Chromoendoscopy as an Adjunct to Colonoscopy

Description

Chromoendoscopy refers to the application of dyes or stains during endoscopy to enhance tissue differentiation or characterization. When used with colonoscopy, the intent is to increase the sensitivity of the procedure by facilitating the identification of mucosal abnormalities. There are 2 types of chromoendoscopy; one involves actual spraying of dyes or stains through the working channel of an endoscope. The other type, known as virtual chromoendoscopy, uses a computer algorithm to simulate different colors of light that result from dye or stain spraying.

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 test. A recent systematic review pooled findings from tandem (ie back-to-back) colonoscopy studies and found that 22% of polyps were missed on the first colonoscopy. (1) Most of the missed polyps, though, were small and, thus, lower-risk of becoming cancerous. The pooled miss rate by polyp size was 2% for polyps 10 mm and larger, 13% for polyps 5-10 mm, and 26% for polyps 1-5 mm.

Several adjunct endoscopic techniques, including chromoendoscopy, could potentially enhance the sensitivity of colonoscopy. Chromoendoscopy, also known as chromoscopy and chromocolonoscopy, refers to the application of topical stains or dyes during endoscopy in order to enhance and facilitate the 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 (pan-colonic 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:** These stains are preferentially absorbed by certain types of epithelial cells.
- **Contrast**: These stains seep through mucosal crevices and highlight surface topography.
- **Reactive**: These stains undergo chemical reactions when in contact with specific cellular constituents, which results in a color change.

Reactive stains are primarily used to identify gastric abnormalities and are not used with colonoscopy. 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 individuals with chronic ulcerative colitis. In addition, crystal violet (also known as gentian violet), stains cell nuclei and has been applied in the colon to enhance visualization of pit patterns (i.e., superficial mucosal detail).

Potential applications of chromoendoscopy as an alternative 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 (IBD).
- Screening the general population for colorectal cancer.

The equipment used in regular chromoendoscopy is widely available. Several authors of review articles and technology assessments have stated that, although the techniques are simple, procedure, e.g., concentration of dye and amount of dye sprayed is variable and 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 potentially be an alternative to dye spraying. One system is the Fujinon® Intelligent Color Enhancement (FICE®) feature (Fujinon, Inc.). This technology uses post-processing computer algorithms to modify the light reflected from the mucosa from conventional white light to various other wavelengths.

**Regulatory Status**

In August 2014, the Fujifilm EPX-4440HD Digital Video Processor with FICE and Light Source was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA documents state that FICE can be used to supplement white-light endoscopy but is not intended to replace histopathologic sampling as a means of diagnosis.

Prior to this, on February 7, 2011, FDA had sent an Urgent Medical Device Corrective Action letter advising users that the FICE feature, which had been added by the manufacturer to enhance the appearance of images for virtual chromoendoscopy, should not be used, because this feature had not been reviewed under the 510(k) process. (2)
In April 2003, the i-scan™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by FDA through the 510(k) process. (3) This is a digital image enhancement technology and is part of the Pentax EPK-i5010 Video Processor. The i-scan has several modes that digitally enhance images in real–time during endoscopy. FDA documents state that i-scan is intended as an adjunct following white-light endoscopy and is 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 FDA for use in chromoendoscopy.

Related Policies

2.01.87 Confocal Laser Endomicroscopy
6.01.32 Virtual Colonoscopy/CT Colonography

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Chromoendoscopy is considered **medically necessary** as an adjunct to diagnostic or surveillance colonoscopy in patients at high risk for colonic neoplasia.

Chromoendoscopy is considered **not medically necessary** as an adjunct to diagnostic or surveillance colonoscopy in patients with average risk for colonic neoplasia.

Virtual chromoendoscopy is considered **not medically necessary** as an adjunct to diagnostic or surveillance colonoscopy.

Policy Guidelines

Individuals at increased risk of colorectal cancer may be at higher risk due to family or personal history, or symptoms suggestive of colorectal disease (excluding patients with known inflammatory bowel disease). Heightened surveillance is the most common approach to high-risk patients.

Rationale

No controlled studies were identified that evaluated the impact of chromoendoscopy on subsequent development of colorectal cancer (CRC) or on mortality from CRC. The review thus focused instead on outcomes related to polyp detection, particularly higher-risk polyps such as those that are at least 5 mm or 10 mm in size.

**Evidence That Chromoendoscopy Results in Higher Detection Rates of Clinically Important Adenomas/Neoplastic Lesions Compared With Standard Colonoscopy**
Individuals at increased risk of colorectal cancer

Individuals may be at higher risk 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 patients who are at extremely high-risk.

A 2010 Cochrane review identified randomized controlled trials (RCTs) comparing 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. (4) The review excluded studies of individuals with IBD or a known polyposis syndrome. Five RCTs with a total of 1059 participants met inclusion criteria; only 1 of the 5 studies had any sites in the United States. Three of the studies used some type of ‘back to back’ design in which each participant underwent the equivalent of 2 colonoscopies.

A meta-analysis pooling results of the 5 studies found that a significantly higher number of polyps (all types) were detected with chromoendoscopy than with non-chromoendoscopy interventions; pooled mean difference, 0.80, 95% confidence interval (CI), 0.60 to 1.00, p<0.001. In addition a meta-analysis found that the mean number of neoplastic lesions detected was significantly higher with chromoendoscopy than nonchromoendoscopy (pooled mean difference, 0.39, 95% CI, 0.27 to 0.50; p<0.001. Tests for heterogeneity were statistically significant in both of the above analyses. According to the study authors, potential reasons for clinical heterogeneity may have been differences in study design and differences in experience level of the endoscopists.

In a pooled analysis of per-patient data from the 5 studies, 234/524 (45%) patients in the chromoendoscopy group and 176/535 (33%) patients in the non-chromoendoscopy group had at least one 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 47/497 (9%) in the chromoendoscopy group and 20/512 (4%) in the non-chromoendoscopy group were found to have 3 or more neoplastic lesions (pooled OR, 2.55, 95% CI, 1.49 to 4.36, p=0.006). The Cochrane review 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 colorectal cancer. Such lesions, which presumably would be missed with conventional colonoscopy, could contribute to the interval cancer numbers on any surveillance programme.” The Cochrane review did not report differences between groups in the number of large lesions.

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

Le Rhun et al in France published findings of a study with 203 patients who had a history of familial or personal colonic neoplasia or alarm symptoms (eg change in bowel habit, abdominal pain) after age 60 years. (5) Patients were randomized to undergo 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, number of adenomas per patient, did not differ significantly between groups. Means (SD) were 0.5 (0.9) in the
standard colonoscopy group and 0.6 (1.0) in the chromoendoscopy group. The number of flat adenomas per patient that were at least 5 mm also did not differ significantly between groups; there were a mean 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 with 5 sites in 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 of 50 (34%) patients had adenomas identified, 11 of 23 (48%) in the intensive inspection group and 6 (27%) in the chromoendoscopy group (p value not reported). During the second colonoscopy, additional adenomas were found in 4 of 23 (17%) in the intensive inspection group and 12 of 27 (44%) 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 to 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).

In 2011, Pohl et al in Germany published a large RCT comparing pancolonic chromoendoscopy with indigo carmine dye to standard colonoscopy. The study included both 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, and 16 dropped out, leaving 496 patients in the chromoendoscopy group and 512 patients in the standard colonoscopy 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 adenomas, differed significantly between groups (p=0.002). A total of 223 patients (46.2%) in the chromoendoscopy group and 186 (36.3%) in the standard colonoscopy group had at least 1 adenoma identified.

The Pohl trial also reported differences in lesion detection rate by size of lesion. There were 151 (30.4%) patients in the chromoendoscopy group and 119 (23.2%) patients in the standard colonoscopy group found to have at least 1 adenoma that was 5 mm or larger in size; the difference between groups was statistically significant (p=0.012). A total of 64 (12.9%) patients in the chromoendoscopy group and 48 (9.4%) patients in the standard colonoscopy group were found to have at least one adenoma that was 10 mm or larger, p=0.092. The difference between groups in the detection of adenomas 10 mm or larger did not differ significantly between groups; the study may have been underpowered for this analysis.
Section Summary: Individuals at Increased Risk of CRC

Multiple RCTs and back-to-back colonoscopy studies have evaluated chromoendoscopy in patients at increased risk of CRC. A Cochrane review of trials comparing chromoendoscopy to standard colonoscopy in high-risk patients (but excluding those with IBD) found a significantly higher rate of adenoma detection and rate of 3 or more adenomas with chromoendoscopy compared to standard colonoscopy. The evidence for detecting larger polyps, either 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 for polyps greater than 10 mm.

Average-Risk Patients Undergoing Screening Colonoscopy:

There are fewer trials evaluating chromoendoscopy for CRC screening of average-risk individuals. Some trials include mixed populations of patients undergoing screening and diagnostic colonoscopy but do not report results separately for each group. For example, in the Pohl et al (2011) study, previously described (7), approximately half of the study participants were undergoing screening colonoscopy, but results were not reported separately for this group.

One large randomized trial was identified; it was conducted at 4 centers in the U.S. and included 660 subjects. (8) Eligible subjects were at average risk of CRC, aged 50 years and older, and were undergoing screening colonoscopy for the first time. Participants were randomized to undergo chromoendoscopy with indigo carmine dye (n=321) or standard colonoscopy (n=339). The primary outcomes were differences between groups in the proportion of patients with at least one adenoma and the mean number of adenomas per patient. Neither of these outcomes differed significantly between groups. A total of 178 (56%) of individuals in the chromoendoscopy group and 164 (48%) individuals in the standard colonoscopy group had 1 or more adenomas (p=0.07). The mean number of adenomas per patient that were 5 mm or smaller differed significantly in the chromoendoscopy group and the standard endoscopy group; mean number of adenomas was 0.8 and 0.7, respectively (p=0.03). However, there was not a statistically significant difference between groups in the number of larger adenomas. The mean number of adenomas per patient that were 10 mm or larger was 0.11 in the chromoendoscopy group and 0.12 in the standard colonoscopy group, p=0.70. A total of 39 (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. They concluded that "findings do not support the use of high-definition chromocolonoscopy for CRC (colorectal cancer) screening in average-risk patients."

Section Summary: Average-Risk Patients Undergoing Screening Colonoscopy

There is insufficient evidence on chromoendoscopy in an average-risk screening population. The single RCT that focused on this issue 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 recent trial from Germany were average-risk individuals seeking screening colonoscopy, but results of the trial were not stratified by indication for colonoscopy.
Patients with Inflammatory Bowel Disease (IBD)

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 needed to be prospective, evaluate surveillance colonoscopy in patients with IBD, and compare chromoendoscopy to white light colonoscopy. Six published studies with a total of 1,277 patients met the inclusion criteria. Only one of the studies was included in the United States; 3 used indigo carmine dye, and 3 used methylene blue dye. Data from 4 studies with 1,120 patients on duration of the procedure were pooled. In the 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). The authors stated that chromoendoscopy procedures lasted significantly longer than white light endoscopy but did not report the exact p value for this analysis.

When findings from all 6 studies were pooled, 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, 3.2% to 11.3%). The number needed to treat with chromoendoscopy to detect 1 extra patient with dysplasia was 14. The authors did not report separately the difference in detection of high-grade dysplasia. A pooled analysis of 4 studies (total n=1,118) found a 27% (95% CI, 11% to 42%) increase in detection of flat dysplastic lesions with chromoendoscopy compared to white light colonoscopy. In another pooled analysis of data from all 6 studies, there was a 44% (95% CI, 29% to 59%) increase in detection of dysplasia using targeted biopsies with chromoendoscopy compared to targeted biopsies with white light colonoscopy. The authors 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 compared to 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 does not address the miss rate of larger lesions.

Another meta-analysis of studies on the diagnostic accuracy of chromoendoscopy for identifying dysplasia in patients with IBD and using histopathologic diagnosis as the reference standard also included 6 RCTs. (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%). The authors of the meta-analyses concluded that chromoendoscopy has high diagnostic accuracy compared with white-light colonoscopy for patients with colonic IBD. However, the impact of this increased rate of detection on patient outcomes is not clear.

Representative trials including patients with IBD follow.

In 2015, Mooiweer et al published a retrospective analysis of 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 (1,802 procedures in 772 patients). Neoplasia was detected in 48 of 440 colonoscopies performed with chromoendoscopy (11%; 95% CI, 8% to 14%) and 189 of 1,802 procedures performed
with white-light colonoscopy (10%; 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, Friere 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 undergo conventional colonoscopy or colonoscopy with chromoendoscopy (using methylene blue). Seventeen patients were excluded from the analysis due to 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 and 6 in the conventional colonoscopy group). All neoplasias were low grade; no high-grade lesions or carcinomas were found. Compared with standard histological evaluation, the sensitivity and specificity of chromoendoscopy for detecting intraepithelial neoplasia was 85.7% and 97.9%, respectively.

In 2008, Marion et al evaluated 115 patients with extensive ulcerative colitis or Crohn’s colitis involving at least one-third of the colon. (13) Thirteen patients had insufficient bowel preparation and data on 102 patients were analyzed. Patients underwent 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. In addition, any visible lesions were either biopsied or removed. During the second pass, methylene blue dye was segmentally applied throughout the colon. A targeted biopsy approach was used in which any additional visible lesions were biopsied. The study included blinded evaluation of specimens. In the first pass of the colonoscope using random biopsy, 3 of 102 (3%) patients were found to have dysplasia. In 1 of the 3 patients, an additional dysplastic lesion was found using chromoendoscopy during the second pass of the colonoscope. No carcinomas were identified by any method. A total of 3264 random biopsies were taken using standard colonoscopic analysis; 3 of these (0.09%) showed low-grade dysplasia and 16 (0.4%) were indefinite. In addition, before dye spraying, 50 biopsies or resections were performed of visible lesions; 12 (24%) showed low-grade dysplasia, 1 (2%) showed high-grade dysplasia, and 2 (4%) were indefinite. 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.

**Section Summary: Patients With IBD**

Among patients with IBD, a meta-analysis of clinical trials focusing on patients with IBD found a statistically significantly higher yield of chromoendoscopy over white light colonoscopy for detecting dysplasia. This evidence establishes that chromoendoscopy improves the polyp detection rate, but it is unclear whether the additional polyps detected are clinically important, and therefore whether the improved polyp detection rate will translate to improved health outcomes. In addition, there are concerns about the comparison group in some of these trials. It is uncertain whether the control groups received optimal colonoscopy; therefore the improved detection rate by chromoendoscopy may be a function of suboptimal standard colonoscopy.
Evidence That Virtual Chromoendoscopy Results in Increased Detection of Clinically Important Polyps Compared With Standard Colonoscopy or Standard Chromoendoscopy

A meta-analysis by Omata et al, published in 2014, compared the polyp detection rate with virtual chromoendoscopy (ie, FICE or i-scan) and white light colonoscopy. (14) The study included patients of all risk levels and was limited to RCTs. Five trials on FICE/i-scan met eligibility criteria and the analysis did not find a significantly higher detection rate with virtual chromoendoscopy. The pooled relative risk (RR) of the efficacy of virtual chromoendoscopy compared with conventional chromoendoscopy for adenoma/neoplasia detection was 1.09 (95% CI, 0.97 to 1.23 (p>0.05).

Individuals at Increased Risk of CRC

In 2010, Cha et al in South Korea evaluated patients who were at increased risk of CRC due to personal history of polyps or gastrointestinal symptoms. (15) A total of 135 patients underwent colonoscopy, and 7 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. A total of 31 patients (49.2%) in the FICE group and 23 (35.4%) in the white light group were found to have one 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. A total of 28 (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 2012 study using a modified back-to-back colonoscopy design was published in 2012 by Kiriyama et al in Japan. (16) The study included 102 consecutive patients who received virtual chromoendoscopy using FICE and 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. Individuals with known IBD, bleeding, and polyposis syndrome were excluded. The right-sided colon was examined. 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 of the detected lesions, 59 (91%) of those found using FICE and 38 (84%) of those detected using white-light colonoscopy were neoplastic. The miss rate was defined as the proportion of total lesions in that group detected on the second examination. Significantly more lesions were missed by FICE as the second procedure (28/61 lesions [46%]) than with white-light colonoscopy (12/39 lesions [24%]) (p=0.03) as the second procedure. There was not a statistically significant difference between the FICE and white-light examinations in terms of the number of neoplastic lesions that were 5 mm or larger. Twenty-six of 59 (44%) neoplastic lesions detected by FICE and 14 of 38 (37%) 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.
Section Summary: Individuals at Increased Risk of CRC
There are few RCTs evaluating virtual chromoendoscopy in patients at increased risk of CRC and these have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard colonoscopy.

Average-Risk Patients Undergoing Screening Colonoscopy:
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 2013, included 1650 average-risk adults, 550 in each of 3 groups. During the colonoscopy, the endoscope was fully inserted and each of 3 colonic segments (ascending, transverse, descending) was inspected twice during withdrawal. Participants were randomized to first withdrawal with narrow-band imaging (NBI), virtual chromoendoscopy using FICE or white-light colonoscopy. White light was used in all groups for the second inspection. Ninety-one patients (5.5%) were excluded from analysis due to inadequate bowel preparation. For the primary outcome, the adenoma detection rate, there was not a statistically significant difference 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% by FICE, and 20.8% in the white-light-only group. The miss rate in the enhanced screening groups was not significantly higher than in the white-light group (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.

A 2010 study by Chung et al included 359 asymptomatic patients receiving screening colonoscopies. They 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). In the initial colonoscopy, a total of 60 (33.7%) of patients in the FICE group and 55 (30.4%) in the white-light group were found to have at least one 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; the difference in miss rates was not statistically significant (p=0.59). All of the missed adenomas were low-grade and nonpedunculated. All but one (which was 6 mm) were 5 mm or less in size. In both of these studies, virtual chromoendoscopy was not found to improve the rate 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 study included 871 individuals presenting for screening (57%) or diagnostic (43%) colonoscopy. All patients were examined using high resolution zoom endoscopes. Patients in the standard chromoendoscopy group 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 that were identified. In the FICE group withdrawal was performed using FICE at the preset for examining colorectal mucosa. Data were available for analysis on a total of 794 patients (398 in the FICE group and 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 were found to have at least 1 adenoma; the difference between groups was not statistically significant (p=1.0). The number of small adenomas (here defined as no more than 10 mm) did not differ significantly between groups (p=0.41). The proportion of large adenomas >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 and 12 (3.0%) in the standard chromoendoscopy group (p=0.85).

**Section Summary: Average-Risk Patients Undergoing Screening Colonoscopy**

There are few RCTs evaluating virtual chromoendoscopy in average-risk patients, and these have no found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard colonoscopy.

**Patients with IBD**

One RCT was identified that evaluated virtual chromoendoscopy in patients with IBD. This was a 2013 trial by Neumann et al in Germany in which 83 patients with mild or inactive IBD were randomized to high-definition white-light endoscopy or virtual chromoendoscopy. (20) Seventy-eight (94%) patients completed the study; the other 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 agreed with histopathologic findings in 19 of 39 (48.7%) of the white-light group and 36 of 29 (92.3%) of the virtual chromoendoscopy group. The difference between groups was statistically significant, favoring virtual chromoendoscopy. In terms of disease activity, the agreement between endoscopic prediction and disease activity and histopathologic findings was 21 of 39 (53.9%) in the white-light group and 36 of 39 (89.0%) in the virtual chromoendoscopy group, p=0.066. Although agreement was higher in the virtual chromoendoscopy group, there was not a significantly significant difference between groups at the p<0.05 level.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

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<td>Comparison of Surveillance Colonoscopy Techniques in Patients With IBD</td>
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NCT: national clinical trial.
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 IBD. (21) The statement was developed by an international multidisciplinary group representing a variety of stakeholders, and 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)."

For this recommendation, the evidence cited consisted of 8 trials using standard-definition colonoscopy that compared white-light colonoscopy alone to chromoendoscopy. The proportion of patients with dysplasia detected was 0% to 10% greater in the individual studies and the difference was not statistically significant in any study. However, the authors stated that meta-analyses found a significantly greater proportion of patients with dysplasia were detected when chromoendoscopy was used. The document also stated that chromoendoscopy increased the duration of colonoscopy and that it is not known whether the additional lesions detected with chromoendoscopy are associated with the same increased risk of CRC as those detected by white-light colonoscopy.

"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 regarding the use of chromoendoscopy in random biopsies of patients with IBD undergoing surveillance.

Commentaries in 2 gastroenterology journals questioned whether the SCENIC guidelines would be accepted as standard of care in IBD surveillance. (22, 23) Both commentaries noted that the guidelines consider the outcome of detection of dysplasia and not disease progression or survival. Moreover, the authors note the lack of longitudinal data on clinical outcomes in patients with dysplastic lesions detected using chromoendoscopy.
American Society for Gastrointestinal Endoscopy
In 2011, the American Society for Gastrointestinal Endoscopy reaffirmed a guideline on endoscopy in the diagnosis and treatment of IBD. Among other recommendations, the guideline recommends colonoscopic surveillance for patients with long-standing ulcerative colitis and extensive Crohn disease colitis. The guideline states: “Chromoendoscopy offers the potential for improved sensitivity during colonoscopic surveillance by allowing for targeted biopsies of enhanced mucosal abnormality. While promising, chromoendoscopy has not yet been adopted in routine practice.” (24)

American Cancer Society and U.S. Multi-Society Task Force on CRC
In 2006, they published 2 consensus guidelines on surveillance colonoscopy after cancer resection or polypectomy. The postcancer resection guideline stated, “chromoendoscopy (dye-spraying) and magnification endoscopy are not established as essential to screening or surveillance.” Similarly, the postpolypectomy guideline states, “the application of evolving technologies such as chromoendoscopy, magnification endoscopy, narrow-band imaging, and computed tomography colonography are not established for post-polypectomy surveillance at this time.” (25,26)

U.S. Multi-Society Task Force on Colorectal Cancer
This guideline 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 guideline noted that, at this point, these technologies do not have an impact on surveillance interval. (27)

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for chromoendoscopy were identified.

Summary of Evidence
The evidence for chromoendoscopy in patients who have an average risk of colorectal cancer undergoing colonoscopy 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.

The evidence for chromoendoscopy in patients who have an increased risk of colorectal cancer undergoing colonoscopy 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. The single RCT did not find that high-definition chromoendoscopy identified validity, and change in disease status. A Cochrane review of trials comparing chromoendoscopy with standard colonoscopy in high-risk patients (but excluding those with inflammatory bowel disease) found a significantly higher rate of adenoma detection and rate of 3 or more adenomas with chromoendoscopy compared with standard colonoscopy. The evidence for detecting larger polyps, either defined as greater than 5 mm or greater than 10 mm, is less robust. While 1 study reported a significantly higher detection rate for polyps greater than 5 mm, no studies
reported increased detection for polyps greater than 10 mm. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for chromoendoscopy in patients who have inflammatory bowel disease undergoing colonoscopy 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 establishes that chromoendoscopy improves the polyp detection rate, but it is unclear whether the additional polyps detected are clinically important and therefore, whether the improved polyp detection rate will translate to improved health outcomes. In addition, there are concerns about the comparison group used in some of these trials. It is uncertain whether the control groups received optimal colonoscopy; therefore, the improved detection rate by chromoendoscopy may be a function of suboptimal standard colonoscopy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for virtual chromoendoscopy in patients who have an average risk of colorectal cancer undergoing colonoscopy, an increased risk of colorectal cancer undergoing colonoscopy, or with inflammatory bowel disease undergoing colonoscopy includes several RCTs. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, and change in disease status. The available RCTs in these populations have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

References


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<tbody>
<tr>
<td></td>
<td>September</td>
<td>New Policy</td>
<td>Policy updated with literature search, No change to policy statements, References added, some renumbered or removed.</td>
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<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, no change in policy statements. References 10, 15, 18, and 20 added.</td>
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</table>
June 2016 Update Policy Policy updated with literature review through October 7, 2015; references 11 and 21-23 added. Policy statements unchanged.

Keywords

Chromoendoscopy
Chromoscopy
Chromocolonoscopy

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 24, 2016 and is effective July 15, 2016.

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