

<b>2.01.84</b>	<b>Chromoendoscopy as an Adjunct to Colonoscopy</b>		
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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 24

### Policy Statement

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

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

### Policy Guidelines

#### Coding

There is no specific CPT code for chromoendoscopy. The additional work of the chromoendoscopy would probably be reported with the following CPT code:

- **44799:** Unlisted procedure, small intestine

### 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 two types of chromoendoscopy: one 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 2014, the Fujifilm EPX-4440HD Digital Video Processor with Fujinon Intelligent Color Enhancement (FICE®) and Light Source was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. 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.

In 2013, the i-SCAN™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by the FDA through the 510(k) process.<sup>2</sup> 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 (CRC) screening and diagnosis of colorectal disease. However, colonoscopy is an imperfect procedure. A systematic review by van Rijn et al (2006) pooled findings from tandem (i.e., back-to-back) colonoscopy studies and found that 22% of polyps were missed on the first colonoscopy.<sup>1</sup> Most polyps missed were small and thus had a lower risk of becoming cancerous. The pooled miss rate by polyp size was 2% for polyps 10 mm and larger, 13% for polyps 5 to 10 mm, and 26% for polyps 1 to 5 mm.

### Adjunctive Procedures

Several adjunct endoscopic techniques, including chromoendoscopy, could enhance the sensitivity of colonoscopy. Chromoendoscopy, also known as chromoscopy and chromo-colonoscopy, 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 chromo-endoscopy) 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 the most commonly used stain with colonoscopy to enhance the detection of colorectal neoplasms. Several absorptive stains are also used with colonoscopy. Methylene blue, which stains the normal absorptive epithelium of the small intestine and colon, has been used to detect colonic neoplasia and to aid in the detection of intraepithelial neoplasia in patients 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 patients at increased risk of CRC due to a family history of CRC, a personal history of adenomas, etc.
- Identification of mucosal abnormalities for targeted biopsy as an alternative to multiple random biopsies in patients with inflammatory bowel disease.
- Screening the general population for CRC.

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.

### **Chromoendoscopy for Average-Risk Patients Undergoing Colonoscopy**

#### **Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does the use of chromoendoscopy improve the net health outcome in individuals at average risk or at increased risk of CRC?

The following PICOs were used to select literature to inform this review.

#### **Patients**

The relevant populations of interest are individuals at average risk or at increased risk of CRC.

#### **Interventions**

The test being considered is chromoendoscopy. Chromoendoscopy involves the application of dyes to facilitate tissue visualization and is administered in an outpatient setting by gastroenterologists.

#### **Comparators**

The following test is currently being used to diagnose or monitor CRC: standard white-light colonoscopy, which is administered in an outpatient setting by gastroenterologists.

#### **Outcomes**

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

The benefit of a true-positive or true-negative test is accurate diagnosis and clinical management as indicated by test results.

The harm of a false-positive or false-negative test is inaccurate diagnosis and unnecessary treatment or lack of treatment.

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

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

**Study Selection Criteria**

For the evaluation of the clinical validity of this test, 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.

There are few trials evaluating chromoendoscopy for CRC screening of average-risk individuals. Some trials have included mixed populations of patients undergoing screening and diagnostic colonoscopy but have not reported results separately for each group. For example, in the study by Pohl et al (2011), although approximately half of the study participants were undergoing screening colonoscopy, the group results were not reported separately.<sup>3</sup>

One large randomized trial by Kahi et al (2010) evaluated 660 patients at 4 centers in the U. S.<sup>4</sup> Those eligible for inclusion had an average risk of CRC, 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 one 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=0.07). The mean number of adenomas per subject that were less than 5 mm in diameter differed significantly between groups (0.8 for chromoendoscopy vs 0.7 for standard endoscopy; p=0.03). The difference between groups in the mean number of adenomas 10 mm or larger was not statistically significant (0.11 for chromoendoscopy vs 0.12 for standard colonoscopy; p=0.70). 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=0.40). 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 randomized controlled trial (RCT) comparing pancolonoscopic chromoendoscopy using indigo carmine dye with standard colonoscopy.<sup>3</sup> The trial included patients presenting for primary CRC 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 ( $p=0.002$ ). 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 ( $p=0.012$ ). 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 ( $p=0.092$ ), 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

In patients at average risk of CRC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of chromoendoscopy in the subsequent development of CRC or on CRC mortality.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of chromoendoscopy for this population has not been established, a chain of evidence supporting the clinical utility of the procedure cannot be established.

### **Section Summary: Chromoendoscopy for Average-Risk Patients Undergoing Colonoscopy**

There is a lack of evidence on the use of chromoendoscopy in an average-risk screening population. The single RCT that focused on this patient group did not find that high-definition chromoendoscopy identified more clinically meaningful lesions than high-definition white-light colonoscopy. Moreover, about half of the participants in a trial from Germany were average-risk individuals seeking screening colonoscopy, but the trial results were not stratified by population. No controlled studies have evaluated the impact of chromoendoscopy vs standard colonoscopy on health outcomes (e.g., CRC mortality) in this patient population.

### **Chromoendoscopy for Patients at Increased Risk of CRC Undergoing Colonoscopy**

#### **Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does the use of chromoendoscopy improve the net health outcome in individuals at increased risk of CRC?

The following PICOs were used to select literature to inform this review.

### **Patients**

The relevant populations of interest are individuals at increased risk of CRC.

**Interventions**

The test being considered is chromoendoscopy. Chromoendoscopy involves the application of dyes to facilitate tissue visualization and is administered in an outpatient setting by gastroenterologists.

**Comparators**

The following test is currently being used to diagnose or monitor CRC: standard white-light colonoscopy, which is administered in an outpatient setting by gastroenterologists.

**Outcomes**

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

The benefit of a true-positive or true-negative test is accurate diagnosis and clinical management as indicated by test results.

The harm of a false-positive or false-negative test is inaccurate diagnosis and unnecessary treatment or lack of treatment.

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

**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).

**Study Selection Criteria**

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria are described in the first indication.

Individuals may be at higher risk for CRC 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 5mm to 10 mm in size, is described next.

**Systematic Reviews**

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 CRC resection.<sup>5</sup> Reviewers excluded studies of individuals with IBD or a known polyposis syndrome. Five RCTs (total n=1059 participants) 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 two colonoscopies. (An update of this Cochrane review by Brown et al [2016] included studies of patients at increased risk of CRC and those at average risk; meta-analyses did not stratify by patient population.<sup>6</sup> 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% confidence interval [CI], 0.60 to 1.00;  $p<0.001$ ). 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;  $p<0.001$ ). 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;  $p < 0.001$ ). 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;  $p = 0.006$ ). 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 CRC. 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**

Representative trials included in the Cochrane review and those published more recently follow.

Stoffel et al (2008) published findings of a study drawing on 5 sites across the U. S., Canada, and Israel.<sup>7</sup> Eligibility criteria included a personal history of CRC or at least three 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 one additional adenoma on the second examination ( $p=0.04$ ).

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.<sup>8</sup> 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. 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 ( $p=0.17$ ).

### **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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

In patients at increased risk of CRC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of chromoendoscopy in the subsequent development of CRC or CRC mortality.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of chromoendoscopy for this population has not been established, a chain of evidence supporting the clinical utility of the procedure cannot be established.

**Section Summary: Chromoendoscopy for Patients at Increased Risk of CRC Undergoing Colonoscopy**

Several RCTs and back-to-back colonoscopy studies have evaluated chromoendoscopy in patients at increased risk of CRC. A Cochrane review comparing chromoendoscopy with standard colonoscopy in high-risk patients (but excluding those with IBD) found significantly higher rates of adenoma detection and rates of three or more adenomas with chromoendoscopy compared with standard colonoscopy. The evidence for detecting larger polyps, defined as those greater than 5 mm or greater than 10 mm, is less robust. While one study has reported a significantly higher detection rate for polyps greater than 5 mm, no studies reported increased detection for polyps greater than 10 mm. No controlled studies have evaluated the impact of chromoendoscopy vs standard colonoscopy on health outcomes (e.g., CRC mortality) in this patient population. Although increased detection of adenomas could lower the incidence rate of CRC, robust evidence of this improved detection-and a strong chain of evidence, such as evidence gathered by rigorous modeling studies-is not available.

**Chromoendoscopy for Patients With IBD Undergoing Colonoscopy****Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does the use of chromoendoscopy improve the net health outcome in individuals with IBD?

The following PICOs were used to select literature to inform this review.

**Patients**

The relevant populations of interest are individuals with IBD.

**Interventions**

The test being considered is chromoendoscopy. Chromoendoscopy involves the application of dyes to facilitate tissue visualization and is administered in an outpatient setting by gastroenterologists.

**Comparators**

The following test is currently being used to diagnose or monitor IBD: standard white-light colonoscopy, which is administered in an outpatient setting by gastroenterologists.

**Outcomes**

The general outcome of interest is symptom reduction.



The benefit of a true-positive or true-negative test is accurate diagnosis and clinical management as indicated by test results.

The harm of a false-positive or false-negative test is inaccurate diagnosis and unnecessary treatment or lack of treatment.

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

**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).

**Study Selection Criteria**

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria are described in the first indication.

**Systematic Reviews**

A meta-analysis by Wu et al (2012) on the diagnostic accuracy of chromoendoscopy for identifying dysplasia in patients with IBD and using the histopathologic diagnosis as the reference standard included 6 studies.<sup>9</sup> The primary endpoints were the sensitivity and specificity of chromoendoscopy compared with the histologic diagnosis. Pooled sensitivity of chromoendoscopy was 83.3% (95% CI, 35.9% to 99.6%) and the pooled specificity was 91.3% (95% CI, 43.8% to 100%). Reviewers concluded that chromoendoscopy had high diagnostic accuracy compared with white-light colonoscopy for patients with colonic IBD.

Subramanian et al (2011) published a meta-analysis of studies evaluating the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with IBD.<sup>10</sup> To be included in the meta-analysis, studies had to be prospective, evaluate surveillance colonoscopy in patients with IBD, and compare chromoendoscopy with white-light colonoscopy. Six published studies (total n=1277 patients) met the inclusion criteria. Only one study was conducted in the U. S.; three used indigo carmine dye and three used methylene blue dye.

In a pooled analysis of all 6 studies, the incremental yield of chromoendoscopy over white-light endoscopy for the detection of any grade of dysplasia on a per-patient basis was 7% (95% CI, 3% to 11%). The number needed to treat with chromoendoscopy to detect 1 extra patient with dysplasia was 14. Reviewers did not report separately the difference in detection of high-grade dysplasia. A pooled analysis of 4 studies (n=1118 patients) found a 27% (95% CI, 11% to 42%) increase in the detection of flat dysplastic lesions with chromoendoscopy than with white-light colonoscopy.

In another pooled analysis of data from the 6 studies, there was a 44% (95% CI, 29% to 59%) increase in the detection of dysplasia using targeted biopsies obtained by chromoendoscopy vs targeted biopsies obtained by white-light colonoscopy. Reviewers also calculated the miss rates (lesions found only on random biopsies) with chromoendoscopy and white-light endoscopy. Significantly fewer dysplastic lesions were detected by random biopsy when chromoendoscopy was used vs white-light endoscopy. The pooled reduction in dysplastic lesions detected by random biopsy alone with chromoendoscopy vs white-light colonoscopy was -40% (95% CI, -53% to -27%). The meta-analysis did not address the miss rate of larger lesions.

**Prospective and Retrospective Studies**

Gasia et al (2016) retrospectively analyzed data from a cohort of 454 patients who had IBD for at least 8 years and were undergoing surveillance at a single tertiary care center.<sup>11</sup> The endoscopic approach used was at physician discretion; however, only one of the eight endoscopists had training in chromoendoscopy. A total of 126 patients had a standard colonoscopy, 182 had a high-definition colonoscopy (124 with random biopsies, 58 with targeted biopsies), 28 had chromoendoscopy (4 with random biopsies, 24 with targeted

biopsies), and 118 had virtual chromoendoscopy (64 with random biopsy, 54 with targeted biopsies). Rates of neoplasia detection were significantly higher in the targeted biopsy groups (19.1%; 95% CI, 13.4% to 26.5%) than in the random biopsy groups (8.2%; 95% CI, 5.6% to 11.7%). Rates of neoplasia detection did not differ significantly across the high-definition colonoscopy, chromoendoscopy, and virtual chromoendoscopy groups that received with targeted biopsy.

Mooiweer et al (2015) retrospectively analyzed data on 937 patients with ulcerative colitis or Crohn disease who were undergoing surveillance with colonoscopy.<sup>12</sup> The study compared neoplasia detection with chromoendoscopy (440 procedures in 401 patients) and white-light colonoscopy (1802 procedures in 772 patients). Neoplasia was detected in 48 (11%) of 440 colonoscopies performed with chromoendoscopy (95% CI, 8% to 14%) and in 189 (10%) of 1802 procedures performed with white-light colonoscopy (95% CI, 9% to 12%). The between-group difference in the detection rate was not statistically significant ( $p=0.80$ ). Chromoendoscopy was not associated with an increased rate of neoplasia detection; however, patients were not randomized to the treatment groups and might not have been comparable.

Freire et al (2014) reported on 162 patients with a confirmed diagnosis of longstanding (at least 8 years) left-sided or extending ulcerative colitis that was clinically inactive.<sup>13</sup> Patients were randomized to conventional colonoscopy or to colonoscopy with chromoendoscopy (using methylene blue). Seventeen patients were excluded from the analysis (poor bowel preparation). A total of 104 lesions were identified in the chromoendoscopy group, and 63 were identified in the conventional colonoscopy group. The primary study outcome (number of intraepithelial neoplasias detected) did not differ significantly between groups (seven in the chromoendoscopy group vs six in the conventional colonoscopy group). All neoplasias were low grade. Compared with standard histologic evaluation, the sensitivity and specificity of chromoendoscopy for detecting intraepithelial neoplasia were 85.7% and 97.9%, respectively.

Marion et al (2008) reported on a prospective cohort of patients with ulcerative colitis or Crohn colitis.<sup>14</sup> Data were available on 102 patients. The study involved a single examination with two passes of the colonoscope. During the first pass, 4 random biopsies were taken every 10 cm for a total of at least 32 biopsies. At that time, any visible lesions were either biopsied or removed using a targeted biopsy protocol. During the second pass, methylene blue dye was segmentally applied throughout the colon, accompanied by a targeted biopsy of any abnormality or lesion identified through spraying. The study included a blinded evaluation of specimens. In the first pass of the colonoscope using random biopsy, 3 (3%) of 102 patients were found to have dysplasia. In one of the three patients, an additional dysplastic lesion was found using chromoendoscopy during the second pass. No carcinomas were identified by either method. A total of 3264 random biopsies were taken using standard colonoscopic analysis; 3 (0.09%) samples showed low-grade dysplasia, and 16 (0.4%) were indeterminate. Moreover, before dye spraying, 50 biopsies or resections of visible lesions were performed; 12 (24%) showed low-grade dysplasia, 1 (2%) showed high-grade dysplasia, and 2 (4%) were indeterminate. After dye spraying, 82 biopsies were taken. Of these, 21 (26%) showed low-grade dysplasia, 1 (1%) showed high-grade dysplasia, and 13 (16%) were indeterminate.

Follow-up data were reported by Marion et al (2016) on 68 (67%) of the 102 patients in the cohort.<sup>15</sup> The median length of follow-up was 28 months. Surveillance intervals varied from 6 to 12 months, depending on findings from the initial examination. During follow-up, patients underwent a mean of 3.15 endoscopy procedures (range, 1-5) with random biopsies. Follow-up endoscopies appeared to use a protocol similar to the index examination. Using random biopsies, six dysplastic lesions were identified in five patients. White-light targeted biopsy identified 11 dysplastic lesions in 11 patients, and methylene blue dye with targeted biopsy identified 27 dysplastic lesions from 27 patients. Targeted biopsy with chromoendoscopy and targeted biopsy with white-light colonoscopy were each significantly more likely to detect dysplasia than random biopsy. Four patients were referred for colectomy after the index examination, and six additional patients were referred during follow-up. A positive chromoendoscopy examination was significantly associated with having colectomy sooner (hazard

ratio, 12.1; 95% CI, 3.2 to 46.2;  $p < 0.001$ ). The study was not powered to estimate survival rates with white-light vs chromoendoscopy targeted biopsies. No carcinomas were found in any patient during the study, and no adverse events were reported.

### **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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

For patients with IBD, no RCTs identified evaluated the impact of chromoendoscopy in the subsequent development of CRC or on mortality from CRC.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The study by Marion et al (2008) (described above) was a nonrandomized comparative that study followed patients for a mean of 28 months.<sup>15</sup> Authors found that chromoendoscopy was associated with earlier colectomy, but the study was not powered to evaluate differences in the survival rates with chromoendoscopy and standard colonoscopy. It is difficult to generalize from this study's findings on colectomy because only a single endoscopist was trained in chromoendoscopy techniques. More generally, concerns remain about the learning curve with chromoendoscopy and the ability to use the technique in a variety of practice settings.

### **Section Summary: Chromoendoscopy for Patients With IBD Undergoing Colonoscopy**

Meta-analysis of clinical trials focusing on patients with IBD has found a statistically significant higher yield for chromoendoscopy over white-light colonoscopy in detecting dysplasia. More recent studies have reported mixed findings. It remains uncertain whether chromoendoscopy is more accurate for detecting dysplasia, especially compared with high-definition colonoscopy with targeted biopsies. In addition, there are concerns about physician learning curves with chromoendoscopy, and there is a lack of evidence that increased lesions detection by chromoendoscopy results in improved health outcomes.

### **Virtual Chromoendoscopy for Average-Risk Patients Undergoing Colonoscopy**

#### **Clinical Context and Test Purpose**

The purpose of virtual chromoendoscopy in patients at average risk of CRC is to inform a decision whether to proceed to the standard of care or to invasive treatment.

The question addressed in this evidence review is: Does the use of virtual chromoendoscopy improve the net health outcome in individuals at average risk or at increased risk of CRC?

The following PICO's were used to select literature to inform this review.

#### **Patients**

The relevant populations of interest are individuals at average risk of CRC.

#### **Interventions**

The test being considered for each indication is virtual chromoendoscopy. Virtual chromoendoscopy involves the application of dyes to highlight tissue to facilitate imaging and is administered in an outpatient setting by gastroenterologists.

**Comparators**

The following test is currently being used to diagnose or monitor CRC: standard white-light colonoscopy, which is administered in an outpatient setting by gastroenterologists.

**Outcomes**

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

The benefit of a true-positive or true-negative test is accurate diagnosis and clinical management as indicated by test results.

The harm of a false-positive or false-negative test is inaccurate diagnosis and unnecessary treatment or lack of treatment.

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

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

**Study Selection Criteria**

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria are described in the first indication.

**Systematic Reviews**

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.<sup>16</sup> 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 vs conventional chromoendoscopy was 1.09 (95% CI, 0.97 to 1.23;  $p>0.05$ ).

**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 CRC, who were randomized across 3 groups.<sup>17</sup> During the colonoscopy, the endoscope was fully inserted, and each of three colonic segments (ascending, transverse, descending) was inspected twice during withdrawal. Participants received first withdrawal with narrow-band imaging (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 analysis due to inadequate bowel preparation. For the primary outcome of adenoma detection rate, no statistically significant differences were found among the three 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 ( $p=0.75$ ). 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 ( $p=0.59$ ). 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 ( $p=0.30$ ). 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.<sup>18</sup> 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=0.74). 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=0.59). All missed adenomas were low grade and nonpedunculated. All but one (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.<sup>19</sup> 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=0.41). 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 vs 12 [3.0%] in the standard chromoendoscopy group; p=0.85).

### **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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

In patients at average risk of CRC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of virtual chromoendoscopy in the subsequent development of CRC or on CRC mortality.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of virtual chromoendoscopy for this population has not been established, a chain of evidence supporting the clinical utility of the procedure cannot be established.

### **Section Summary: Virtual Chromoendoscopy for Average-Risk Patients Undergoing Colonoscopy**

Several RCTs have evaluated virtual chromoendoscopy in average-risk patients. None found that virtual chromoendoscopy improved the detection of clinically important polyps compared with standard colonoscopy. There is a lack of studies on the impact of virtual chromoendoscopy on CRC incidence and mortality compared with standard colonoscopy.

### **Virtual Colonoscopy for Patients at Increased Risk Undergoing Colonoscopy**

#### **Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does the use of virtual chromoendoscopy improve the net health outcome in individuals at increased risk of CRC?

The following PICOs were used to select literature to inform this review.

#### **Patients**

The relevant populations of interest are individuals at increased risk of CRC.

#### **Interventions**

The test being considered is virtual chromoendoscopy. Virtual chromoendoscopy involves the application of dyes to highlight tissue to facilitate imaging and is administered in an outpatient setting by gastroenterologists.

#### **Comparators**

The following test is currently being used to diagnose or monitor CRC: standard white-light colonoscopy, which is administered in an outpatient setting by gastroenterologists.

#### **Outcomes**

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

The benefit of a true-positive or true-negative test is accurate diagnosis and clinical management as indicated by test results.

The harm of a false-positive or false-negative test is inaccurate diagnosis and unnecessary treatment or lack of treatment.

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

#### **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)

#### **Study Selection Criteria**

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria are described in the first indication.

#### **Randomized Trials**

A study using a modified back-to-back colonoscopy design was published by Kiriya et al (2012) in Japan.<sup>20</sup> 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;  $p=0.03$ ). Twenty-six (44%) of 59 neoplastic lesions detected by FICE and 14 (37%) of 38 of 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 CRC due to a personal history of polyps or gastrointestinal symptoms.<sup>21</sup> 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 ( $p=0.12$ ). 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 ( $p=0.46$ ). The number of adenomas less than 5 mm in size (the primary study outcome) differed significantly between groups. Twenty-eight (44.4%) of patients in the FICE group and 14 (21.5%) in the white-light group ( $p=0.006$ ) 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

In patients at increased risk of CRC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of virtual chromoendoscopy in the subsequent development of CRC or on CRC mortality.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There is no strong chain of evidence that would support an argument that the differences in lesion detection rates would result in improved patient outcomes.

### **Section Summary: Virtual Chromoendoscopy for Patients at Increased Risk Undergoing Colonoscopy**

A few RCTs have evaluated virtual chromoendoscopy in patients at increased risk of CRC. None found that virtual chromoendoscopy improved the detection of clinically important polyps compared with standard colonoscopy. There is a lack of evidence demonstrating the impact of virtual chromoendoscopy on CRC incidences or mortality compared with standard colonoscopy, and a strong chain of evidence cannot be constructed.

**Virtual Chromoendoscopy for Patients With IBD Undergoing Colonoscopy****Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does the use of virtual chromoendoscopy improve the net health outcome in individuals with IBD?

The following PICOs were used to select literature to inform this review.

**Patients**

The relevant populations of interest are individuals with IBD.

**Interventions**

The test being considered is virtual chromoendoscopy. Virtual chromoendoscopy involves the application of dyes to highlight tissue to facilitate imaging and is administered in an outpatient setting by gastroenterologists.

**Comparators**

The following test is currently being used to diagnose or monitor IBD: standard white-light colonoscopy, which is administered in an outpatient setting by gastroenterologists.

**Outcomes**

The general outcome of interest is symptom reduction.

The benefit of a true-positive or true-negative test is accurate diagnosis and clinical management as indicated by test results.

The harm of a false-positive or false-negative test is inaccurate diagnosis and unnecessary treatment or lack of treatment.

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

**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).

**Study Selection Criteria**

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria are described in the first indication.

**Randomized Controlled Trials**

One RCT has evaluated virtual chromoendoscopy in patients with IBD. This trial by Neumann et al (2013) in Germany randomized 83 patients with mild or inactive IBD to high-definition white-light endoscopy or virtual chromoendoscopy.<sup>22</sup> 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 ( $p=0.001$ ). 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 ( $p=0.066$ ). Although the agreement was higher in the virtual



chromoendoscopy group, the between-group difference was not statistically significant at  $p$  less than 0.05.

### **Retrospective Studies**

The retrospective cohort study by Gasia et al (2016), discussed in the section on chromoendoscopy, included a group assigned to virtual chromoendoscopy.<sup>11</sup> In brief, this study included 454 patients with IBD undergoing surveillance. Rates of neoplasia detection did not differ significantly for a high-definition colonoscopy, chromoendoscopy, or virtual chromoendoscopy when used with targeted biopsy. However, rates of neoplasia detection were significantly higher in patients who had targeted biopsy with high-definition colonoscopy, chromoendoscopy, and virtual chromoendoscopy (19.1%; 95% CI, 13.4% to 26.5%) than those undergoing random biopsy (8.2%; 95% CI, 5.6% to 11.7%).

### **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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

In patients with IBD, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of virtual chromoendoscopy in the subsequent development of CRC or on CRC mortality.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of virtual chromoendoscopy for this population has not been established, a chain of evidence supporting the clinical utility of the procedure cannot be established.

### **Section Summary: Virtual Chromoendoscopy for Patients With IBD Undergoing Colonoscopy**

One RCT has compared virtual chromoendoscopy and white-light endoscopy in patients with IBD. It found a significant likelihood that virtual chromoendoscopy would correctly identify the extent of disease inflammation but no significant difference in the likelihood of identifying disease activity. A retrospective cohort study found that targeted biopsy resulted in higher rates of neoplasia detection regardless of the endoscopy method used. There is a lack of studies demonstrating the impact of virtual chromoendoscopy on CRC incidences or mortality compared with standard colonoscopy, and a strong chain of evidence supporting improved outcomes cannot be constructed.

### **Summary of Evidence**

#### **Chromoendoscopy**

For individuals who have an average risk of CRC who receive chromoendoscopy, the evidence includes an RCT evaluating this population. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), test validity, and change in disease status. The single RCT did not find that high-definition chromoendoscopy identified more clinically meaningful lesions than high-definition white-light colonoscopy. The evidence is insufficient to determine the effects of technology on net health outcomes.

For individuals who have an increased risk of CRC who receive chromoendoscopy, the evidence includes multiple RCTs, back-to-back colonoscopy studies, and systematic reviews. The 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 IBD) found significantly higher rates of adenoma detection and rates of three 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 one study reported a significantly higher detection rate for polyps greater than 5 mm, no studies reported increased detection of polyps greater than 10 mm. The evidence is insufficient to determine the effects of technology on net health outcomes.

For individuals who have IBD who receive chromoendoscopy, the evidence includes observational studies and meta-analyses of observational data. The relevant outcomes are OS, DSS, test validity, and change in disease status. One meta-analysis found a statistically significant higher yield of chromoendoscopy over white-light colonoscopy for detecting dysplasia. This evidence established that chromoendoscopy improves polyp detection rates; however, it is unclear whether the additional polyps detected are clinically important and, therefore, 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. The evidence is insufficient to determine the effects of technology on net health outcomes.

### **Virtual Chromoendoscopy**

For individuals who have an average risk of CRC who receive virtual chromoendoscopy, the evidence includes several RCTs and a meta-analysis. The 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 CRC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals who have an increased risk of CRC who receive virtual chromoendoscopy, the evidence includes several RCTs and a meta-analysis. The 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 CRC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine the effects of technology on net health outcomes.

For individuals who have IBD who receive virtual chromoendoscopy, the evidence includes an RCT and nonrandomized comparative study. The relevant outcomes are OS, DSS, test validity, and change in disease status. The 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. A retrospective cohort study found that targeted biopsy resulted in a higher rate of neoplasia detection regardless of the endoscopy method used. There is a lack of studies assessing the impact of virtual chromoendoscopy on CRC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine the effects of technology on net health outcomes.

## Supplemental Information

### 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.

In response to requests from Blue Cross Blue Shield Association, input was received through 1 physician specialty society and 5 academic medical centers in 2012. There was general agreement that chromoendoscopy and virtual chromoendoscopy are considered investigational as adjuncts to diagnostic or surveillance colonoscopy. However, for chromoendoscopy, two reviewers and, for virtual chromoendoscopy, one reviewer argued that the technology may have a role in screening select higher-risk patients. Most respondents, including four of the five 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 three reviewers who thought that only detection of larger adenomatous polyps is clinically important, two considered the size threshold to be 5 mm; the other considered it to be 10 mm.

## Practice Guidelines and Position Statements

### American Society for Gastrointestinal Endoscopy and the American Gastroenterological Association

The ASGE and the American Gastroenterological Association (2015) published the SCENIC consensus statement on surveillance and management of dysplasia in patients with inflammatory bowel disease (IBD).<sup>23</sup> The statement, developed by an international multidisciplinary group representing a variety of stakeholders, incorporated systematic reviews of the literature. Table 1 summarizes relevant recommendations.

**Table 1. Recommendations on Surveillance and Management of Dysplasia in Patients With IBD**

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

IBD: inflammatory bowel disease; 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 two gastroenterology journals questioned whether the SCENIC guidelines would be accepted as the standard of care in IBD surveillance.<sup>24,25</sup> 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.

The ASGE (2015) issued guidelines on endoscopy in the diagnosis and treatment of IBD, which made the following recommendations about chromoendoscopy: "Chromoendoscopy with pancolonoscopic dye spraying and targeted biopsies is sufficient for surveillance in inflammatory bowel disease; consider 2 biopsies from each colon segment for histologic staging."<sup>26</sup>

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.<sup>27</sup> 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 for both the 'diagnose-and-leave' strategy for diminutive ( $\leq 5$  mm) rectosigmoid hyperplastic polyps and the 'resect-and-discard' strategy for diminutive ( $\leq 5$  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 for the use of these strategies in clinical practice.

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

The Multi-Society Task Force (2012) 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.<sup>28</sup> The guidelines noted that these technologies currently do not have an impact on surveillance intervals.

### U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2016) recommendations on screening for colorectal cancer do not mention chromoendoscopy.<sup>29</sup>

### 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 2.

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01505842	Randomized Controlled Trial (RCT) to Compare Dysplasia Detection Rate in Colonoscopy Without Chromoendoscopy Versus Colonoscopy With Chromoendoscopy in Detecting Dysplasia in Ulcerative Colitis and Crohn's Colitis Patients	300	Apr 2019 (active, not recruiting)
<b>Unpublished</b>			
NCT02822352 *	A Comparison Of High Definition White Light And High Definition Virtual Chromoendoscopy For The Detection Of Intraepithelial Neoplasia In Longstanding Colitis: A Randomised Controlled Trial	204	Aug 2018 (completed)
NCT02543762	Usefulness of Chromoendoscopy for the Early Detection of Colorectal Cancer Associated With Inflammatory Bowel Disease	350	May 2015 (completed; last updated Sep 2015)

NCT: national clinical trial. \* No results posted on clinicaltrials.gov for NCT02822352.

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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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

### IE

The following services may be considered investigational.

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
02/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. 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 (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](http://www.blueshieldca.com/provider).

*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.*