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## Chromoendoscopy as an Adjunct to Colonoscopy

<b>Audience</b>
Providers, Members, Brokers, MHC

<b>Purpose</b>
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<b>Definition</b>
<p>Chromoendoscopy, also known as chromoscopy and chromocolonoscopy, refers to the application of topical stains or dyes during an endoscopic procedure. When used with colonoscopy, the intent is to increase the sensitivity of the procedure by facilitating the identification of mucosal abnormalities, particularly flat or depressed lesions. There are two 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. Chromoendoscopy can be used in the whole colon (pancolonic chromoendoscopy) on an</p>

untargeted basis or can be directed to a specific lesion or lesions (targeted chromoendoscopy). Surveillance for colorectal, esophageal, gastric or small bowel dysplasia as well as surveillance of dysplasia in high risk population such as those with inflammatory bowel disease are other usages.

The equipment used in regular chromoendoscopy is widely available however the preprocedure setup is more in depth than routine endoscopy. For optimal use of chromoendoscopy, SURFACE guidelines have been developed to facilitate the use of chromoendoscopy during routine surveillance colonoscopy that include proper bowel preparation, the avoidance of active colitis, the use of an antispasmodic agent, and the ability to identify pit patterns. Optimal bowel preparation is especially necessary for adequate visualization during chromoendoscopy given that these pit patterns is used to guide targeted biopsies. Several review articles and technology assessments have indicated that, although the techniques are simple, the procedure (e.g., the concentration of dye and amount of dye sprayed) is variable and the results dependent on the endoscopist's experience using chromoendoscopy, and thus classification of mucosal staining patterns for identifying specific conditions is not standardized and varies widely.

Indigo carmine, a contrast stain, is the most commonly used stain with colonoscopy to enhance the detection of colorectal neoplasms. 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. Also, 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).

## Policy/Procedure

**Mountain health Co-Op Health Plans does NOT cover chromoendoscopy and/or virtual chromoendoscopy as adjunct to diagnostic or screening colonoscopies as they are considered investigational.**

### 1. Clinical Rationale

**1.1** As outlined in the Hayes Search and Summary from 2018, there are a number of studies on use of chromoendoscopy. Sixteen studies were identified and included in their review. They noted the studies had too many conflicting findings to conclude the safety and effectiveness chromoendoscopy; therefore, Hayes gave this technology a low rating until a full assessment can be conducted.

**1.2** Studies identified, which assessed chromoendoscopy, include Kahi et al. who conducted a large randomized trial in 2010 to determine if using high-definition chromocolonoscopy in average-risk patients would increase the findings of flat depressed neoplasms. The authors evaluated 660 patients at 4 centers in the United States, who had an average risk of colorectal cancer (CRC), were aged  $\geq 50$  years, and were having their first screening colonoscopy. Participants were randomized to High-definition chromoendoscopy with indigo carmine dye (n=321) or to High-definition white-light colonoscopy (WLC) (n=339). The primary outcomes

were compared between the groups by the proportion of patients with at least 1 adenoma and the mean number of adenomas per patient. 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 statistically significantly between groups (0.8 for chromoendoscopy vs 0.7 for standard endoscopy;  $p=0.03$ ) though the clinical meaningfulness of this difference is questionable. 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 found chromocolonoscopy marginally increased detection overall for adenomas; including flat and small adenomas over WLC. The findings of advanced neoplasms were similar between the two methods. The high adenoma detection rate could have been due to the use of high-definition technology used in both groups; therefore the use of chromocolonoscopy in average-risk patients is not recommended for CRC screening.

**1.3** A 2012 pilot study (Kiriya et al.) assessed the utility of using computed virtual chromoendoscopy with the flexible spectral imaging color enhancement (FICE) for colon neoplasia screening. One hundred consecutive patients (2 were excluded because insertion was not possible) referred for a colonoscopy following a sigmoidoscopy or for postoperative surveillance after anterior resection; received virtual chromoendoscopy using FICE or white-light colonoscopy (WLC) in random order. All lesions (a total of 110) were identified and removed during either examination and evaluated. Of these, 65 lesions were detected using FICE and 45 with WLC; 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 WLC. The miss rate for all polyps with FICE (12/39 [31%] lesions) was significantly lower than with WLC (28/61 [46%] lesions;  $p=0.03$ ). Twenty-six (44%) of 59 neoplastic lesions detected by FICE and 14 (37%) of 38 of neoplastic lesions detected by WLC were at least 5 mm in size. There was no statistically significant difference between the 2 procedures in terms of the number of lesions larger than 5 mm detected. In conclusion, under proper bowel preparation, colonoscopy using FICE may enhance the detection of flat and/or diminutive adenomatous lesions compared with WLC.

**1.4** Wanders et al. evaluated 3 types of endoscopic technologies, in this 2013 meta-analysis, to see if any of them could allow optical diagnosis and resection of colonic polyps without histopathological testing. The authors analyzed the sensitivity, specificity, and real-time negative predictive value of narrowed spectrum endoscopy (narrow-band imaging (NBI), image-enhanced endoscopy [i-scan], Fujinon intelligent chromoendoscopy [FICE]), confocal laser endomicroscopy (CLE), and auto-fluorescence imaging for differentiation between neoplastic and non-neoplastic colonic lesions. The authors concluded that all endoscopic imaging techniques other than auto-fluorescence imaging could be used if the endoscopists

are appropriately trained to make a reliable optical diagnosis for colonic lesions in daily practice. However, further research is needed focusing on whether training could help to improve negative predictive values.

- 1.5** In a 2014 randomized trial, Freire et al. analyzed 145 patients (17 were excluded for poor bowel preparation) with longstanding (at least 8 years) distal/extensive ulcerative colitis without primary sclerosing cholangitis and/or a history of intraepithelial neoplasia that were clinically inactive. Patients were prospectively randomized to undergo conventional colonoscopy or colonoscopy with chromoendoscopy (using methylene blue). 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 low grade intraepithelial neoplasias detected) did not differ significantly between groups (7 with chromoendoscopy vs 6 with conventional colonoscopy). Compared with standard histologic evaluation, the sensitivity and specificity of chromoendoscopy for detecting intraepithelial neoplasia were 85.7% and 97.9%, respectively. The study concluded, chromoendoscopy takes longer and does not improve the detection of intraepithelial neoplasia in the endoscopic screening of patients with ulcerative colitis.
- 1.6** A 2015 large retrospective study (Mooiweer et al.) examined data on 937 patients for the detection of dysplasia in patients with inflammatory bowel disease (IBD), from 3 referral centers, who had undergone surveillance from Jan 2000 through November 2013 and had a diagnosis of ulcerative colitis or Crohn disease. The detection of neoplasia was evaluated between chromoendoscopy (440 procedures in 401 patients) and white-light colonoscopy (WLC) (1802 procedures in 772 patients). Neoplasia was detected in 48 (11%) of 440 colonoscopies performed with chromoendoscopy (95% CI, 8% to 14%) and in 189 (10%) of 1802 procedures performed with WLC (95% CI, 9% to 12%). Targeted biopsies yielded 59 dysplastic lesions in the chromoendoscopy group, comparable to the 211 dysplastic lesions detected in the WLC group (P=0.30). The study concluded that implementation of chromoendoscopy for IBD surveillance did not increase dysplasia detection compared with WLC for targeted and random biopsies.
- 1.7** In a 2016 retrospective cohort study, Gasia et al. evaluated data from 454 patients with IBD who had undergone surveillance for at least 8 years, at a single tertiary care center. The physicians chose which endoscopic approach they wanted to use between high-definition colonoscopy, chromoendoscopy, and virtual chromoendoscopy; although only one of the 8 endoscopists had training in chromoendoscopy. A total of 126 patients had a standard colonoscopy, 182 had a high-definition colonoscopy (124 with random biopsies, 58 with targeted biopsies), 28 had chromoendoscopy (4 with random biopsies, 24 with targeted biopsies), and 118 had virtual chromoendoscopy (64 with random biopsy, 54 with targeted biopsies). Rates of neoplasia detection were significantly higher in the targeted biopsy groups (19.1%; 95% CI, 13.4% to 26.5%) than in the random biopsy groups (8.2%; 95% CI, 5.6% to 11.7%). However, there were no significant differences in neoplasia detection rates with targeted biopsy throughout any of the endoscopic approaches that were used within the groups.

- 1.8** UpToDate performed a literature review current through February 2022 on chromoendoscopy and surveillance of dysplasia in patients with inflammatory bowel disease (IBD). Those studies found some limitations to chromoendoscopy such as it can be time consuming, providers are not trained appropriately in using this technology, and there is lack in the standardization for classifications of the findings; which may contribute to misinterpretations of results. There are limited studies on the impact of patient's outcomes and some studies found that chromoendoscopy increases adenoma detection rates in the colon, while other have not. Some experts caution the use of chromoendoscopy for surveillance until further studies have demonstrated the efficacy in clinical practice or its long term benefit. In conclusion, screening colonoscopies continue to be the best tool to detect dysplasia and colorectal cancer in patients with IBD.
- 1.9** Some specialty society's support for chromoendoscopy has evolved despite the limited evidence supporting its impact on health outcomes. In 2014, the European Society of Gastrointestinal Endoscopy (ESGE) issued guidelines on advanced endoscopic imaging (i.e. chromoendoscopy) for the detection and differentiation of colorectal neoplasia in which it suggested the use of advanced endoscopic imaging for margin assessment and prediction of deep submucosal invasion in lesions with a depressed component or non-granular or mixed-type laterally spreading tumors (LSTs). Even though the quality of evidence supporting these recommendations was considered very low and moderate for margin delineation and assessment of depth of submucosal invasion. Since 2017 there has been no new evidence with clinically relevant endpoints for the patients (incomplete resection, interrupted procedure, cancer detection) published to further support its use. The authors concluded, "The availability, feasibility, and minimum standard of advanced imaging use, particularly in the community setting, are unknown. Colonoscopy services should set up structured monitoring and initiate audit to generate further evidence for advanced imaging."
- 1.10** The European Society of Gastrointestinal Endoscopy (ESGE) Guidelines of 2016 address the utilization of advanced endoscopic imaging in gastrointestinal (GI) endoscopy. The ESGE suggests:
- a)** Advanced endoscopic imaging technologies may improve mucosal visualization and enhance fine structural and microvascular detail; however, only low quality of evidence was found. "Expert endoscopic diagnosis may be improved by advanced imaging, but as yet in community-based practice no technology has been shown consistently to be diagnostically superior to current practice with high definition white light."
  - b)** The use of validated classification systems to support the use of optical diagnosis with advanced endoscopic imaging in the upper and lower GI tracts; although only moderate quality of evidence was found.
  - c)** Training may improve performance in the use of advanced endoscopic imaging techniques and should be a prerequisite for use in clinical practice. A learning curve exists and training alone does not guarantee sustained high performances in clinical practice. The ESGE concluded that "advanced endoscopic imaging can improve mucosal visualization and endoscopic diagnosis; however it requires training and the use of validated classification systems."

**1.11** The 2015 consensus statement approved by the American Gastroenterology Association (AGA) and the American Society of Gastrointestinal Endoscopy (ASGE) regarding Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) was that although chromoendoscopy is a promising surveillance tool for inflammatory bowel disease patients, larger trials of chromoendoscopy using high-definition colonoscopy is needed and at this time, it can only be suggested over the use of white-light colonoscopy.

**1.12** The National Comprehensive Cancer Network (NCCN) guidelines for Genetic/Familial High-Risk Assessment: Colorectal version 1.2018 states that "chromoendoscopy may be considered in patients with Lynch syndrome, but larger prospective randomized trials are needed to better understand its role in Lynch syndrome."

**1.13** In conclusion, although chromoendoscopy has been shown to be beneficial in patients with a high risk of dysplasia such as IBD patients, the ASGE and the AGA do not universally recommend or endorse the broad use of chromoendoscopy at this time except in IBD patients where this technology can be considered as an alternative to standard colonoscopy as is detailed in the SCENIC consensus. The American College of Gastroenterology (ACG) has also stated that chromocolonoscopy with targeted biopsies could be done by a trained endoscopist instead of random biopsies used during routine white-light colonoscopy and could be useful in IBD patients who are at a high risk of cancer (such as those with a history of dysplasia), however not in low risk IBD patients. A significant limitation of all studies that is recognized by the AGA, ASGE and ACG is that the results of these procedures are operational dependent and are limited by the experience of the endoscopist and likely accounts for the variability in the results. Although the results are promising, the results of chromoendoscopy have not been found to be universally accurate and therefore cannot be broadly implemented at this time. The cost of the equipment and adequate training at this time continue to be important concerns and must be addressed before this technology is part of the standard of care for community gastroenterologists.

### **Applicable Coding**

#### **CPT Codes**

45399 Unlisted procedure, colon

#### **HCPCS Codes**

No applicable codes

### **Vendors**

- **Personify**
- **HPS**

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Review/Revision/Approval History	
Date	Description
07/08/2025	New Policy
04/27/2026	Reviewed and approved by Mountain Health CO-OP Policy Committee

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