Policy Number	**MED201.022**
Policy Effective Date	**10/01/2025**

Chromoendoscopy as an Adjunct to Colonoscopy

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
MED201.038: Confocal Laser Endomicroscopy (CLE)

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Chromoendoscopy **is considered experimental, investigational and/or unproven** as an adjunct to diagnostic or surveillance colonoscopy.

Virtual chromoendoscopy **is considered experimental, investigational and/or unproven** as an adjunct to diagnostic or surveillance colonoscopy.

Policy Guidelines

None.

Description

Chromoendoscopy refers to the use of dyes or stains during endoscopy to enhance tissue differentiation or characterization. When used with colonoscopy, the intent is to increase the sensitivity of the procedure by facilitating the identification of mucosal abnormalities. There are 2 types of chromoendoscopy: 1 involves actual spraying of dyes or stains through the working

channel of an endoscope; the other, known as virtual chromoendoscopy, uses a computer algorithm to simulate different colors of light that result from dye or stain spraying.

Colonoscopy

Colonoscopy, a procedure during which colonic and rectal polyps can be identified and removed, is considered the criterion standard test for colorectal cancer (CC) screening and diagnosis of colorectal disease. However, colonoscopy is an imperfect procedure. A systematic review and meta-analysis by Zhao et al. (2019) pooled findings from more than 15,000 tandem (i.e., back-to-back) colonoscopies in 43 publications and found a miss rate of 26% for adenomas, 9% for advanced adenomas, and 27% for serrated polyps. (1) Miss rates were higher for proximal advanced adenomas (14%), serrated polyps (27%), flat adenomas (34%), and in individuals at high risk for CC (33%).

Adjunctive Procedures

Several adjunct endoscopic techniques, including chromoendoscopy, could enhance the sensitivity of colonoscopy. Chromoendoscopy, also known as chromoscopy and chromocolonoscopy, refers to the application of topical stains or dyes during endoscopy to enhance tissue differentiation or characterization and facilitate identification of mucosal abnormalities. Chromoendoscopy may be particularly useful for detecting flat or depressed lesions. A standard colonoscopy uses white-light to view the colon. In chromoendoscopy, stains are applied, resulting in color highlighting of areas of surface morphology of epithelial tissue. The dyes or stains are applied via a spray catheter that is inserted down the working channel of the endoscope. Chromoendoscopy can be used in the whole colon (pancolonic chromoendoscopy) on an untargeted basis or can be directed to a specific lesion or lesions (targeted chromoendoscopy). Chromoendoscopy differs from endoscopic tattooing in that the former uses transient stains, whereas tattooing involves the use of a long-lasting pigment for future localization of lesions.

Stains and dyes used in chromoendoscopy can be placed in the following categories:

- Absorptive stains are preferentially absorbed by certain types of epithelial cells.
- Contrast stains seep through mucosal crevices and highlight surface topography.
- Reactive stains undergo chemical reactions when in contact with specific cellular constituents, which results in a color change.

Indigo carmine, a contrast stain, is one of the most commonly used stains with colonoscopy to enhance the detection of colorectal neoplasms. Several absorptive stains are also used with colonoscopy. Methylene blue is widely used; it stains the normal absorptive epithelium of the small intestine and colon, and has been used to detect colonic neoplasia and to aid in the detection of intraepithelial neoplasia in individuals with chronic ulcerative colitis. In addition, crystal violet (also known as gentian violet) stains cell nuclei and has been applied in the colon to enhance visualization of pit patterns (i.e., superficial mucosal detail). Reactive stains are primarily used to identify gastric abnormalities and are not used with colonoscopy.

Potential applications of chromoendoscopy as an adjunct to standard colonoscopy include:

- Diagnosis of colorectal neoplasia in symptomatic individuals at increased risk of CC due to a family history of CC, a personal history of adenomas, etc.
- Identification of mucosal abnormalities for targeted biopsy as an alternative to multiple random biopsies in individuals with inflammatory bowel disease.
- Screening the general population for CC.

The equipment used in regular chromoendoscopy is widely available. Several review articles and technology assessments have indicated that, although the techniques are simple, the procedure (e.g., the concentration of dye and amount of dye sprayed) is variable, and thus classification of mucosal staining patterns for identifying specific conditions is not standardized.

Virtual chromoendoscopy (also called electronic chromoendoscopy) involves imaging enhancements with endoscopy systems that could be an alternative to dye spraying. One system is the Fujinon Intelligent Color Enhancement feature (Fujinon Inc.). This technology uses postprocessing computer algorithms to modify the light reflected from the mucosa from conventional white-light to various other wavelengths.

Regulatory Status
In August 2014, the EPX-4440HD Digital Video Processor with Fujinon Intelligent Color Enhancement (FICE®) and Light Source (FujiFilm) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K140149). The FDA documents stated that FICE could be used to supplement white-light endoscopy but is not intended to replace histopathologic sampling as a means of diagnosis. (2)

In June 2012, the i-SCAN™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by the FDA through the 510(k) process (K113873). (3) This digital image enhancement technology is part of the Pentax EPK-i5010 Video Processor. The i-SCAN has several modes that digitally enhance images in real-time during endoscopy. The FDA documents stated that i-SCAN is intended as an adjunct following white-light endoscopy but not intended to replace histopathologic analysis.

FDA product codes: GCT, PEA, FET (endoscopes and accessories).

No dye or stain product has been specifically approved by the FDA for use in chromoendoscopy.

Rationale

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these policies, and credible information on technical reliability is available from other sources.

Chromoendoscopy for Individuals at Average Risk of Colorectal Cancer Undergoing Colonoscopy

Clinical Context and Test Purpose

The purpose of chromoendoscopy in individuals at average risk of colorectal cancer (CC) is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals at average risk of CC.

Interventions

The test being considered is chromoendoscopy. Chromoendoscopy involves the application of dyes to facilitate tissue visualization.

Comparators

The following test is currently being used to diagnose or monitor CC: standard white-light colonoscopy.

Outcomes

The general outcomes of interest are tumor detection and tumor recurrence for CC.

Study Selection Criteria

For the evaluation of the clinical validity of the tests included in this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Some trials evaluating chromoendoscopy for CC screening in average-risk individuals have included mixed populations of individuals undergoing screening and diagnostic colonoscopy but have not reported results separately for each group.

Meta-analysis

Antonelli et al. (2022) conducted a meta-analysis to evaluate the efficacy of dye-based chromoendoscopy in detecting colorectal neoplasia. (4) The analysis included 10 RCTs of individuals at average or increased risk of CC undergoing conventional (standard or high-definition white light) colonoscopy, or colonoscopy with dye-based chromoendoscopy. Patients with IBD or genetic/familial syndromes were excluded. Table 1 lists the RCTs included in the meta-analysis, and Tables 2 and 3 summarize the characteristics and results of the meta-analysis, respectively. In patients at average or increased risk of CC, the meta-analysis showed that dye-based chromoendoscopy increased adenoma detection rate by 20%, and adenomas per colonoscopy by 50%, corresponding to a number needed to treat of 12 to detect 1 additional patient with adenoma. Limitations of the meta-analysis included unclear indication for use of colonoscopy in the studies and some heterogeneity in mean adenomas per patient.

Table 1. Trials Included in the Meta-analysis

Study	Antonelli et al. (2022) (4)
Hurt et al. (2019) (5)	●
Repici et al. (2019) (6)	●
Lesne et al. (2017) (7)	●
Pohl et al. (2011) (8)	●
Kahi et al. (2010) (9)	●
Stoffel et al. (2008) (10)	●
Le Rhun et al. (2006) (11)	●
LaPalus et al. (2006) (12)	●
Hurtstone et al. (2004) (13)	●
Brooker et al. (2002) (14)	●

Table 2. Characteristics of the Meta-analysis

Study	Search Dates	Trials	Participants	N (Range)	Design	Duration
Antonelli et al. (2022) (4)	Up to 2022	10	Patients at average or increased risk of CC undergoing standard or high-definition white light colonoscopy (screening or surveillance) in a nonemergency setting or dye-based chromoendoscopy.	5334	RCTs	Not started

CC: colorectal cancer; N: number; RCT: randomized controlled trial.

Table 3. Results of the Meta-analysis

Study	Adenoma detection	Advanced adenoma detection	Sessile serrated adenoma/traditional	Mean no. of	Mean no. of non-neoplastic

	rate per patient	rate per patient	serrated adenomas per patient	adenoma per patient	lesions per patient
Antonelli et al. (2022) (4)					
N	5334 (10 studies)	2073 (3 studies)	2607 (3 studies)	4598 (9 studies)	2077 (6 studies)
Conventional colonoscopy	1142	202	46	0.62	0.52
DCE	1349	2252	79	0.92	0.90
Risk difference (95% CI)	1.20 (1.11 to 1.29)	1.21 (1.03 to 1.42)	1.68 (1.15 to 2.47)	0.29 (0.17 to 0.42)	0.38 (0.20 to 0.51)
I^2	29%	0.0%	9.8%	65.4%	I^2 not stated; p<.001

CI: confidence interval; DCE: dye chromoendoscopy; N/no: number.

Randomized Controlled Trials

One large, randomized trial by Kahi et al. (2010) evaluated 660 patients at 4 centers in the U.S. (9) Those eligible for inclusion had an average risk of CC, were ages 50 years and older, and were undergoing screening colonoscopy for the first time. Participants were randomized to chromoendoscopy with indigo carmine dye (n=321) or to standard colonoscopy (n=339). The primary outcomes were the proportion of patients with at least 1 adenoma and the mean number of adenomas per patient, which were then compared between groups. No significant between-group differences were noted for either outcome. A total of 178 (55.5%) subjects in the chromoendoscopy group and 164 (48.4%) subjects in the standard colonoscopy group had 1 or more adenomas (p=.07). The mean number of adenomas per subject that were less than 5 mm in diameter differed significantly between groups (0.8 for chromoendoscopy versus 0.7 for standard endoscopy; p=.03). The difference between groups in the mean number of adenomas 10 mm or larger was not statistically significant (0.11 for chromoendoscopy versus 0.12 for standard colonoscopy; p=.70). Thirty-nine (12%) subjects in the chromoendoscopy group and 49 (15%) subjects in the standard colonoscopy group had 3 or more adenomas; the difference between groups was not statistically significant (p=.40). The trialists stated that the high rate of adenoma detection in both groups might have been due to the use of high-definition colonoscopy.

Pohl et al. (2011) in Germany published a large RCT comparing pancolonic chromoendoscopy using indigo carmine dye with standard colonoscopy. (8) The trial included patients presenting for primary CC screening (51%) and patients undergoing diagnostic colonoscopy (49%). Patients with known inflammatory bowel disease (IBD), overt bleeding, polyposis syndromes, or a history of surgical resection were excluded. A total of 1024 patients were randomized; 16 dropped out, leaving 496 patients in the chromoendoscopy group and 512 patients in the standard colonoscopy (i.e., control) group. The primary study outcome (the proportion of patients with adenomas) differed significantly between groups (p=.002). A total of 223 (46.2%) patients in the chromoendoscopy group and 186 (36.3%) in the standard colonoscopy group

had at least 1 adenoma identified. The trial also reported differences in lesion detection rates by lesion size. For lesions 5 mm or larger, 151 (30.4%) patients in the chromoendoscopy group and 119 (23.2%) patients in the standard colonoscopy group had at least 1 adenoma; the difference between groups was statistically significant (p=.012). For lesions 10 mm or larger, 64 (12.9%) patients in the chromoendoscopy group and 48 (9.4%) patients in the standard colonoscopy group had at least 1 adenoma. The between-group difference in the detection rates of adenomas 10 mm or larger did not differ significantly (p=.092), but the trial might have been underpowered for this analysis.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. Several RCTs were included in the meta-analysis that showed that the use of dye-based chromoendoscopy improved detection of colorectal neoplasia compared to conventional colonoscopy, but clinical outcomes were lacking.

Section Summary: Chromoendoscopy for Individuals at Average Risk of Colorectal Cancer Undergoing Colonoscopy

For individuals who have an average risk of CC who receive chromoendoscopy, the evidence includes RCTs and a recent meta-analysis. The meta-analysis demonstrated that dye-based chromoendoscopy increased the adenoma detection rate and adenomas per colonoscopy in patients at average or increased risk of CC compared to standard or high-definition white light colonoscopy. However, limitations included unclear indication for colonoscopy in the studies (which included patients with screening and surveillance), and some heterogeneity in mean adenomas per patient. Literature regarding clinical outcomes is lacking. The single RCT performed in the U.S. did not find that high-definition chromoendoscopy identified more clinically meaningful lesions than high-definition white-light colonoscopy.

Chromoendoscopy for Individuals at Increased Risk of Colorectal Cancer Undergoing Colonoscopy

Clinical Context and Test Purpose

The purpose of chromoendoscopy in individuals at increased risk of CC is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals at increased risk of CC.

Interventions
The test being considered is chromoendoscopy. Chromoendoscopy involves the application of dyes to facilitate tissue visualization.

Comparators
The following test is currently being used to diagnose or monitor CC: standard white-light colonoscopy.

Outcomes
The general outcomes of interest are tumor detection and tumor recurrence for CC.

Study Selection Criteria
For the evaluation of the clinical validity of the tests included in this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Individuals may be at higher risk for CC due to family or personal history or symptoms suggestive of colorectal disease (excluding patients with known IBD). Heightened surveillance is the most common approach to high-risk patients. Prophylactic colectomy is sometimes considered for those at extremely high-risk. The evidence on polyp detection with chromoendoscopy compared with standard colonoscopy, particularly higher risk polyps (such as those that are at least 5 mm to 10 mm in size) is described in this section.

Meta-analyses
Har-Noy et al. (2019) conducted a meta-analysis of 4 studies that compared neoplasia detection rates with white-light colonoscopy and chromoendoscopy in patients with Lynch syndrome, who are at an increased risk of CC. (15) Overall, chromoendoscopy was associated with improved overall lesion detection (pooled rate ratio, 1.97; 95% confidence interval [CI], 1.63 to 2.38), adenoma detection (pooled rate ratio, 1.53; 95% CI, 1.07 to 2.17), flat lesion detection (pooled rate ratio, 3.4; 95% CI, 2.47 to 4.67), and proximally-located lesion detection (pooled rate ratio, 2.93; 95% CI, 1.91 to 4.5). Additionally, chromoendoscopy was associated with higher odds of having any lesion detected as compared to white-light colonoscopy (odds ratio, 2.42, 95% CI, 1.56 to 3.75); however, the odds of having any adenoma detected were not significantly different between the modalities (odds ratio, 1.81; 95% CI, 0.65 to 5.01). The authors noted that none of the included studies were of a randomized, controlled design and that sample

sizes were small; however, the heterogeneity between studies was minimal for most evaluated outcomes.

A Cochrane review by Brown and Baraza (2010) identified RCTs that compared chromoendoscopy with conventional colonoscopy for the detection of colorectal lesions in individuals at increased risk of colorectal neoplasia due to family history, previous polyp detection, or previous CC resection. (16) Reviewers excluded studies of individuals with IBD or a known polyposis syndrome. Five RCTs (N=1059) met inclusion criteria; only 1 of the 5 studies had sites in the U.S. Three studies used some type of "back-to-back" design in which each participant underwent the equivalent of 2 colonoscopies. (An update of this Cochrane review by Brown et al. [2016] included studies of patients at increased risk of CC and those at average risk; meta-analyses did not stratify by patient population. [17] The individual studies, none of which was published more recently than 2011, are discussed in the appropriate sections of this medical policy.)

A meta-analysis pooling results of the 5 studies in the 2010 Cochrane review found that a significantly higher number of polyps (all types) were detected with chromoendoscopy rather than with nonchromoendoscopy interventions (pooled mean difference, 0.80; 95% CI, 0.60 to 1.00; p<.001). Further, a meta-analysis found that the mean number of neoplastic lesions detected was significantly higher with chromoendoscopy than with nonchromoendoscopy interventions (pooled mean difference, 0.39; 95% CI, 0.27 to 0.50; p<.001). Tests for heterogeneity were statistically significant in both analyses. According to reviewers, potential reasons for clinical heterogeneity might have been differences in study design and differing levels of experience among endoscopists performing the procedure.

In a pooled analysis of per-patient data from the 5 studies, 234 (45%) of 524 patients in the chromoendoscopy group and 176 (33%) of 535 patients in the nonchromoendoscopy group had at least 1 neoplastic lesion detected. The difference between groups was statistically significant (odds ratio, 1.67; 95% CI, 1.29 to 2.15; p<.001). A pooled analysis of 4 studies found that 47 (9%) of 497 in the chromoendoscopy group and 20 (4%) of 512 in the nonchromoendoscopy group had 3 or more neoplastic lesions (odds ratio, 2.55; 95% CI, 1.49 to 4.36; p=.006). Reviewers concluded: "There appears to be strong evidence that chromoscopy enhances the detection of neoplasia in the colon and rectum. Patients with neoplastic polyps, particularly those with multiple polyps, are at increased risk of developing CC. Such lesions, which presumably would be missed with conventional colonoscopy, could contribute to the interval cancer numbers on any surveillance programme." Reviewers did not report differences between groups in the number of large lesions.

Randomized Controlled Trials

Haanstra et al. (2019) conducted a prospective, multicenter, randomized study in the Netherlands that evaluated the effect of chromoendoscopy (n=123) versus conventional white-light colonoscopy (n=123) in the proximal colon on detection of neoplastic lesions in patients with Lynch syndrome. (18) The primary outcome was the proportion of patients with at least 1 neoplastic lesion at baseline and at the follow-up colonoscopy after 2 years. Results revealed a

baseline neoplasia detection rate of 27% for white-light colonoscopy versus 30% for chromoendoscopy (odds ratio, 1.23; 95% CI, 0.69 to 2.2; p=.56). Similar nonsignificant findings were observed in the proximal colon, with detection rates of 16% for white-light colonoscopy versus 24% for chromoendoscopy (odds ratio, 1.6; 95% CI, 0.9 to 3.1; p=.13). At 2 years follow-up, neoplasia detection rates remained similar (26% for white-light colonoscopy vs. 28% for chromoendoscopy; p=.81).

Stoffel et al. (2008) published findings of a study drawing on 5 sites across the U.S., Canada, and Israel. (10) Eligibility criteria included a personal history of CC or at least 3 colorectal adenomas. The study involved back-to-back colonoscopies, the first of which was a standard colonoscopy with removal of all visualized polyps. Patients were then randomized to a second standard colonoscopy with intensive inspection (n=23) or chromoendoscopy (n=27). During the first colonoscopy, 17 (34%) of 50 patients had adenomas identified: 11 (48%) of 23 in the intensive inspection group and 6 (27%) in the chromoendoscopy group (p not reported). During the second colonoscopy, additional adenomas were found in 4 (17%) of 23 in the intensive inspection group and 12 (44%) of 27 in the chromoendoscopy group (p not reported). The mean size of adenomas found on the second examination was 3.2 mm in the intensive inspection group and 2.7 mm in the chromoendoscopy group. This compared with a mean size of 3.6 mm in the intensive inspection group and 4.7 mm in the chromoendoscopy group during the first examination. In a multivariate analysis, the use of chromoendoscopy was significantly associated with an increased likelihood of finding at least 1 additional adenoma on the second examination (p=.04).

Le Rhun et al. (2006) published findings of a French study involving 203 patients with a history of familial or personal colonic neoplasia or alarm symptoms (e.g., change in bowel habit, abdominal pain) after age 60 years. (11) Patients were randomized to standard colonoscopy (n=100) or high-resolution colonoscopy with chromoendoscopy (n=103). In the chromoendoscopy group, each segment of the colon was examined before and after spraying indigo carmine dye. The primary endpoint of the total number of adenomas per patient did not differ significantly between groups. The mean standard deviation number of adenomas was 0.5 (0.9) in the standard colonoscopy group and 0.6 (1.0) in the chromoendoscopy group. The number of flat adenomas (at least 5 mm) per patient also did not differ significantly between groups, with a mean standard deviation of 0.04 (0.20) in the standard colonoscopy group and 0.10 (0.39) in the chromoendoscopy group (p=.17).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the

preferred evidence would be from RCTs. No controlled studies have evaluated the effect on health outcomes, such as a lower incidence of CC.

Section Summary: Chromoendoscopy for Individuals at Increased Risk of Colorectal Cancer Undergoing Colonoscopy

For individuals who have an increased risk of CC who receive chromoendoscopy, the evidence includes multiple RCTs and systematic reviews. A Cochrane systematic review of trials comparing chromoendoscopy with standard colonoscopy in high-risk patients (but excluding those with IBD) found significantly higher rates of adenoma detection and rates of 3 or more adenomas with chromoendoscopy than with standard colonoscopy. The evidence for detecting larger polyps, defined as greater than 5 mm or greater than 10 mm, is less robust. While 1 study reported a significantly higher detection rate for polyps greater than 5 mm, no studies reported increased detection of polyps greater than 10 mm. A recent RCT and systematic review involving patients with Lynch syndrome also found equivocal results. Results from the RCT showed similar neoplasia detection rates with chromoendoscopy and conventional white-light colonoscopy, while the systematic review concluded that chromoendoscopy is associated with significantly improved detection of certain lesions; however, the odds of having an adenoma detected were not significantly different between the modalities.

Chromoendoscopy for Individuals With Inflammatory Bowel Disease Undergoing Colonoscopy

Clinical Context and Test Purpose

The purpose of chromoendoscopy in individuals with IBD is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with IBD.

Interventions

The test being considered is chromoendoscopy. Chromoendoscopy involves the application of dyes to facilitate tissue visualization.

The following test is currently being used to diagnose or monitor IBD: standard white-light colonoscopy.

Outcomes

The general outcomes of interest are tumor, dysplasia, and other mucosal abnormalities detection in IBD.

Based on pathology results, the follow-up would be similar to standards for colonoscopy.

Study Selection Criteria

For the evaluation of the clinical validity of the tests included in this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Meta-analyses

Mohamed et al. (2024) published a meta-analysis of 6 RCTs (N=978) comparing dye-based chromoendoscopy with high-definition white light endoscopy. (19) Of the included RCTs, 4 were published subsequent to the earlier meta-analyses. Dye-based chromoendoscopy improved detection rates compared with high-definition white light colonoscopy. Mortality, cancer risk, and other long-term outcomes were not analyzed.

Two meta-analyses were published in 2020 that compared different endoscopic methods of surveillance for dysplasia in patients with IBD. (20, 21) Resende et al. (2020) compared the detection of dysplastic lesions between dye-based chromoendoscopy, virtual chromoendoscopy (narrow-band imaging [NBI], i-SCAN, FICE), standard white-light colonoscopy, and high-definition white light colonoscopy. (20) The study found that dye-based chromoendoscopy was superior to standard-definition white light colonoscopy. No difference was found in the number of patients with dysplasia when dye-based chromoendoscopy was compared with high-definition white light colonoscopy. No difference was observed between dye-based chromoendoscopy and virtual chromoendoscopy for all outcomes except procedure time. Study shortcomings included lack of information on the training of endoscopists to perform chromoendoscopy appropriately, and inability to assess risk of bias since some included studies were abstracts. Gondal et al. (2020) compared the detection of dysplasia between high-definition white light colonoscopy, standard definition colonoscopy, high-definition chromoendoscopy, and high-definition NBI (virtual chromoendoscopy). (21) For dysplasia per biopsy, direct meta-analysis showed superiority of NBI over high-definition white light colonoscopy, and of dye-based chromoendoscopy over standard white light colonoscopy. Network meta-analysis showed the rank order (rank 1 to 4, rank 1 being the best) of best modality as NBI, dye-based chromoendoscopy, high-definition white light colonoscopy, and standard white light colonoscopy. For dysplasia detection rates per patient, direct meta-analyses demonstrated equivocal results between the modalities, and for dysplasia numbers per patient, superiority of dye-based chromoendoscopy was found over standard white light colonoscopy. For both dysplasia detection rates and numbers per patient, network meta-analysis showed the rank order of best modality as high-definition white light colonoscopy, NBI, dye-based chromoendoscopy, and standard white light colonoscopy. Limitations of the meta-

analysis included small sample size and potential risks of bias related to allocation concealment and blinding of outcome assessment in some of the included studies.

Feuerstein et al. (2019) completed a systematic review and meta-analysis that evaluated the comparative efficacy of standard white-light colonoscopy or high-definition white-light colonoscopy versus dye-based chromoendoscopy in patients with IBD at increased risk of CC. (22) The review included 10 studies, 6 of which were RCTs. Results from an analysis of the RCTs revealed a small benefit favoring chromoendoscopy for dysplasia detection as compared to white-light endoscopy (17% vs. 11%; relative risk, 1.50; 95% CI, 1.08 to 2.10). However, when evaluating standard-definition and high-definition white-light colonoscopy individually, chromoendoscopy was only shown to be beneficial when compared to the standard-definition approach (relative risk, 2.2; 95% CI, 1.15 to 3.91); no benefit was seen when chromoendoscopy was compared to the high-definition modality (relative risk, 1.36; 95% CI, 0.84 to 2.18). The overall quality of the evidence in the RCTs was moderate. Results from an analysis of the non-RCTs found that dysplasia was identified by 16% of patients with chromoendoscopy versus 6% with white-light endoscopy (relative risk, 3.41; 95% CI, 2.13 to 5.47). On individual analysis, chromoendoscopy was more effective than both the standard definition (relative risk, 3.52; 95% CI, 1.38 to 8.99) and high-definition (relative risk, 3.15; 95% CI, 1.62 to 6.13) white light modalities. The quality of evidence in the non-RCTs was very low. Study limitations included inclusion of some studies with abstracts only, and variability of contrast agents and dilutions used for chromoendoscopy across studies which may limit generalizability.

Table 4 compares the RCTs included in these meta-analyses, and Tables 5 and 6 summarize the characteristics and results of the meta-analyses.

Table 4. Comparison of Trials/Studies Included in Meta-analyses

Study	Mohamed et al. (2024) (19)	Resende et al. (2020) (20)	Gondal et al. (2020) (21)	Feuerstein et al. (2019) (22)
Alexandersson et al. (2020) (23)	●			
Feuerstein et al. (2020) (24)	●			
Wan et al. (2021) (25)	●			
Yang et al. (2019) (26)	●			
Gulati et al. (2018) (27)		●		
Iacucci et al. (2018) (28)	●	●		●
Bisschops et al. (2018) (29)		●		

Vleugels et al. (2018) (30)		●		
Alexandersson et al. (2018) (71)		●		
Park et al. (2016) (31)		●		●
Watanabe et al. (2016) (33)		●	●	
Gasia et al. (2016) (33)				●
Cassinotti et al. (2015) (34)		●		
Mohammed et al. (2015) (35)	●	●		●
Leifeld et al. (2015) (36)			●	
Freire et al. (2014) (37)		●		●
Iacucci et al. (2014) (38)				●
Ignjatovic et al. (2012) (39)		●	●	
Feitosa et al. (2011) (40)		●		
Pellisé et al. (2011) (41)		●		
van den Broek et al. (2011) (42)		●	●	
Gunther et al. (2011) (43)				●
Hlavaty et al. (2011) (44)				●
van den Broek et al. (2008) (45)		●		
Kiesslich et al. (2007) (46)		●		●
Dekker et al. (2006) (47)			●	
Kiesslich et al. (2003) (48)		●	●	●

Table 5. Characteristics of Meta-analyses

Study	Search Dates	Trials	Participants	N	Design	Duration
Mohamed et al. (2024) (19)	Up to Nov 2022	6	Patients with IBD undergoing dye-based chromo-endoscopy or high-definition white light colonoscopy	978	RCTs	NR
Resende et al. (2020) (20)	Up to 2019	17	Patients with UC or CD undergoing screening with dye-based chromo-endoscopy, virtual chromoendoscopy (NBI, i-SCAN, FICE), standard white-light colonoscopy, and high-definition white light colonoscopy	2457	RCTs	NR
Gondal et al. (2020) (21)	1980-2016	6	Patients with UC undergoing screening with high-definition white light colonoscopy, standard definition colonoscopy, high-definition dye-based chromoendoscopy, or high-definition virtual chromoendoscopy (NBI)	384	Prospective RCTs	NR
Feuerstein et al. (2019) (22)	Up to 2018	10	Patients with IBD undergoing screening with standard or high-definition white light colonoscopy, or dye-based chromoendoscopy	1562	RCTs and non-randomized trials	NR

CD: Crohn disease; FICE: Fujinon Intelligent Color Enhancement; IBD: inflammatory bowel disease; N: number; NBI: narrow band imaging; NR: not rated; RCT: randomized controlled trial; UC: ulcerative colitis.

Table 6. Results of Meta-analyses

Study	Patients diagnosed with dysplastic lesions (n)	Diagnostic lesions detected (n)	Procedure time (minutes)	Dysplasia detection rates per biopsy	Dysplasia detection rates per patient	Detected dysplasia per patient
Mohamed et al. (2024) (19)						
DCE vs. WLE-HD			19.39 vs. 15.84		18.8% vs. 9.4%	

Risk difference (95% CI)			3.5 (0.37 to 7.38)		1.95 (1.21 to 3.11)	
I^2			96%		28%	
Resende et al. (2020) (20)						
DCE vs. WLE-SD	400 vs. 394	400 vs. 394	236 vs. 227			
Risk difference (95% CI)	0.06 (0.03 to 0.10)	0.13 (0.04 to 0.23)	13.41 (7.51 to 19.32)			
I^2	0%	77%	91%			
DCE vs. WLE-HD	242 vs. 251	140 vs. 143	242 vs. 251			
Risk difference (95% CI)	0.06 (-0.01 to 0.13)	-0.00 (-0.33 to 0.33)	2.42 (-2.20 to 7.04)			
I^2	14%	90%	96%			
Total (DCE vs. WLE-SD *and* DCE vs. WLE-HD)	642 vs. 645	540 vs. 537	478 vs. 478			
Risk difference (95% CI)	0.06 (0.03 to 0.10)	0.09 (-0.01 to 0.19)	7.81 (2.76 to 12.86)			
I^2	0%	82%	97%			
DCE vs. NBI	244 vs. 265	244 vs. 265	83 vs. 93			
Risk difference (95% CI)	0.04 (-0.05 to 0.13)	0.06 (-0.08 to 0.21)	9.64 (6.88 to 12.41)			
I^2	45%	69%	0%			
DCE vs. i-SCAN	90 vs. 90	90 vs. 90	90 vs. 90			
Risk difference (95% CI)	0.09 (-0.03 to 0.21)	0.04 (-0.09 to 0.18)	0.90 (-0.30 to 2.10)			
I^2	NA	NA	NA			
DCE vs. FICE	23 vs. 25	23 vs. 25	23 vs. 25			
Risk difference (95% CI)	0.26 (0.08 to 0.45)	0.30 (0.11 to 0.50)	5.70 (2.39 to 9.01)			
I^2	NA	NA	NA			

Total (DCE vs. NBI *and* DCE vs. i-SCAN *and* DCE vs. FICE)	357 vs. 380	357 vs. 380	196 vs. 208			
Risk difference (95% CI)	0.08 (-0.01 to 0.17)	0.10 (-0.02 to 0.21)	6.33 (1.29 to 11.37)			
I^2	59%	71%	92%			
Gondal et al. (2020) (21)						
DCE (high-definition)						
SUCRA[a]				0.66	0.42	0.02
95% CI				0.29 to 1.03	0.06 to 0.79	0.11 to 0.84
Rank				Rank 2	Rank 3	Rank 3
NBI (high-definition)						
SUCRA[a]				0.78	0.71	0.52
95% CI				0.41 to 1.14	0.34 to 1.08	0.25 to 0.99
Rank				Rank 1	Rank 2	Rank 2
WLE-HD						
SUCRA[a]				0.24	0.81	0.88
95% CI				-0.13 to 0.61	0.45 to 1.18	0.51 to 1.24
Rank				Rank 4	Rank 1	Rank 1
WLE-SD						
SUCRA[a]				0.33	0.06	0.03
95% CI				-0.04 to 0.70	-0.31 to 0.43	-0.33 to 0.40
Rank				Rank 3	Rank 4	Rank 4
Feuerstein et al. (2019) (22)						
DCE vs. WLE (RCTs)	84 vs. 55					
Relative risk (95% CI)	1.50 (1.08 to 2.10)					
DCE vs. WLE-HD (RCTs)		245 vs. 248				
Relative risk (95% CI)		1.36 (0.84 to 2.18)				
DCE vs. WLE-SD (RCTs)		249 vs. 248				

Relative risk (95% CI)		2.12 (1.15 to 3.91)				
DCE vs. WLE (non-RCTs)	114 vs. 62					
Relative risk (95% CI)	3.41 (2.13 to 5.47)					
DCE vs. WLE-HD (non-RCTs)		113 vs. 257				
Relative risk (95% CI)		3.15 (1.62 to 6.13)				
DCE vs. WLE-SD (non-RCTs)		58 vs. 141				
Relative risk (95% CI)		3.52 (1.38 to 8.99)				

CI: confidence interval; DCE: dye chromoendoscopy; FICE: Fujinon Intelligent Color Enhancement; n: number; NA: not applicable; NBI: narrow band imaging; RCT: randomized controlled trial; SUCRA: surface under the cumulative ranking; WLE: white light endoscopy; WLE-HD: white light endoscopy high definition; WLE-SD: white light endoscopy standard definition.

[a] Rank number 1 is best.

Randomized Controlled Trial

Wan et al. (2021) conducted a prospective, multicenter RCT in patients with longstanding (at least 6 years) ulcerative colitis. (25) The study compared chromoendoscopy with targeted biopsies to white-light endoscopy with targeted biopsies and random biopsies. In the full-analysis data set, a total of 122 patients with 447 colonoscopies were analyzed, and the randomized groups were as follows: chromoendoscopy (n=39), white-light endoscopy-targeted (n=43), and white-light endoscopy-random (n=40). The primary outcome of the study was the number of colonoscopies that diagnosed dysplasia in each group. The median follow-up period during the study was 55 months; white-light endoscopy-random and chromoendoscopy-treated patients had more colonoscopies that diagnosed dysplasia than white-light endoscopy-targeted treated patients (8.0% vs. 1.9%, p=.013; 9.3% vs. 1.9%, p=.004, respectively). There was no significant difference found between the white-light endoscopy-random and chromoendoscopy groups. In a subgroup analysis in the second half of the follow-up period (37 to 69 months), chromoendoscopy had more colonoscopies that diagnosed dysplasia than white-light endoscopy-targeted (13.3% vs. 1.6%, p=.015) and had results that indicated a trend for increasing dysplasia detection rates compared to white-light endoscopy-random (13.3% vs. 4.9%, p=.107).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. It is uncertain whether chromoendoscopy is more accurate for detecting dysplasia.

Section Summary: Chromoendoscopy for Individuals With Inflammatory Bowel Disease Undergoing Colonoscopy
For individuals who have IBD who receive chromoendoscopy, the evidence includes meta-analyses and a recent RCT. Several meta-analyses found a statistically significant higher yield of chromoendoscopy over standard white-light colonoscopy for detecting dysplasia. The evidence supported that chromoendoscopy improves polyp detection rates; however, the studies had limitations such as lack of information regarding the timing of the screening modalities. However, it is unclear whether improved polyp detection rates will translate into improved health outcomes. Moreover, there are concerns about comparison groups used in some of these trials. It is uncertain whether the control groups received optimal colonoscopy; therefore, the improved detection rates by chromoendoscopy might have been a function of suboptimal standard colonoscopy.

Virtual Chromoendoscopy for Individuals at Average Risk of Colorectal Cancer Undergoing Colonoscopy
Clinical Context and Test Purpose
The purpose of virtual chromoendoscopy in individuals at average risk of CC is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals at average risk of CC.

Interventions
The test being considered for each indication is virtual chromoendoscopy. Virtual chromoendoscopy involves the application of dyes to highlight tissue to facilitate imaging.

Comparators
The following test is currently being used to diagnose or monitor CC: standard white-light colonoscopy.

Outcomes
The general outcome of interest is tumor detection and tumor recurrence in individuals at risk of colorectal cancer.

Based on pathology results, the follow-up would be similar to standards for colonoscopy.

Study Selection Criteria

For the evaluation of the clinical validity of the tests included in this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Meta-analyses

Hussain et al. (2024) compared i-SCAN with high-definition white light in a systematic review and meta-analysis of 4 RCTs (conducted between May 2009 and December 2017). (49) A total of 1495 patients (risk not stated) undergoing colorectal cancer screening or diagnosis, post-polypectomy surveillance, or follow up of a positive occult blood test were included. The adenoma detection rate was 42.2% with i-Scan and 33.5% with high-definition white light (relative risk, 1.25; 95% CI, 1.10 to 1.42; I^2 0.02%; low certainty of evidence). The absolute increase in adenoma detection was 8 per 100 (95% CI, 3 to 14). The proceduralists were not blind to study intervention in any of the study; thus, increasing the risk of bias. No long-term outcomes were reported.

In 2019, Desai et al. published a systematic review and meta-analysis that assessed the adenoma miss rate of white-light colonoscopy compared with virtual chromoendoscopy (e.g., narrow-band imaging [NBI] Fujinon intelligent chromoendoscopy, blue-light imaging, linked-color imaging, and i-SCAN) in a total of 3507 patients (CC risk status not stated) from 7 eligible RCTs. (50) Of these patients, 1423 underwent a white-light colonoscopy as the first of tandem examinations; the remaining patients underwent virtual chromoendoscopy first. Results revealed a pooled adenoma miss rate for virtual chromoendoscopy compared to white-light colonoscopy of 17.9% versus 21% (odds ratio, 0.72; 95% CI, 0.67 to 1.11; p=.13). Additionally, the pooled adenoma detection rate was not significantly different with virtual chromoendoscopy as compared to white-light colonoscopy (odds ratio, 1.02; 95% CI, 0.88 to 1.19; p=.78).

A systematic review by Omata et al. (2014) compared rates of polyp detection by virtual chromoendoscopy (i.e., Fujinon Intelligent Color Enhancement [FICE] or i-SCAN) with white-light colonoscopy. (51) Reviewers included patients of all risk levels and selected only RCTs. Five trials on FICE and i-SCAN met eligibility criteria. Analyses did not find significantly higher detection rates with virtual chromoendoscopy. The pooled relative risk for the adenoma and neoplasia detected by virtual chromoendoscopy versus conventional chromoendoscopy was 1.09 (95% CI, 0.97 to 1.23; p>.05).

Randomized Controlled Trials

Two studies using modified back-to-back designs in patients undergoing screening colonoscopy were conducted by Chung et al. (2014) in South Korea. The larger study included 1650 adults at average risk of CC, who were randomized across 3 groups. (52) During the colonoscopy, the endoscope was fully inserted, and each of 3 colonic segments (ascending, transverse, descending) was inspected twice during withdrawal. Participants received first withdrawal with NBI, virtual chromoendoscopy using FICE, or white-light colonoscopy (n=550 each group). White-light was used in all groups for the second inspection. Ninety-one (5.5%) patients were excluded from the analysis due to inadequate bowel preparation. For the primary outcome of adenoma detection rate, no statistically significant differences were found among the 3 groups. The percentage of patients with at least 1 adenoma was 24.5% in the NBI group, 23.6% in the FICE group, and 25.3% in the white-light group (p=.75). Moreover, the mean number of adenomas per patient was 0.35 in the NBI group, 0.36 in the FICE group, and 0.37 in the white-light group (p=.59). The adenoma miss rate, defined as an adenoma identified only during the second inspection, was 22.9% in the NBI group, 26.0% in the FICE group, and 20.8% in the white-light only group; the difference was not statistically significant (p=.30). The mean size of the missed adenomas was 3.6 mm, which was smaller than the mean size of adenomas found during the first withdrawal (4.4 mm).

The other study by Chung et al. (2010) included 359 asymptomatic patients receiving screening colonoscopies. (53) All received back-to-back examinations with white-light colonoscopy or FICE in random order (n=181 received white-light first, n=178 received FICE first). During the initial colonoscopy, 60 (33.7%) of patients in the FICE group and 55 (30.4%) in the white-light group were found to have at least 1 adenoma; the difference between groups was not statistically significant (p=.74). The adenoma miss rate was 6.6% in the FICE group and 8.3% in the white-light group; again, the difference was not statistically significant (p=.59). All missed adenomas were low-grade and nonpedunculated. All but 1 (which was 6 mm) was 5 mm or less in size. In both the Chung et al. (2010, 2014) studies, virtual chromoendoscopy did not improve rates of adenoma detection compared with white-light endoscopy and did not identify more large adenomas.

An industry-supported multicenter RCT by Pohl et al. (2009) in Germany compared FICE with targeted standard chromoendoscopy using indigo carmine stain. (54) The trial enrolled 871 patients presenting for screening (57%) or diagnostic (43%) colonoscopy. All patients were examined using high-resolution zoom endoscopes. Patients in the group receiving standard chromoendoscopy underwent withdrawal using white-light colonoscopy. Indigo carmine was applied. In the FICE group, withdrawal was performed using FICE at the preset for examining colorectal mucosa. Data were available for 764 patients (368 in the FICE group, 396 in the standard chromoendoscopy group); 107 patients were excluded for poor bowel preparation, incomplete colonoscopy, or incomplete documentation. A total of 131 (35.6%) patients in the FICE group and 140 (35.4%) patients in the standard chromoendoscopy group had at least 1 adenoma (p=1.0). The number of small adenomas (defined as ≤10 mm) did not differ significantly between groups (p=.41). The proportion of large adenomas greater than 10 mm identified in both groups was not reported. The proportion of patients with carcinoma was

small in both groups and did not differ significantly (12 [3.3%] in the FICE group versus 12 [3.0%] in the standard chromoendoscopy group; p=.85).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs found improvement in the detection of clinically important polyps.

Section Summary: Virtual Chromoendoscopy for Individuals at Average Risk of Colorectal Cancer Undergoing Colonoscopy

For individuals who have an average risk of CC who receive virtual chromoendoscopy, the evidence includes several RCTs and systematic reviews with meta-analyses. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy.

Virtual Chromoendoscopy for Individuals at Increased Risk of Colorectal Cancer Undergoing Colonoscopy

Clinical Context and Test Purpose

The purpose of virtual chromoendoscopy in individuals at increased risk of CC is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals at increased risk of CC.

Interventions

The test being considered for each indication is virtual chromoendoscopy. Virtual chromoendoscopy involves the application of dyes to highlight tissue to facilitate imaging.

Comparators

The following test is currently being used to diagnose or monitor CC: standard white-light colonoscopy.

Outcomes

The general outcome of interest is tumor detection and tumor recurrence in individuals at risk of CC.

Based on pathology results, the follow-up would be similar to standards for colonoscopy.

Study Selection Criteria

For the evaluation of the clinical validity of the tests included in this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Randomized Trials

A study using a modified back-to-back colonoscopy design was published by Kiriyama et al. (2012) in Japan. (55) It included 102 consecutive patients who received virtual chromoendoscopy using FICE or white-light colonoscopy in random order. Patients were eligible for study inclusion if they had been referred for a colonoscopy following sigmoidoscopy or for postoperative surveillance after anterior resection. Those with known IBD, bleeding, and polyposis syndrome were excluded; the right-sided colon was examined in the remaining patients. All lesions identified during either examination were removed, and specimens were evaluated. Two patients were excluded from the analysis because insertion was not possible, leaving 100 patients in the analysis. A total of 110 lesions were detected. Of these, 65 lesions were detected using FICE and 45 with white-light; the difference in the number of detected lesions did not differ significantly between groups. Most lesions detected were neoplastic; of these, 59 (91%) were found using FICE and 38 (84%) using white-light colonoscopy. The miss rate was defined as the proportion of total lesions in that grouping detected on the second examination. The miss rate for all polyps with FICE (12/39 [31%] lesions) was significantly lower than with white-light (28/61 [46%] lesions; p=.03). Twenty-six (44%) of 59 neoplastic lesions detected by FICE and 14 (37%) of 38 neoplastic lesions detected by white-light colonoscopy were at least 5 mm in size. For neoplastic lesions larger than 5 mm, there was no statistically significant difference between the FICE and white-light examinations in terms of the number of lesions detected.

Cha et al. (2010) evaluated South Korean patients at increased risk of CC due to a personal history of polyps or gastrointestinal symptoms. (56) A total of 135 patients underwent colonoscopy. Seven were excluded due to poor bowel preparation or diagnosis of colon cancer or intestinal disease. Thus, 128 patients were randomized to white-light colonoscopy (n=65) or virtual chromoendoscopy with FICE (n=63). The overall percentage of adenomas and the overall

number of polyps did not differ significantly between groups. Thirty-one (49.2%) patients in the FICE group and 23 (35.4%) in the white-light group had 1 or more adenomas (p=.12). The mean number of adenomas identified per patient was also similar between groups: 1.39 in the FICE group and 1.96 in the white-light group (p=.46). The number of adenomas less than 5 mm in size (the primary study outcome) differed significantly between groups. Twenty-eight (44.4%) patients in the FICE group and 14 (21.5%) in the white-light group (p=.006) were found to have adenomas between 0 mm and 5 mm. All adenomas identified were low grade and no complications were reported in either group.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs found improvement in the detection of clinically important polyps.

Section Summary: Virtual Chromoendoscopy for Individuals at Increased Risk of Colorectal Cancer Undergoing Colonoscopy

For individuals who have an increased risk of CC who receive virtual chromoendoscopy, the evidence includes RCTs. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy.

Virtual Chromoendoscopy for Individuals With Inflammatory Bowel Disease Undergoing Colonoscopy

Clinical Context and Test Purpose

The purpose of virtual chromoendoscopy in individuals with IBD is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with IBD.

Interventions

The test being considered is virtual chromoendoscopy. Virtual chromoendoscopy involves the application of dyes to highlight tissue to facilitate imaging.

Comparators

The following test is currently being used to diagnose or monitor IBD: standard white-light colonoscopy.

Outcomes
The general outcomes of interest are tumor detection, dysplasia, and other mucosal abnormalities in IBD.

Based on pathology results, the follow-up would be similar to standards for colonoscopy.

Study Selection Criteria
For the evaluation of the clinical validity of the tests included in this review, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Meta-analyses
The meta-analyses by Resende et al. (2020) and Gondal et al. (2020), discussed above in the section on dye-based chromoendoscopy, compared the effectiveness of multiple endoscopic methods (including virtual chromoendoscopy) of surveillance for dysplasia in patients with IBD. (20, 21) In brief, Resende et al. (2020) found no difference between dye-based chromoendoscopy and virtual chromoendoscopy for all outcomes (related to dysplasia detection) except procedure time. (20) In Gondal et al. (2020), a direct meta-analysis showed superiority of NBI (virtual chromoendoscopy) over high-definition white light colonoscopy for dysplasia per biopsy, and network meta-analysis ranked NBI as the best screening modality for detecting dysplasia per biopsy compared to other methods. (21) For both dysplasia detection rates and numbers per patient, network meta-analysis ranked NBI as the second best screening modality.

Randomized Controlled Trials
Neumann et al. (2013) randomized 83 patients with mild or inactive IBD to high-definition white-light endoscopy or virtual chromoendoscopy. (57) Seventy-eight (94%) patients completed the trial; 5 were excluded due to insufficient bowel preparation. During endoscopy, biopsies were taken from the most distal part of mucosal inflammation; random biopsies were taken to determine the extent and severity of inflammation. Histopathologic analysis was done by a pathologist blinded to endoscopic findings. Endoscopic examination findings on the extent of disease concurred with histopathologic findings in 19 (48.7%) of 39 patients in the white-light group and in 36 (92.3%) of 39 patients in the virtual chromoendoscopy group. The difference

between groups was statistically significant, favoring virtual chromoendoscopy (p=.001). In terms of disease activity, the agreement between the endoscopic prediction of disease activity and histopathologic findings was 21 (53.9%) of 39 white-light patients and 35 (89.7%) of 39 virtual chromoendoscopy patients (p=.066). Although the agreement was higher in the virtual chromoendoscopy group, the between-group difference was not statistically significant (p<.05).

Kandiah et al. (2021), in the United Kingdom, published a multicenter RCT comparing the performance of high-definition white light versus high-definition virtual chromoendoscopy in patients with longstanding (at least 8 years) ulcerative or Crohn colitis. (58) Patients were randomized, prior to starting surveillance colonoscopy, to either white light (n=92) or virtual chromoendoscopy (n=92) for a total of 184 patients included in the final analysis. The primary outcome was the difference in neoplasia detection rate between the 2 arms. Twenty-five neoplastic lesions were found in 14 patients in the virtual chromoendoscopy arm; 27 lesions were found in 22 patients in the white light arm. Compared to the virtual chromoendoscopy arm, neoplasia detection rate was higher in the white light arm (23.4% vs. 14.9%), but this was not statistically significant (p=.14). The mean number of biopsies taken per patient was 35.9 in each arm of the study, and the difference in the mean number of neoplasia per patient was not statistically significant between the 2 arms (p=.75).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. One RCT found no improvement in identifying disease activity.

Section Summary: Virtual Chromoendoscopy for Individuals With Inflammatory Bowel Disease Undergoing Colonoscopy

For individuals who have IBD who receive virtual chromoendoscopy, the evidence includes meta-analyses and RCTs. One meta-analysis showed superiority of virtual chromoendoscopy over high-definition white light colonoscopy for dysplasia per biopsy, and ranked virtual chromoendoscopy as the best option for screening among the different modalities in comparison. The second meta-analysis found no difference between dye-based chromoendoscopy and virtual chromoendoscopy for dysplasia detection. One RCT found a significantly greater likelihood that virtual chromoendoscopy would correctly identify the extent of disease inflammation than standard colonoscopy but no significant difference in the likelihood of identifying disease activity. The other RCT found that there was no significant difference in the detection of neoplasia between high definition white light versus high-definition virtual chromoendoscopy in patients with long-standing IBD. There is a lack of studies

assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy.

Summary of Evidence

Chromoendoscopy

For individuals who have an average risk of colorectal cancer (CC) who receive chromoendoscopy, the evidence includes randomized controlled trials (RCTs) and a meta-analysis of these RCTs. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), test validity, and change in disease status. The meta-analysis demonstrated that dye-based chromoendoscopy increased the adenoma detection rate and adenomas per colonoscopy in patients at average or increased risk of CC compared to standard or high-definition white light colonoscopy. However, limitations included unclear indication of colonoscopy in the studies (which included patients with screening and surveillance), and some heterogeneity in mean adenomas per patient. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have an increased risk of CC who receive chromoendoscopy, the evidence includes systematic reviews and a recent RCT. Relevant outcomes are OS, DSS, test validity, and change in disease status. A Cochrane systematic review of trials comparing chromoendoscopy with standard colonoscopy in high-risk patients (but excluding those with inflammatory bowel disease [IBD]) found significantly higher rates of adenoma detection and rates of 3 or more adenomas with chromoendoscopy than with standard colonoscopy. The evidence for detecting larger polyps, defined as greater than 5 mm or greater than 10 mm, is less robust. While 1 study reported a significantly higher detection rate for polyps greater than 5 mm, no studies reported increased detection of polyps greater than 10 mm. A recent RCT and systematic review involving patients with Lynch syndrome also found equivocal results. Results from the RCT showed similar neoplasia detection rates with chromoendoscopy and conventional white-light colonoscopy, while the systematic review concluded that chromoendoscopy is associated with significantly improved detection of certain lesions; however, the odds of having an adenoma detected were not significantly different between the modalities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBD who receive chromoendoscopy, the evidence includes meta-analyses and RCTs. Relevant outcomes are OS, DSS, test validity, and change in disease status. Several meta-analyses found a statistically significant higher yield of chromoendoscopy over standard white-light colonoscopy for detecting dysplasia. The evidence supported improved polyp detection rates with chromoendoscopy; however, the studies had limitations such as lack of information regarding the timing of the screening modalities A recent RCT found increased detection of dysplasia with chromoendoscopy compared to white-light endoscopy, although the benefit was only observed in a subgroup analysis in the second half of the study follow-up period. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Virtual Chromoendoscopy

For individuals who have an average risk of CC who receive virtual chromoendoscopy, the evidence includes several RCTs and systematic reviews with meta-analyses. Relevant outcomes are OS, DSS, test validity, and change in disease status. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have an increased risk of CC who receive virtual chromoendoscopy, the evidence includes RCTs. Relevant outcomes are OS, DSS, test validity, and change in disease status. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBD who receive virtual chromoendoscopy, the evidence includes 2 meta-analyses and 2 RCTs. Relevant outcomes are OS, DSS, test validity, and change in disease status. One meta-analysis showed superiority of virtual chromoendoscopy over high-definition white light colonoscopy for dysplasia per biopsy, and ranked virtual chromoendoscopy as the best option for screening among the different modalities in comparison. The second meta-analysis found no difference between dye-based chromoendoscopy and virtual chromoendoscopy for dysplasia detection. One RCT found a significantly greater likelihood that virtual chromoendoscopy would correctly identify the extent of disease inflammation than standard colonoscopy but no significant difference in the likelihood of identifying disease activity. The other RCT found that there was no significant difference in the detection of neoplasia between high definition white light versus high-definition virtual chromoendoscopy in patients with long-standing IBD. There is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Gastroenterological Association

In 2021, the American Gastroenterological Association (AGA) published a clinical practice update on the surveillance and management of colorectal dysplasia in patients with inflammatory bowel disease (IBD). (59) This was an expert review that underwent internal peer review by the AGA Clinical Practice Updates Committee and external peer review through standard procedures undertaken by the publishing journal (*Gastroenterology*). Table 7 summarizes relevant best practice statements.

Table 7. Best Practice Advice on Surveillance and Management of Dysplasia in Patients With Inflammatory Bowel Disease

Best Practice Statement
"Dye spray chromoendoscopy, performed by appropriately trained endoscopists, should be considered in all persons with colonic inflammatory bowel disease undergoing surveillance colonoscopy, particularly if a standard definition endoscope is used or if there is a history of dysplasia."
"Virtual chromoendoscopy is a suitable alternative to dye spray chromoendoscopy for dysplasia detection in persons with colonic inflammatory bowel disease when using high-definition endoscopy."
"Extensive nontargeted biopsies (roughly 4 adequately spaced biopsies every 10 cm) should be taken from flat colorectal mucosa in areas previously affected by colitis when white light endoscopy is used without dye spray chromoendoscopy or virtual chromoendoscopy. Additional biopsies should be taken from areas of prior dysplasia or poor mucosal visibility. Nontargeted biopsies are not routinely required if dye spray chromoendoscopy or virtual chromoendoscopy is performed using a high-definition endoscope, but should be considered if there is a history of dysplasia or primary sclerosing cholangitis."
"A finding of invisible dysplasia should prompt repeat examination by an experienced endoscopist using high-definition dye spray chromoendoscopy under optimized viewing conditions, with extensive nontargeted biopsies in the area of prior dysplasia if no lesion is seen. A finding of unresectable visible dysplasia or of invisible multifocal or high-grade dysplasia on histology should prompt colectomy. For visible lesions that can be resected or if histologic dysplasia is not confirmed on a high-quality dye spray chromoendoscopy examination, continued endoscopic surveillance at frequent intervals is appropriate."
"Targeted biopsies of representative or concerning pseudopolyps is appropriate during colonoscopy. Removal and sampling of all lesions is neither required nor practical. Surgery should be a last resort to manage colorectal cancer risk in the setting of severe pseudopolyposis. Dye spray chromoendoscopy should not be used to detect flat or subtle lesions within a field of pseudopolyps."

American Society for Gastrointestinal Endoscopy and the American Gastroenterological Association

In 2015, the American Society for Gastrointestinal Endoscopy (ASGE) and the American Gastroenterological Association (AGA) published a SCENIC consensus statement on the surveillance and management of dysplasia in patients with IBD. (60) This statement, developed by an international multidisciplinary group representing a variety of stakeholders, incorporated systematic reviews of the literature. Table 8 summarizes relevant recommendations.

Table 8. Recommendations on Surveillance and Management of Dysplasia in Patients With Inflammatory Bowel Disease

Recommendation	LOA	SOR	QOE
"When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition."	80%	Strong	Low

"When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy."	85%	Strong	Moderate
"When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy."	84%	Conditional	Low

LOA: level of agreement; QOE: quality of evidence; SOR: strength of recommendation.

Panelists did not reach consensus on the use of chromoendoscopy in random biopsies of patients with IBD undergoing surveillance.

Commentaries in 2 gastroenterology journals questioned whether the SCENIC guidelines would be accepted as the standard of care in IBD surveillance. (61, 62) Both commentaries noted that the guidelines considered the outcome of the detection of dysplasia and not disease progression or survival. Moreover, the commentators noted the lack of longitudinal data on clinical outcomes in patients with dysplastic lesions detected using chromoendoscopy. Two other articles published in 2022 comment on how the approach to dysplasia surveillance in IBD has changed significantly since the publication of the SCENIC guidelines, and therefore, updates to the recommendations are warranted based on findings from recent meta-analyses and randomized trials (discussed in this review). (63, 64)

The ASGE (2015) issued guidelines on endoscopy in the diagnosis and treatment of IBD, which made the following recommendations about chromoendoscopy: "Chromoendoscopy with pancolonic dye spraying and targeted biopsies is sufficient for surveillance in inflammatory bowel disease; consider 2 biopsies from each colon segment for histologic staging." (65) The ASGE (2015) also published a systematic review and meta-analysis assessing narrow-band imaging, i-SCAN, and Fujinon Intelligent Color Enhancement for predicting adenomatous polyp histology of small or diminutive colorectal polyps to determine whether they have met previously established criteria or thresholds to incorporate into clinical practice. (66) The ASGE assessment confirmed that: "....The thresholds have been met for narrow-band imaging with endoscopists who are experts in using these advanced imaging technologies and when assessments are made with high confidence. The ASGE Technology Committee endorsed the use of NBI [narrow band imaging] for both the 'diagnose-and-leave' strategy for diminutive (≤5 mm) rectosigmoid hyperplastic polyps and the 'resect-and-discard' strategy for diminutive (≤5 mm) adenomatous polyps."

The report addressed the "trepidation" of patients, endoscopists, and pathologists with the "diagnose-and-leave" strategy, indicating there are challenges for implementation of the use of these strategies in clinical practice.

U.S. Multi-Society Task Force on Colorectal Cancer

In 2020, the U.S. Multi-Society Task Force issued guidelines on the endoscopic removal of colorectal lesions. Regarding lesion assessment and description, the Task Force suggested "proficiency in the use of electronic- (e.g., NBI, i-SCAN, and Fuji Intelligent Chromoendoscopy,

or blue light imaging) or dye (chromoendoscopy)-based image-enhanced endoscopy techniques to apply optical diagnosis classifications for colorectal lesion histology [conditional recommendation, moderate-quality evidence]." (67) The Task Force also suggested "careful examination of the post-mucosectomy scar site using enhanced imaging, such as dye-based (chromoendoscopy) or electronic-based methods, as well as obtaining targeted biopsies of the site. Post-resection scar sites that show both normal macroscopic and microscopic (biopsy) findings have the highest predictive value for long-term eradication [conditional recommendation, moderate-quality evidence]."

In 2012, the U.S. Multi-Society Task Force guidelines on colonoscopy surveillance after screening and polypectomy (consensus update) stated that chromoendoscopy and narrow-band imaging might enable endoscopists to accurately determine if lesions are neoplastic and if there is a need to remove them and send specimens to pathology. (68) The guidelines noted that these technologies currently do not have an impact on surveillance intervals. In 2020, the U.S. Multi-Society Task Force published updated recommendations for follow-up after colonoscopy and polypectomy (consensus update); however, there was no mention of chromoendoscopy. (69)

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2021) recommendations on screening for colorectal cancer do not mention chromoendoscopy. (70)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT06596317	Impact of Indigo Carmine Pump Spraying on the Adenoma Detection Rate: A Prospective Randomized Controlled Trial	688	Oct 2024
NCT04403997[†]	Virtual Chromoendoscopy with Second Generation NBI (HQ190) vs Chromoendoscopy in Inflammatory Bowel Disease	175	Feb 2022
NCT04257084[†]	Surveillance in Ulcerative Colitis: Narrow Band Image Versus Chromoendoscopy for High-risk Groups (SUNRISE-High)	188	Jan 2023
NCT04291976	Back-to-back Endoscopy Versus Single-pass Endoscopy and Chromoendoscopy in IBD Surveillance (HELIOS)	560	Nov 2023

NCT: national clinical trial.

[†] Studies have passed estimated completion date but status is unknown

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	44799, 45999
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Zhao S, Wang S, Pan P, et al. Magnitude, Risk Factors, and Factors Associated With Adenoma Miss Rate of Tandem Colonoscopy: A Systematic Review and Meta-analysis. Gastroenterology. May 2019; 156(6):1661-1674.e11. PMID 30738046
2. U.S. Food & Drug Administration. 510(k) Premarket Notification (K140149) (2014). Available at <https://www.accessdata.fda.gov> (accessed September 22, 2024).
3. U.S. Food and Drug Administration (FDA). 510(k) Summary: Pentax EPK-i5010 Video Processor (2013) (PMA K122470). Available at <https://www.accessdata.fda.gov> (accessed September 23, 2024).
4. Antonelli G, Correale L, Spadaccini M, et al. Dye-based chromoendoscopy for the detection of colorectal neoplasia: meta-analysis of randomized controlled trials. Gastrointest Endosc. Sep 2022; 96(3):411-422. PMID 35588768
5. Hurt C, Ramaraj R, Farr A, et al. Feasibility and economic assessment of chromocolonoscopy for detection of proximal serrated neoplasia within a population-based colorectal cancer screening programme (CONSCOP): an open-label, randomised controlled non-inferiority trial. Lancet Gastroenterol Hepatol. May 2019; 4(5):364-375. PMID 30885505
6. Repici A, Wallace MB, East JE, et al. Efficacy of per-oral methylene blue formulation for screening colonoscopy. Gastroenterology. Jun 2019; 156(8):2198-2207.e1. PMID 30742834
7. Lesne A, Rouquette O, Touzet S, et al. Adenoma detection with blue-water infusion colonoscopy: a randomized trial. Endoscopy. Aug 2017; 49(8):765-775. PMID 28399611
8. Pohl J, Schneider A, Vogell H, et al. Pancolonic chromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: a randomised two-centre trial. Gut. Apr 2011; 60(4):485-490. PMID 21159889
9. Kahi CJ, Anderson JC, Waxman I, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. Am J Gastroenterol. Jun 2010; 105(6):1301-1307. PMID 20179689

10. Stoffel EM, Turgeon DK, Stockwell DH, et al. Chromoendoscopy detects more adenomas than colonoscopy using intensive inspection without dye spraying. Cancer Prev Res (Phila). Dec 2008; 1(7):507-513. PMID 19139000
11. Le Rhun M, Coron E, Parlier D, et al. High resolution colonoscopy with chromoscopy versus standard colonoscopy for the detection of colonic neoplasia: a randomized study. Clin Gastroenterol Hepatol. Mar 2006; 4(3):349-354. PMID 16527699
12. Lapalus MG, Helbert T, Napoleon B, et al. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy. May 2006; 38(5):444-448. PMID 16767577
13. Hurlstone DP, Cross SS, Slater R, et al. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut. Mar 2004; 53(3):376-380. PMID 14960519
14. Brooker JC, Saunders BP, Shah SG, et al. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc. Sep 2002; 56(3):333-338. PMID 12196768
15. Har-Noy O, Yung DE, Koulaouzidis A, et al. Chromoendoscopy or white light endoscopy for neoplasia detection in Lynch syndrome, a meta-analysis. Dig Liver Dis. Nov 2019; 51(11):1515-1521. PMID 31526715
16. Brown SR, Baraza W. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. Cochrane Database Syst Rev. Oct 06 2010; (10):CD006439. PMID 20927746
17. Brown SR, Baraza W, Din S, et al. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. Cochrane Database Syst Rev. 2016; 4(4):CD006439. PMID 27056645
18. Haanstra JF, Dekker E, Cats A, et al. Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial. Gastrointest Endosc. Oct 2019; 90(4):624-632. PMID 31028782
19. Mohamed MFH, Marino D, Elfert K, et al. Dye Chromoendoscopy Outperforms High-Definition White Light Endoscopy in Dysplasia Detection for Patients With Inflammatory Bowel Disease: An Updated Meta-Analysis of Randomized Controlled Trials. Am J Gastroenterol. Apr 01 2024; 119(4):719-726. PMID 38038351
20. Resende RH, Ribeiro IB, de Moura DTH, et al. Surveillance in inflammatory bowel disease: is chromoendoscopy the only way to go? A systematic review and meta-analysis of randomized clinical trials. Endosc Int Open. May 2020; 8(5):E578-E590. PMID 32355874
21. Gondal B, Haider H, Komaki Y, et al. Efficacy of various endoscopic modalities in detecting dysplasia in ulcerative colitis: A systematic review and network meta-analysis. World J Gastrointest Endosc. May 16 2020; 12(5):159-171. PMID 32477450
22. Feuerstein JD, Rakowsky S, Sattler L, et al. Meta-analysis of dye-based chromoendoscopy compared with standard- and high-definition white-light endoscopy in patients with inflammatory bowel disease at increased risk of colon cancer. Gastrointest Endosc. Aug 2019; 90(2):186-195.e1. PMID 31009609
23. Alexandersson B, Hamad Y, Andreasson A, et al. High-Definition Chromoendoscopy Superior to High-Definition White-Light Endoscopy in Surveillance of Inflammatory Bowel Diseases in

a Randomized Trial. Clin Gastroenterol Hepatol. Aug 2020; 18(9):2101-2107. PMID 32353535
24. Feuerstein JD, El-Dallal M, Rosenwald N, et al. Chromoendoscopy and high definition white light colonoscopy are equally effective to screen for colon cancer in inflammatory bowel diseases: a randomized control trial preliminary analysis. Gastroenterology. 2020; 158(6 Suppl 1):S930-931.
25. Wan J, Zhang Q, Liang SH, et al. Chromoendoscopy with targeted biopsies is superior to white-light endoscopy for the long-term follow-up detection of dysplasia in ulcerative colitis patients: a multicenter randomized-controlled trial. Gastroenterol Rep (Oxf). Jan 2021; 9(1):14-21. PMID 33747522
26. Yang DH, Park SJ, Kim HS, et al. High-Definition Chromoendoscopy Versus High-Definition White Light Colonoscopy for Neoplasia Surveillance in Ulcerative Colitis: A Randomized Controlled Trial. Am J Gastroenterol. Oct 2019; 114(10):1642-1648. PMID 31567166
27. Gulati S, Dubois P, Carter B, et al. A Randomized Crossover Trial of Conventional vs Virtual Chromoendoscopy for Colitis Surveillance: Dysplasia Detection, Feasibility, and Patient Acceptability (CONVINCE). Inflamm Bowel Dis. May 04 2019; 25(6):1096-1106. PMID 30576449
28. Iacucci M, Kaplan GG, Panaccione R, et al. A Randomized Trial Comparing High Definition Colonoscopy Alone With High Definition Dye Spraying and Electronic Virtual Chromoendoscopy for Detection of Colonic Neoplastic Lesions During IBD Surveillance Colonoscopy. Am J Gastroenterol. Feb 2018; 113(2):225-234. PMID 29134964
29. Bisschops R, Bessissow T, Joseph JA, et al. Chromoendoscopy versus narrow band imaging in UC: a prospective randomised controlled trial. Gut. Jun 2018; 67(6):1087-1094. PMID 28698230
30. Vleugels JLA, Rutter MD, Ragunath K, et al. Chromoendoscopy versus autofluorescence imaging for neoplasia detection in patients with longstanding ulcerative colitis (FIND-UC): an international, multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. May 2018; 3(5):305-316. PMID 29567006
31. Park SJ, Kim HS, Yang DH, et al. High definition chromoendoscopy with water-jet versus high definition white light endoscopy in the detection of dysplasia in long standing ulcerative colitis: a multicenter prospective randomized controlled study. Gastroenterology. Apr 2016; 150:S1270.
32. Watanabe K, Nishishita M, Shimamoto F, et al. 722 Comparison Between Newly-Developed Narrow Band Imaging and Panchromoendoscopy for Surveillance Colonoscopy in Patients With Longstanding Ulcerative Colitis: A Prospective Multicenter Randomized Controlled Trial, Navigator Study. Gastrointestinal Endoscopy. May 2016; 83(5):AB172.
33. Gasia MF, Ghosh S, Panaccione R, et al. Targeted biopsies identify larger proportions of patients with colonic neoplasia undergoing high-definition colonoscopy, dye chromoendoscopy, or electronic virtual chromoendoscopy. Clin Gastroenterol Hepatol. May 2016; 14(5):704-712.e4. PMID 26804384
34. Cassinotti A, Buffoli F, Fociani P, et al. Virtual Chromoendoscopy With FICE for the Classification of Polypoid and Nonpolypoid Raised Lesions in Ulcerative Colitis. J Clin Gastroenterol. Apr 2019; 53(4):269-276. PMID 29394176

35. Mohammed N, Kant P, Abid F, et al. OC-028 High-definition white light endoscopy (HDWLE) versus high definition with chromoendoscopy (HDCE) in the detection of dysplasia in long standing ulcerative colitis: a randomised controlled trial. Gut. 2015; 64(1):A14-A15.
36. Leifeld L, Rogler G, Stallmach A, et al. White-Light or Narrow-Band Imaging Colonoscopy in Surveillance of Ulcerative Colitis: A Prospective Multicenter Study. Clin Gastroenterol Hepatol. Oct 2015; 13(10):1776-1781.e1. PMID 25952309
37. Freire P, Figueiredo P, Cardoso R, et al. Surveillance in ulcerative colitis: is chromoendoscopy-guided endomicroscopy always better than conventional colonoscopy? A randomized trial. Inflamm Bowel Dis. Nov 2014; 20(11):2038-2045. PMID 25185683
38. Iacucci M, Hassan C, Fort Gasia M, et al. Serrated adenoma prevalence in inflammatory bowel disease surveillance colonoscopy, and characteristics revealed by chromoendoscopy and virtual chromoendoscopy. Can J Gastroenterol Hepatol. Dec 2014; 28(11):589-594. PMID 25575106
39. Ignjatovic A, East JE, Subramanian V, et al. Narrow band imaging for detection of dysplasia in colitis: a randomized controlled trial. Am J Gastroenterol. Jun 2012; 107(6):885-890. PMID 22613903
40. Feitosa F, Carlos A, Guilherme Nogueira J, et al. Narrow-band imaging and chromoendoscopy for the detection of colonic dysplasia in inflammatory bowel disease: a prospective and randomized study. Inflamm Bowel Dis. 2011; 17:S14-S15.
41. Pellise M, Lopez-Ceron M, Rodriguez de Miguel C, et al. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. Gastrointest Endosc. Oct 2011; 74(4):840-848. PMID 21802681
42. van den Broek FJ, Fockens P, van Eeden S, et al. Narrow-band imaging versus high-definition endoscopy for the diagnosis of neoplasia in ulcerative colitis. Endoscopy. Feb 2011; 43(2):108-115. PMID 21165822
43. Günther U, Kusch D, Heller F, et al. Surveillance colonoscopy in patients with inflammatory bowel disease: comparison of random biopsy vs. targeted biopsy protocols. Int J Colorectal Dis. May 2011; 26(5):667-672. PMID 21279369
44. Hlavaty T, Huorka M, Koller T, et al. Colorectal cancer screening in patients with ulcerative and Crohn's colitis with use of colonoscopy, chromoendoscopy and confocal endomicroscopy. Eur J Gastroenterol Hepatol. Aug 2011; 23(8):680-689. PMID 21602687
45. van den Broek FJ, Fockens P, van Eeden S, et al. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. Gut. Aug 2008; 57(8):1083-1089. PMID 18367559
46. Kiesslich R, Goetz M, Lammersdorf K, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology. Mar 2007; 132(3):874-882. PMID 17383417
47. Dekker E, van den Broek FJ, Reitsma JB, et al. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy. Mar 2007; 39(3):216-221. PMID 17385106

48. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. Apr 2003; 124(4):880-888. PMID 12671882
49. Hussain MR, Ali FS, Tangri A, et al. The incremental yield of adenoma detection with I-Scan versus high-definition white light colonoscopy-a systematic review and meta-analysis of randomized studies. Int J Colorectal Dis. Sep 27 2023; 38(1):240. PMID 37755588
50. Desai M, Viswanathan L, Gupta N, et al. Impact of Electronic Chromoendoscopy on Adenoma Miss Rates During Colonoscopy: A Systematic Review and Meta-analysis. Dis Colon Rectum. Sep 2019; 62(9):1124-1134. PMID 31162375
51. Omata F, Ohde S, Deshpande GA, et al. Image-enhanced, chromo, and cap-assisted colonoscopy for improving adenoma/neoplasia detection rate: a systematic review and meta-analysis. Scand J Gastroenterol. Feb 2014; 49(2):222-237. PMID 24328858
52. Chung SJ, Kim D, Song JH, et al. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. Gut. May 2014; 63(5):785-791. PMID 23853211
53. Chung SJ, Kim D, Song JH, et al. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. Gastrointest Endosc. Jul 2010; 72(1):136-142. PMID 20493487
54. Pohl J, Lotterer E, Balzer C, et al. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. Gut. Jan 2009; 58(1):73-78. PMID 18838485
55. Kiriyama S, Matsuda T, Nakajima T, et al. Detectability of colon polyp using computed virtual chromoendoscopy with flexible spectral imaging color enhancement. Diagn Ther Endosc. 2012; 2012:596303. PMID 22474404
56. Cha JM, Lee JI, Joo KR, et al. A prospective randomized study on computed virtual chromoendoscopy versus conventional colonoscopy for the detection of small colorectal adenomas. Dig Dis Sci. Aug 2010; 55(8):2357-2364. PMID 19834809
57. Neumann H, Vieth M, Gunther C, et al. Virtual chromoendoscopy for prediction of severity and disease extent in patients with inflammatory bowel disease: a randomized controlled study. Inflamm Bowel Dis. Aug 2013; 19(9):1935-1942. PMID 23839228
58. Kandiah K, Subramaniam S, Thayalasekaran S, et al. Multicentre randomised controlled trial on virtual chromoendoscopy in the detection of neoplasia during colitis surveillance high-definition colonoscopy (the VIRTUOSO trial). Gut. Sep 2021; 70(9):1684-1690. PMID 33214162
59. Murthy SK, Feuerstein JD, Nguyen GC, et al. AGA clinical practice update on endoscopic surveillance and management of colorectal dysplasia in inflammatory bowel diseases: expert review. Gastroenterology. Sep 2021; 161(3):1043-1051.e4. PMID 34416977
60. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. Mar 2015; 148(3):639-651.e28. PMID 25702852

61. Higgins PD. Miles to go on the SCENIC route: should chromoendoscopy become the standard of care in IBD surveillance? Am J Gastroenterol. Jul 2015; 110(7):1035-1037. PMID 26148262
62. Marion JF, Sands BE. The SCENIC consensus statement on surveillance and management of dysplasia in inflammatory bowel disease: praise and words of caution. Gastroenterology. Mar 2015; 148(3):462-467. PMID 25702851
63. Rabinowitz LG, Kumta NA, Marion JF. Beyond the SCENIC route: updates in chromoendoscopy and dysplasia screening in patients with inflammatory bowel disease. Gastrointest Endosc. Jan 2022; 95(1):30-37. PMID 34363806
64. Kiesslich R. SCENIC update 2021: Is chromoendoscopy still standard of care for inflammatory bowel disease surveillance? Gastrointest Endosc. Jan 2022; 95(1):38-41. PMID 34801222
65. Shergill AK, Lightdale JR, Bruining DH, et al. The role of endoscopy in inflammatory bowel disease. Gastrointest Endosc. May 2015; 81(5):1101-1121.e1-e13. PMID 25800660
66. Abu Dayyeh BK, Thosani N, Konda V, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc. Mar 2015; 81(3):502.e501-502.e516. PMID 25597420
67. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic Removal of Colorectal Lesions-Recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. Mar 2020; 158(4):1095-1129. PMID 32122632
68. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. Sep 2012; 143(3):844-857. PMID 22763141
69. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: A consensus update by the US multi-society task force on colorectal cancer. Am J Gastroenterol. Mar 2020; 115(3):415-434. PMID 32039982
70. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA. May 18 2021; 315(19):1965-1977. PMID 34003218
71. Alexandersson B, Hamad Y, Andreasson A, et al. Su1689 Comparison of Chromoendoscopy Versus White Light Endoscopy In Surveillance of Chronic Colitis - A Randomized Single Center Study Including Random Biopsies. Gastrointest Endosc. 2018; 87:AB370.

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
10/01/2025	Document updated with literature review. The following change was made to Coverage: Revised to address only chromoendoscopy and virtual chromoendoscopy as an adjunct to diagnostic or surveillance colonoscopy. Added references 19, 24, 26, 49, and 71; others removed. Title changed from: “In-Vivo Analysis of Colorectal Polyps”.
11/15/2024	Document updated with literature review. Coverage unchanged. References 4 and 8 added; others updated.
10/15/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. Added references: 2, 5, 8-11, 16-18, 23, 24, 26-32, 34-36, 38-49, 58, 59, 63, 64 and 69.
09/15/2021	Reviewed. No changes.
01/15/2021	Document updated with literature review. Coverage unchanged. References 10, 13, 16, 24 and 37 added.
04/01/2019	Reviewed. No changes.
06/15/2018	Document updated with literature review. Coverage unchanged. References 31-32 added.
01/15/2018	Reviewed. No changes.
02/01/2017	Document updated with literature review. The following changes were made to Coverage: 1) Added fiberoptic analysis, chromoendoscopy, and electronic (virtual) chromoendoscopy as examples of in-vivo analysis. 2) Added “NOTE: For “Confocal Laser Endomicroscopy (CLE)” see MED201.038”.
08/15/2015	Reviewed. No changes.
02/15/2014	Document updated with literature review. Coverage unchanged. CPT/HCPCS code(s) updated. Title changed from “Fiberoptic Analysis of Colorectal Polyps” to “In Vivo Analysis of Colorectal Polyps”.
05/01/2008	Policy reviewed without literature review.
11/15/2006	Revised/updated entire document
08/15/2006	New medical document