2.01.84  Chromoendoscopy as an Adjunct to Colonoscopy

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<th>Original Policy Date:</th>
<th>July 6, 2012</th>
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<th>December 1, 2017</th>
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**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**

There is no specific CPT code for chromoendoscopy. The additional work of the chromoendoscopy would 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 August 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 April 2003, the i-scan™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by the FDA through the 510(k) process. This digital image enhancement technology is part of
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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 code: 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, 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 2006 systematic review pooled findings from tandem (i.e., back-to-back) colonoscopy studies and found that 22% of polyps were missed on the first colonoscopy. 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.

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. 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 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 colorectal cancer due to family history of colorectal cancer, 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 colorectal cancer
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., 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**

**Chromoendoscopy**

**Average-Risk Patients Undergoing Colonoscopy**

**Detection Rates of Clinically Important Adenomas and Neoplastic Lesions**

There are few trials evaluating chromoendoscopy for colorectal cancer (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 2011 study by Pohl et al, although approximately half of study participants were undergoing screening colonoscopy, the results for this group were not reported separately.³

One large randomized trial involving 660 patients conducted at 4 centers in the United States was identified.⁴ 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 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=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 authors stated that the high rate of adenoma detection in both groups may have been due to the use of high-definition colonoscopy.

In 2011, Pohl et al in Germany published a large RCT comparing pancolonic chromoendoscopy with indigo carmine dye with standard colonoscopy.³ The trial included patients presenting for primary CRC screening (51%) and patients undergoing diagnostic colonoscopy (49%). Patients with known IBD, overt bleeding, polyposis syndromes, or a history of surgical resection were excluded. A total of 1024 patients were randomized; 16 dropped out, leaving 996 patients in the chromoendoscopy group and 512 patients in the standard colonoscopy (i.e., control) group. The mean extubation time was 11.6 minutes in the chromoendoscopy group and 10.1 minutes in the standard colonoscopy group; the difference between groups was statistically significant (p=0.001). The primary study outcome (the proportion of patients with 1 adenoma) 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 were found to have 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 of adenomas 10 mm or larger did not differ significantly (p=0.092), but the study might have been underpowered for this analysis.

**Clinical Utility**
In patients at average risk of CRC, no randomized controlled trials (RCTs) or nonrandomized comparative studies were identified that evaluated the impact of chromoendoscopy on subsequent development of CRC or on CRC mortality.

**Section Summary: 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. In addition, about half of the participants in a trial from Germany were average-risk individuals seeking screening colonoscopy, but trial results were not stratified by population. No controlled studies have evaluated the impact of chromoendoscopy versus standard colonoscopy on health outcomes (e.g., CRC mortality) in this patient population.

**Individuals at Increased Risk of Colorectal Cancer Undergoing Colonoscopy**
Detection Rates of Clinically Important Adenomas and Neoplastic Lesions
Individuals may be at higher risk for CRC due to family or personal history or symptoms suggestive of colorectal disease (excluding patients with known inflammatory bowel disease [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 to 10 mm in size, is described next.

A 2010 Cochrane review by Brown and Baraza identified RCTs that compared chromoendoscopy and 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. 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 United States. Three studies used some type of “back-to-back” design in which each participant underwent the equivalent of 2 colonoscopies. A 2016 update of the Brown Cochrane review included both studies of patients at increased risk of CRC and those at a average risk; meta-analyses did not stratify by patient population. 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 than with nonchromoendoscopy interventions (pooled mean difference, 0.80; 95% confidence interval [CI], 0.60 to 1.00; p<0.001). In addition, 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 may 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 [OR], 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 (pooled OR=2.55; 95% CI, 1.49 to 4.36; p=0.006). The Cochrane reviewers concluded: “There appears to be strong evidence that chromoendoscopy 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 colorectal cancer. 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.

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

Le Rhun et al published findings of a French study in 2006 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. 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 end point of total number of adenomas per patient did not differ significantly between groups. Mean (SD) values were 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 (SD) of 0.04 (0.20) in the standard colonoscopy group and 0.10 (0.39) in the chromoendoscopy group (p=0.17).

In 2008, Stoffel et al published findings of a study drawing on 5 sites across the United States, Canada, and Israel. Eligibility criteria included a personal history of CRC 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, use of chromoendoscopy was significantly associated with an increased likelihood of finding at least 1 additional adenoma on the second examination (p=0.04).

**Clinical Utility**

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

**Section Summary: Individuals at Increased Risk of Colorectal Cancer 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 3 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 1 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 versus 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 indirect evidence, such as might be provided by rigorous modelling studies, are not available.
Patients with Inflammatory Bowel Disease Undergoing Colonoscopy

Detection Rates of Clinically Important Adenomas and Neoplastic Lesions

In 2011, Subramanian et al published a meta-analysis of studies evaluating the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with IBD.9 To be included in the meta-analysis, studies had to be prospective, evaluate surveillance colonoscopy in patients with IBD, and compare chromoendoscopy to white-light colonoscopy. Six published studies (total N=1277 patients) met the inclusion criteria. Only 1 study was conducted in the United States; 3 used indigo carmine dye, and 3 used methylene blue dye. Duration of the procedure was established by pooling data from 1120 patients across 4 studies. In this pooled analysis, procedures using chromoendoscopy took a mean of 11 minutes longer than white-light endoscopy (95% CI, 10 minutes 15 seconds to 11 minutes 43 seconds). Reviewers stated that chromoendoscopy procedures lasted significantly longer than white-light endoscopy but did not report the exact p value for this analysis.

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. The investigators 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 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 detection of dysplasia using targeted biopsies obtained by chromoendoscopy versus targeted biopsies with 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 versus white-light endoscopy. The pooled reduction in dysplastic lesions detected by random biopsy alone with chromoendoscopy versus white-light colonoscopy was -40% (95% CI, -53% to -27%). The meta-analysis did not address the miss rate of larger lesions.

A 2012 meta-analysis by Wu et al on the diagnostic accuracy of chromoendoscopy for identifying dysplasia in patients with IBD and using histopathologic diagnosis as the reference standard included 6 studies.10 The primary end points were the sensitivity and specificity of chromoendoscopy compared with 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 has high diagnostic accuracy compared with white-light colonoscopy for patients with colonic IBD.

A description of key studies published more recently than the meta-analyses are described next.

In 2015, Mooiweer et al retrospectively analyzed data on 937 patients with ulcerative colitis or Crohn disease who were undergoing surveillance with colonoscopy.11 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 in189 (10%) of 1802 procedures performed with white-light colonoscopy (95% CI, 9% to 12%). The between-group difference in the rate of detection 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 2 treatment groups and may not have been comparable.

In 2014, Freire et al reported on 162 patients with a confirmed diagnosis of longstanding (at least 8 years) left-sided or extending ulcerative colitis that was clinically inactive.12 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 (7 in the chromoendoscopy group vs 6 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 reported on a prospective cohort of patients with ulcerative colitis or Crohn colitis in 2008, with long-term follow-up published in 2016. In the initial study, data were available on 102 patients. The study involved a single examination with 2 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 targeted biopsy of any abnormality or lesion identified through spraying. The study included 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 1 of the 3 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%) showed low-grade dysplasia, and 16 (0.4%) were indeterminate. In addition, 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.

In 2016, follow-up data were reported on 68 (67%) of the 102 patients in the cohort. 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, 6 dysplastic lesions were identified in 5 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 6 additional patients were referred during follow-up. A positive chromoendoscopy examination was significantly associated with having colectomy sooner (hazard ratio [HR], 12.1; 95% CI, 3.2 to 46.2; p<0.001). The study was not powered to estimate survival rates with white-light versus chromoendoscopy targeted biopsies. No carcinomas were found in any patient during the study and no adverse events were reported.

In 2016, Gasia et al retrospectively analyzed data from a cohort of 454 patients who had IBD for at least 8 years who were undergoing surveillance at a single tertiary care center. The endoscopic approach used was at physician discretion; however, only 1 of 8 endoscopists had training in chromoendoscopy. A total of 126 patients had standard colonoscopy, 182 had high-definition (HD) 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 in the HD colonoscopy, chromoendoscopy, and virtual chromoendoscopy groups that received with targeted biopsy.

Clinical Utility
For patients with IBD, no RCTs identified evaluated the impact of chromoendoscopy on subsequent development of CRC or on mortality from CRC. The Marion study (described above) was a nonrandomized comparative study followed patients for a mean of 28 months. 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 1 endoscopist was trained in chromoendoscopy techniques. More generally, concerns remain about the learning curve with chromoendoscopy and ability to use the technique in a variety of practice settings.

Section Summary: Patients with Inflammatory Bowel Disease Undergoing Colonoscopy
Meta-analysis of clinical trials focusing on patients with IBD has found a statistically significantly higher yield for chromoendoscopy over white-light colonoscopy in detecting dysplasia. More recent studies had mixed findings. It remains uncertain whether chromoendoscopy is more accurate for detecting dysplasia, especially compared with HD 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
A 2014 systematic review by Omata et al compared rates of polyp detection by virtual chromoendoscopy (i.e., Fujinon Intelligent Color Enhancement [FICE] or i-scan) with white-light colonoscopy.16 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>0.05).

Average-Risk Patients Undergoing Colonoscopy
Detection Rates of Clinically Important Adenomas and Neoplastic Lesions
Two studies using modified back-to-back designs in patients undergoing screening colonoscopy were conducted by Chung et al in South Korea. The larger study, published in 2014, included 1650 adults at average risk of CRC, who were randomly divided across 3 groups.17 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 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 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=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, which was 4.4 mm.

The 2010 study by Chung et al included 359 asymptomatic patients receiving screening colonoscopies.18 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 1 (which was 6 mm) were 5 mm or less in size. In both Chung studies, virtual chromoendoscopy did not improve rates of adenoma detection compared with white-light endoscopy and did not identify more large adenomas.
A 2009 industry-supported multicenter RCT by Pohl et al in Germany compared FICE and targeted standard chromoendoscopy using indigo carmine stain. 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 using a spray catheter through the working channel of the colonoscope for further assessment of any lesions identified. In the FICE group, withdrawal was performed using FICE at the preset for examining colorectal mucosa. Data were available for analysis of 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; the difference between groups was not statistically significant (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 the 2 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).

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

Section Summary: 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.

Individuals at Increased Risk of Colorectal Cancer Undergoing Colonoscopy
Detection Rates of Clinically Important Adenomas and Neoplastic Lesions
In 2010, Cha et al evaluated South Korean patients at increased risk of CRC due to a personal history of polyps or gastrointestinal symptoms. 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 and 5 mm. All adenomas identified were low grade and no complications were reported in either group.

A study using a modified back-to-back colonoscopy design was published in 2012 by Kiriyama et al in Japan. 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 on either examination were removed, and specimens were sent for evaluation. 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 lesions [31%]) was significantly lower than that with white light (28/61 lesions [46%]) (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.

Clinical Utility
In patients at increased risk of CRC, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of virtual chromoendoscopy on the subsequent development of CRC or on CRC mortality. There is no strong indirect chain of evidence that would support the argument that the differences in lesion detection rates would result in improved patient outcomes.

Section Summary: Individuals at Increased Risk of Colorectal Cancer 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 studies demonstrating the impact of virtual chromoendoscopy on CRC incidences or mortality compared with standard colonoscopy and a strong indirect chain of evidence cannot be constructed.

Patients with Inflammatory Bowel Disease Undergoing Colonoscopy
Detection Rates of Clinically Important Adenomas and Neoplastic Lesions
One RCT has evaluated virtual chromoendoscopy in patients with IBD. This 2013 trial by Neumann et al in Germany randomized 83 patients with mild or inactive IBD to high-definition white-light endoscopy or virtual chromoendoscopy.22 Seventy-eight (94%) patients completed the study; 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 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 agreement was higher in the virtual chromoendoscopy group, the between-group difference was not statistically significant at p less than 0.05.

The 2016 retrospective cohort study by Gasia et al (discussed above in the section on chromoendoscopy) included a group assigned to virtual chromoendoscopy.15 In brief, this study included 454 patients with IBD undergoing surveillance. Rates of neoplasia detection did not differ significantly for HD 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 HD 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%]).

Clinical Utility
In patients with IBD, no RCTs or nonrandomized comparative studies were identified that evaluated the impact of virtual chromoendoscopy on the subsequent development of CRC or on CRC mortality.
Section Summary: Patients with Inflammatory Bowel Disease Undergoing Colonoscopy

One RCT compared virtual chromoendoscopy and white-light endoscopy in patients with IBD. It found a significantly 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 indirect chain of evidence supporting improved outcomes cannot be constructed.

Summary of Evidence

For individuals who have an average risk of colorectal cancer undergoing colonoscopy who receive chromoendoscopy, the evidence includes 1 randomized controlled trial (RCT) focused on this population. Relevant outcomes are overall survival, disease-specific survival, test accuracy and 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 the technology on health outcomes.

For individuals who have an increased risk of colorectal cancer undergoing colonoscopy who receive chromoendoscopy, the evidence includes multiple RCTs, back-to-back colonoscopy studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and change in disease status. A Cochrane systematic review of trials comparing chromoendoscopy with standard colonoscopy in high-risk patients 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 rates 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 the technology on health outcomes.

For individuals who have inflammatory bowel disease undergoing colonoscopy who receive chromoendoscopy, the evidence includes observational studies and meta-analyses of observational data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and change in disease status. The 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, but it is unclear whether the additional polyps detected are clinically important and, therefore, whether improved polyp detection rates will translate into improved health outcomes. In addition, 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 may be a function of suboptimal standard colonoscopy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have an average risk of colorectal cancer undergoing colonoscopy who receive virtual chromoendoscopy, the evidence includes several RCTs and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and 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, we lack studies on the impact of virtual chromoendoscopy on colorectal cancer (CRC) incidence or mortality compared with standard colonoscopy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have an increased risk of colorectal cancer undergoing colonoscopy who receive virtual chromoendoscopy, the evidence includes several RCTs and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and 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, we lack studies on the impact of virtual chromoendoscopy on CRC incidence or mortality compared with standard colonoscopy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have inflammatory bowel disease undergoing colonoscopy who receive virtual chromoendoscopy, the evidence includes an RCT and nonrandomized comparative study. Relevant outcomes are overall survival, disease-specific survival, test accuracy and 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 endoscopy method used. We lack studies on the impact of virtual chromoendoscopy CRC incidence or mortality compared with standard colonoscopy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy and American Gastroenterological Association
In 2015, the American Society for Gastrointestinal Endoscopy and the American Gastroenterological Association published the SCENIC consensus statement on surveillance and management of dysplasia in patients with irritable bowel disease.23 The statement, developed by an international multidisciplinary group representing a variety of stakeholders, incorporated systematic reviews of the literature. Relevant recommendations are as follows:

- “When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition. (80% agreement; strong recommendation; low-quality evidence).”
- “When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy (85% agreement; strong recommendation; moderate-quality evidence).”
- “When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy (84% agreement; conditional recommendation; low-quality evidence).”

Panelists did not reach consensus on 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 standard of care in IBD surveillance.24,25 Both commentaries noted that the guidelines considered the outcome of detection of dysplasia and not disease progression or survival. Moreover, the authors noted the lack of longitudinal data on clinical outcomes in patients with dysplastic lesions detected using chromoendoscopy.

American Society for Gastrointestinal Endoscopy
In 2015, the American Society for Gastrointestinal Endoscopy issued guidelines on endoscopy in the diagnosis and treatment of IBD, which makes the following recommendations about chromoendoscopy26: “Chromoendoscopy with pancolonic dye spraying and targeted biopsies is sufficient for surveillance in IBD; consider 2 biopsies from each colon segment for histologic staging.”

U.S. Multi-Society Task Force on Colorectal Cancer
The guidelines on colonoscopy surveillance after screening and polypectomy (consensus update), published in 2012, stated that chromoendoscopy and narrow-band imaging may enable endoscopists to accurately determine if lesions are neoplastic, and if there is a need to
remove them and send specimens to pathology. The guidelines noted that, at this point, these technologies do not have an impact on surveillance interval.  

**U.S. Preventive Services Task Force Recommendations**
The 2016 U.S. Preventive Services Task Force recommendations on screening for colorectal cancer do not mention chromoendoscopy.  

**Medicare National Coverage**
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.  

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.  

Table 1. Summary of Key Trials

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT01505842</td>
<td>Chromoendoscopy for Dysplasia Detection in Chronic Inflammatory Bowel Disease</td>
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<td></td>
<td>NCT02822352</td>
<td>RCT: HDWL vs Virtual Chromoendoscopy in the Detection of Intraepithelial Neoplasia in Longstanding Colitis (VIRTUOSO)</td>
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</table>

NCT: national clinical trial.

**References**


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 a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

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<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>CPT®</td>
<td>44799</td>
<td>Unlisted procedure, small intestine</td>
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<tr>
<td>HCPCS</td>
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<tr>
<td>ICD-10 Procedure</td>
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<tr>
<td>ICD-10 Diagnosis</td>
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Policy History

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

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<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>07/06/2012</td>
<td>Policy title change from Chromoendoscopy Endoscopy</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/30/2015</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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<tr>
<td>06/30/2015</td>
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<td>Medical Policy Committee</td>
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<tr>
<td>01/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
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<td>Policy revision without position change</td>
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<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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.

<table>
<thead>
<tr>
<th>Prior Authorization Requirements (as applicable to your plan)</th>
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</thead>
</table>

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. Please call (800) 541-6652 or visit the provider portal at 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.