2.01.84	Chromoendoscopy as an Adjunct to Colonoscopy		
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Section:	2.0 Medicine	**Page:**	Page 1 of 31

Policy Statement

I. Chromoendoscopy is considered **investigational** as an adjunct to diagnostic or surveillance colonoscopy.

II. Virtual chromoendoscopy is considered **investigational** as an adjunct to diagnostic or surveillance colonoscopy.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

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.

Related Policies

- Confocal Laser Endomicroscopy
- Virtual Colonoscopy/Computed Tomography Colonography

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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

Background

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.

Literature Review

Evidence reviews 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. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 review.

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).

Review of Evidence
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,]	●
Hurlstone 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 stated

CC: colorectal cancer; RCT: randomized controlled trial.

Table 3. Results of the Meta-analysis

Study	Adenoma detection rate per patient	Advanced adenoma detection rate per patient	Sessile serrated adenoma/traditional serrated adenomas per patient	Mean no. of adenoma per patient	Mean no. of non-neoplastic 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	252	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.

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 review.

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).

Review of Evidence
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 evidence review.)

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 review.

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).

Review of Evidence
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)[23],		●		
Park et al (2016)[31],		●		●
Watanabe et al (2016)[32],		●	●	
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 all (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 chromoendoscopy 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 chromoendoscopy, virtual chromoendoscopy (NBI, i-	2457	RCTs	NR

Study	Search Dates	Trials	Participants	N	Design	Duration
			SCAN, FICE), standard white-light colonoscopy, and high-definition white light colonoscopy			
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; 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			

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
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				

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
Relative risk (95% CI)		3.52 (1.38 to 8.99)				

CI: confidence interval; DCE: dye chromoendoscopy; FICE: Fujinon Intelligent Color Enhancement; 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 review.

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).

Review of Evidence

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 bling 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 (ie, 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 review.

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).

Review of Evidence
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 review.

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).

Review of Evidence

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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received through 1 physician specialty society and 5 academic medical centers while this policy was under review in 2012. There was general agreement that chromoendoscopy and virtual chromoendoscopy are considered investigational as adjuncts to diagnostic or surveillance colonoscopy. However, for chromoendoscopy, 2 reviewers and, for virtual chromoendoscopy, 1 reviewer argued that the technology may have a role in screening select higher-risk patients. Most respondents, including 4 of the 5 academic medical centers, did not think that chromoendoscopy could easily be adopted into routine clinical use as an adjunct to colonoscopy. Reviewers were split on whether the detection of adenomatous polyps of any size is clinically important. Of the 3 reviewers who thought that only detection of larger adenomatous polyps is clinically important, 2 considered the size threshold to be 5 mm; the other considered it to be 10 mm.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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."

Best Practice Statement
"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,]

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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 No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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
Unpublished			
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

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	44799	Unlisted procedure, small intestine
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/06/2012	Policy title change from Chromoendoscopy Endoscopy
01/30/2015	Coding Update
06/30/2015	Policy title change from Chromoendoscopy Policy revision without position change
01/01/2016	Coding update
03/01/2016	Policy revision without position change
12/01/2016	Policy revision without position change
12/01/2017	Policy revision without position change
01/01/2018	Policy revision without position change

Effective Date	Action
02/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
02/01/2024	Policy reactivated. Previously archived from 09/01/2020 to 01/31/2024.
01/01/2025	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must

be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Chromoendoscopy as an Adjunct to Colonoscopy 2.01.84 **Policy Statement:** I. Chromoendoscopy is considered **investigational** as an adjunct to diagnostic or surveillance colonoscopy. II. Virtual chromoendoscopy is considered **investigational** as an adjunct to diagnostic or surveillance colonoscopy.	**Chromoendoscopy as an Adjunct to Colonoscopy 2.01.84** **Policy Statement:** I. Chromoendoscopy is considered **investigational** as an adjunct to diagnostic or surveillance colonoscopy. II. Virtual chromoendoscopy is considered **investigational** as an adjunct to diagnostic or surveillance colonoscopy.