   | 15 458 polyps<br>9280 adenomas<br>8511 polyps <5 mm<br>4429 adenomas <5 mm | 12.9<br>25.8 <sup>2</sup>                   | 26.6<br>38.7 <sup>2</sup>              | 87.7<br>86.6 <sup>2</sup>                | —                        | —                        | —                       |
| Chen<br>2006 [118]        |                                                                                                   | 4279 (<6 mm)<br>753 (6–9 mm)                                               | 2.6                                         | 9.7                                    | —                                        | —                        |                          |                         |
| Butterly<br>2006 [119]    | 3291 patients (1235 with<br>polyps)<br>Risk medium and increased<br>Retrospective                 | 1933 adenomas ≤10 mm                                                       | 2.6                                         | 7.8                                    | n.a.                                     | 0.1                      | 0.4                      | n.a.                    |
| Kim<br>2007 [120]         |                                                                                                   | 2955 polyps<br>2006 polyps >5 mm                                           | 0.2                                         | 1.8                                    |                                          | 0.08                     | 2.0                      |                         |
| Yoo<br>2007 [121]         | 7006 patients<br>Risk unknown                                                                     | 5 996 adenomas<br>3 303 adenomas <5 mm                                     | 0.15 <sup>2</sup>                           | 2.1 <sup>2</sup>                       | 15.2 <sup>2</sup>                        | 0 <sup>2</sup>           | 0.5 <sup>2</sup>         | 1.6 <sup>2</sup>        |
| Lieberman<br>2008 [122]   | 13 609 (6360 with polyps)<br>Risk medium 64% (FOBT<br>14%)<br>Risk increased 22%<br>Retrospective | 5977 polyps<br>3493 adenomas<br>1880 adenomas <5 mm<br>3764 polyps         | 1.2 <sup>3</sup><br>1.7 <sup>3,4</sup>      | 5.1 <sup>3</sup><br>6.4 <sup>3,4</sup> | 26.3 <sup>3</sup><br>27.9 <sup>3,4</sup> | 0 <sup>3</sup>           | 0.2 <sup>3</sup>         | 2.6 <sup>3</sup>        |
| Rex<br>2009 [123]         | 10 034 (5079 with polyps)<br>Risk medium 20%, in-<br>creased 31%<br>Retrospective                 | 10 780 polyps<br>8798 polyps <5 mm<br>5084 adenomas                        | 0.9                                         | 5.3                                    | —                                        | 0.05                     | 0                        | —                       |
| Graser<br>2009 [124]      | —                                                                                                 | 511 polyps<br>468 polyps <5 mm                                             | 1.7                                         | 10.7                                   | 51.4                                     | 0                        | 0                        | 2.7                     |
| Bretagne<br>2010 [125]    | 784 patients<br>FOBT-positive<br>Retrospective                                                    | 1284 adenomas<br>520 adenomas <5 mm<br>adenomas                            | 2.8 <sup>2</sup>                            | 15.5 <sup>2</sup>                      | 46.8 <sup>2</sup>                        | 0.4 <sup>2</sup>         | 0.5 <sup>2</sup>         | 12.3 <sup>2</sup>       |

## Appendix e6 (Continuation)

| First author<br>Year                       | Number of patients<br>Baseline risk                                                                 | Lesions, number and type                                      | % Tubulovillous or villous and/or<br>HGD, % |                   |                   | Carcinoma <sup>1</sup> |                |                |
|--------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------|-------------------|-------------------|------------------------|----------------|----------------|
|                                            |                                                                                                     |                                                               | ≤5 mm                                       | 6–10 mm           | >10 mm            | ≤5 mm                  | 6–9 mm         | ≥10 mm         |
| Denis<br>2010 [126]                        | 175 patients<br>FOBT-positive<br>Retrospective                                                      | 350 polyps                                                    | 8.4                                         | 39                | 94                | 0                      | 0              | 3.7            |
|                                            |                                                                                                     | 260 adenomas<br>180 polyps <5 mm                              | 12.2 <sup>2</sup>                           | 44.8 <sup>2</sup> | 100 <sup>2</sup>  | 0                      | 0              | 3.9            |
| Ignjatovic<br>2011 [105]                   | —<br>Risk medium increased<br>Retrospective                                                         | 363 polyps <10 mm                                             | 2.4                                         | 10.4              | n.a.              | —                      | —              | —              |
|                                            |                                                                                                     | 296 polyps <5 mm<br>198 adenomas                              |                                             |                   |                   |                        |                |                |
| Chaput<br>2011 [127]                       | 1468<br>Risk medium 34%, familial<br>25%<br>Risk increased (surveil-<br>lance) 47%<br>Retrospective | 414 polyps <10 mm                                             | 4.7                                         | 35.2              | —                 | 0.6                    | 2.8            | —              |
|                                            |                                                                                                     | 342 polyps <5 mm<br>293 adenomas <10 mm<br>234 adenomas <5 mm |                                             |                   |                   |                        |                |                |
| Repici<br>2011 [128]                       | 823 patients<br>Retrospective<br>Risk medium 29%<br>Risk increased (surveil-<br>lance) 32%          | 1015 <10 mm                                                   | 8.7 <sup>3</sup>                            | 6.1 <sup>3</sup>  | —                 | —                      | —              | —              |
|                                            |                                                                                                     | 627 polyps <5 mm                                              |                                             |                   |                   |                        |                |                |
| Tsai<br>2011 [129]                         | 4967 patients (1361 with<br>polyps)<br>Risk medium 24%<br>Retrospective                             | —                                                             | 10 <sup>3</sup>                             | 27 <sup>3</sup>   | 85 <sup>3</sup>   | 0 <sup>3</sup>         | 0 <sup>3</sup> | 9 <sup>3</sup> |
| Shapiro<br>2012 [130]                      | 741 (741 with polyps)<br>Risk medium 28%, familial<br>51%<br>FOBT-positive 21%<br>Retrospective     | 1192 polyps<br>760 polyps <5 mm                               | 4.1 <sup>5</sup>                            | 13.5 <sup>5</sup> | 68.5 <sup>5</sup> | 0.3                    | 0.9            | 6.9            |
| Kolligs<br>2012 [131]                      | 1 077 956 patients<br>Moderate risk                                                                 | 358 714 polyps                                                | 3.3                                         | 12.0              | 34.6              | 0.4                    | 1.0            | 4.0            |
|                                            |                                                                                                     | 222 688 adenomas<br>198 954 polyps ≤4 mm                      | 6.2 <sup>2</sup>                            | 17.0 <sup>2</sup> | 43.0 <sup>2</sup> |                        |                |                |
| Gupta<br>2012 [132]                        | Moderate risk                                                                                       | 2361 polyps                                                   | 0.5                                         | 1.5               | 15                |                        |                |                |
| Rutter<br>2013 [personal<br>communication] | FOBT-positive                                                                                       | 182 986 polyps                                                | 6.4                                         | 26.1              | 75.3              | 0.07                   | 0.68           | 5.6            |
|                                            |                                                                                                     | 137 624 adenomas                                              | 9.8                                         | 32.1              | 80.1              | 0.11                   | 0.70           | 6.0            |

HGD, high grade dysplasia; n.a., not available; FOBT, fecal occult blood test;

<sup>1</sup> carcinoma only

<sup>2</sup> % expressed per adenoma

<sup>3</sup> % expressed per patient

<sup>4</sup> including serrated adenomas

<sup>5</sup> tubulovillous or villous or high grade dysplasia or carcinoma

**Appendix e7** Interobserver agreement for characterization of polyps as neoplastic or non-neoplastic: kappa values for narrow band imaging (NBI), magnified NBI, i-SCAN, and autofluorescence imaging (AFI).

| Study authors, year              | NBI  | NBI magnified | i-SCAN | AFI  |
|----------------------------------|------|---------------|--------|------|
| Masci et al., 2012 [146]         |      |               | 0.446  |      |
| Pigo et al., 2012 [147]          |      |               | 0.462  |      |
| Ignjatovic et al., 2011 [104]    | 0.48 | 0.63          |        | 0.48 |
| Ignjatovic et al., 2011 [121]    | 0.85 |               |        |      |
| Raghavendra et al., 2011 [122]   | 0.69 |               |        |      |
| Higashi et al., 2010 [124]       |      | 0.85          |        |      |
| Van den Broek et al., 2009 [148] | 0.77 |               |        | 0.33 |
| Rastogi et al., 2009 [149]       | 0.63 |               |        |      |
| East et al., 2007 [151]          |      | 0.48          |        |      |
| Sato et al., 2011 [152]          | 0.54 |               |        | 0.54 |

## Appendix e8 Summary of evidence for the cost-effectiveness of a resect and discard policy.

| Study authors, year                  | Study design                           | Intervention                                                                                                       | Participants                         | Outcomes                                        | Results                                                                                                                                                                                                                                                                                                                                                                                                                                | Conclusions                                                                                                                                                  |
|--------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hassan et al., 2010 [167]            | Markov modelling                       | In vivo diagnosis, NBI<br>Polyps < 5 mm,                                                                           | US screening population              | Reduction in screening costs                    | Savings of \$25 /person, without any meaningful effect on screening efficacy<br>US population undiscounted annual savings of \$33 million.<br>No effect on screening efficacy                                                                                                                                                                                                                                                          | Resect and discard strategy for diminutive polyps detected by screening colonoscopy resulted in a substantial economic benefit without an impact on efficacy |
| Longcroft-Wheaton et al., 2011 [166] | Prospective cohort study               | In vivo diagnosis, FICE and conventional chromoendoscopy (indigo carmine) with reference to PIVI<br>Polyps < 10 mm | UK bowel cancer screening population | Cost of histopathological examination of polyps | Surveillance interval could be set correctly in:<br>– 97% of cases, by BSG guidelines, using FICE or indigo carmine chromoendoscopy<br>– 97% of cases, by ASGE guidelines, using FICE<br>– 99% of cases, by ASGE guidelines, with indigo carmine chromoendoscopy<br>A saving of £ 678 253 (€ 762 767) per annum could be made within the UK Bowel Cancer Screening Programme (£ 55 [€ 62] per person undergoing screening colonoscopy) | FICE and indigo carmine chromoendoscopy can lead to significant cost savings                                                                                 |
| Gupta et al., 2012 [165]             | Retrospective multicenter cohort study | In vivo diagnosis, NBI with reference to PIVI<br>Polyps < 5 mm                                                     | US screening population              | Savings in histopathology costs                 | Total histopathology cost of 1254 polyps, \$ 133 000<br>Total saving of \$ 127 000 possible (\$ 309 [€ 210] per patient)                                                                                                                                                                                                                                                                                                               | Cost savings following PIVI guideline feasible                                                                                                               |
| Ignjatovic et al., 2009 [103]        | Prospective cohort study               | In vivo diagnosis, NBI<br>Polyps < 10 mm                                                                           | UK screening population              | Savings in histopathology costs                 | Reduction in histopathology costs of £ 6783 (\$ 11 000)<br>Overall saving of £ 13 353 (\$ 22 000) or 77% for the cohort of 130 patients (£ 102 [€ 115] per patient)                                                                                                                                                                                                                                                                    |                                                                                                                                                              |

NBI, narrow band imaging; FICE, Fujinon Intelligent Color Enhancement; PIVI, preservation and Incorporation of valuable endoscopic interventions [106]; BSG, British Society of Gastroenterology; ASGE, American Society for Gastrointestinal Endoscopy