



FEP Medical Policy Manual

FEP 2.01.84 Chromoendoscopy as an Adjunct to Colonoscopy

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Related Policies:

2.01.87 - Confocal Laser Endomicroscopy

6.01.32 - Virtual Colonoscopy/Computed Tomography Colonography

Chromoendoscopy as an Adjunct to Colonoscopy

Description

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Chromoendoscopy refers to the use of dyes or stains during endoscopy to enhance tissue differentiation or characterization. When used with colonoscopy, the intent is to increase the sensitivity of the procedure by facilitating the identification of mucosal abnormalities. There are 2 types of chromoendoscopy: 1 involves actual spraying of dyes or stains through the working channel of an endoscope; the other, known as virtual chromoendoscopy, uses a computer algorithm to simulate different colors of light that result from dye or stain spraying.

Several adjunct endoscopic techniques, including chromoendoscopy, could enhance the sensitivity of colonoscopy. Chromoendoscopy, also known as chromoscopy and chromocolonoscopy, refers to the application of topical stains or dyes during endoscopy to enhance tissue differentiation or characterization and facilitate identification of mucosal abnormalities. Chromoendoscopy may be particularly useful for detecting flat or depressed lesions. A standard colonoscopy uses white-light to view the colon. In chromoendoscopy, stains are applied, resulting in color highlighting of areas of surface morphology of epithelial tissue. The dyes or stains are applied via a spray catheter that is inserted down the working channel of the endoscope. Chromoendoscopy can be used in the whole colon (pancolonic chromoendoscopy) on an untargeted basis or can be directed to a specific lesion or lesions (targeted chromoendoscopy). Chromoendoscopy differs from endoscopic tattooing in that the former uses transient stains, whereas tattooing involves the use of a long-lasting pigment for future localization of lesions.

Stains and dyes used in chromoendoscopy can be placed in the following categories:

- Absorptive stains are preferentially absorbed by certain types of epithelial cells.

- Contrast stains seep through mucosal crevices and highlight surface topography.
- Reactive stains undergo chemical reactions when in contact with specific cellular constituents, which results in a color change.

Indigo carmine, a contrast stain, is one of the most commonly used stains with colonoscopy to enhance the detection of colorectal neoplasms. Several absorptive stains are also used with colonoscopy. Methylene blue is widely used; it stains the normal absorptive epithelium of the small intestine and colon, and has been used to detect colonic neoplasia and to aid in the detection of intraepithelial neoplasia in 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 (ie, 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 CC due to a family history of CC, a personal history of adenomas, etc.
- Identification of mucosal abnormalities for targeted biopsy as an alternative to multiple random biopsies in patients with inflammatory bowel disease.
- Screening the general population for CC.

The equipment used in regular chromoendoscopy is widely available. Several review articles and technology assessments have indicated that, although the techniques are simple, the procedure (eg, the concentration of dye and amount of dye sprayed) is variable, and thus classification of mucosal staining patterns for identifying specific conditions is not standardized.

Virtual chromoendoscopy (also called electronic chromoendoscopy) involves imaging enhancements with endoscopy systems that could be an alternative to dye spraying. One system is the Fujinon Intelligent Color Enhancement feature (Fujinon Inc.). This technology uses postprocessing computer algorithms to modify the light reflected from the mucosa from conventional white-light to various other wavelengths.

OBJECTIVE

The objectives of this evidence review are to determine the diagnostic accuracy of chromoendoscopy and virtual chromoendoscopy and to evaluate whether they improve the net health outcome compared with standard white-light for individuals undergoing a colonoscopy to detect colorectal cancer (CC) or diagnose inflammatory bowel syndrome.

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

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

In August 2014, the EPX-4440HD Digital Video Processor with Fujinon Intelligent Color Enhancement (FICE) and Light Source (FujiFilm) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K140149). The FDA documents stated that FICE could be used to supplement white-light endoscopy but is not intended to replace histopathologic sampling as a means of diagnosis.²

In June 2012, the i-SCAN™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by the FDA through the 510(k) process (K113873).³ This digital image enhancement technology is part of the Pentax EPK-i5010 Video Processor. The i-SCAN has several modes that digitally enhance images in real-time during endoscopy. The FDA documents stated that i-SCAN is intended as an adjunct following white-light endoscopy but not intended to replace histopathologic analysis.

FDA product codes: GCT, PEA, FET (endoscopes and accessories).

No dye or stain product has been specifically approved by the FDA for use in chromoendoscopy.

RATIONALE

Summary of Evidence

Chromoendoscopy

For individuals who have an average risk of colorectal cancer (CC) who receive chromoendoscopy, the evidence includes a meta-analysis of randomized controlled trial (RCTs). Relevant outcomes are overall survival (OS), disease-specific survival (DSS), test validity, and change in disease status. The meta-analysis demonstrated that dye-based chromoendoscopy increased the adenoma detection rate and adenomas per colonoscopy in patients at average or increased risk of CC compared to standard or high-definition white light colonoscopy. However, limitations included unclear indication of colonoscopy in the studies (which included patients with screening and surveillance), and some heterogeneity in mean adenomas per patient. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have an increased risk of CC who receive chromoendoscopy, the evidence includes systematic reviews and a recent RCT. Relevant outcomes are OS, DSS, test validity, and change in disease status. A Cochrane systematic review of trials comparing chromoendoscopy with standard colonoscopy in high-risk patients (but excluding those with inflammatory bowel disease [IBD]) found significantly higher rates of adenoma detection and rates of 3 or more adenomas with chromoendoscopy than with standard colonoscopy. The evidence for detecting larger polyps, defined as greater than 5 mm or greater than 10 mm, is less robust. While 1 study reported a significantly higher detection rate for polyps greater than 5 mm, no studies reported increased detection of polyps greater than 10 mm. A recent RCT and systematic review involving patients with Lynch syndrome also found equivocal results. Results from the RCT showed similar neoplasia detection rates with chromoendoscopy and conventional white-light colonoscopy, while the systematic review concluded that chromoendoscopy is associated with significantly improved detection of certain lesions; however, the odds of having an adenoma detected were not significantly different between the modalities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inflammatory bowel disease (IBD) who receive chromoendoscopy, the evidence includes meta-analyses and a recent RCT. Relevant outcomes are OS, DSS, test validity, and change in disease status. Several meta-analyses found a statistically significant higher yield of chromoendoscopy over standard white-light colonoscopy for detecting dysplasia. The evidence supported improved polyp detection rates with chromoendoscopy; however, the studies had limitations such as lack of information regarding the timing of the screening modalities. A recent RCT found increased detection of dysplasia with chromoendoscopy compared to white-light endoscopy, although the benefit was only observed in a subgroup analysis in the second half of the study follow-up period. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Virtual Chromoendoscopy

For individuals who have an average risk of CC who receive virtual chromoendoscopy, the evidence includes several RCTs and systematic reviews. Relevant outcomes are OS, DSS, test validity, and change in disease status. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have an increased risk of CC who receive virtual chromoendoscopy, the evidence includes RCTs. Relevant outcomes are OS, DSS, test validity, and change in disease status. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBD who receive virtual chromoendoscopy, the evidence includes 2 meta-analyses and 2 RCTs. Relevant outcomes are OS, DSS, test validity, and change in disease status. One meta-analysis showed superiority of virtual chromoendoscopy over high-definition white light colonoscopy for dysplasia per biopsy, and ranked virtual chromoendoscopy as the best option for screening among the different modalities in comparison. The second meta-analysis found no difference between dye-based chromoendoscopy and virtual chromoendoscopy for dysplasia detection. One RCT found a significantly greater likelihood that virtual chromoendoscopy would correctly identify the extent of disease inflammation than standard colonoscopy but no significant difference in the likelihood of identifying disease activity. The other RCT found that there was no significant difference in the detection of neoplasia between high definition white light versus high-definition virtual chromoendoscopy in patients with long-standing IBD. There is a lack of studies assessing the impact of virtual chromoendoscopy on CC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American Society for Gastrointestinal Endoscopy and American Gastroenterological Association

In 2021, the American Gastroenterological Association (AGA) published a clinical practice update on the surveillance and management of colorectal dysplasia in patients with inflammatory bowel disease (IBD).⁵⁵ This was an expert review that underwent internal peer review by the AGA Clinical Practice Updates Committee and external peer review through standard procedures undertaken by the publishing journal (*Gastroenterology*). Table 1 summarizes relevant best practice statements.

Table 1. Best Practice Advice on Surveillance and Management of Dysplasia in Patients With Inflammatory Bowel Disease

Best Practice Statement
"Dye spray chromoendoscopy, performed by appropriately trained endoscopists, should be considered in all persons with colonic inflammatory bowel disease undergoing surveillance colonoscopy, particularly if a standard definition endoscope is used or if there is a history of dysplasia."
"Virtual chromoendoscopy is a suitable alternative to dye spray chromoendoscopy for dysplasia detection in persons with colonic inflammatory bowel disease when using high-definition endoscopy."
"Extensive nontargeted biopsies (roughly 4 adequately spaced biopsies every 10 cm) should be taken from flat colorectal mucosa in areas previously affected by colitis when white light endoscopy is used without dye spray chromoendoscopy or virtual chromoendoscopy. Additional biopsies should be taken from areas of prior dysplasia or poor mucosal visibility. Nontargeted biopsies are not routinely required if dye spray chromoendoscopy or virtual chromoendoscopy is performed using a high-definition endoscope, but should be considered if there is a history of dysplasia or primary sclerosing cholangitis."
"A finding of invisible dysplasia should prompt repeat examination by an experienced endoscopist using high-definition dye spray chromoendoscopy under optimized viewing conditions, with extensive nontargeted biopsies in the area of prior dysplasia if no lesion is seen. A finding of unresectable visible dysplasia or of invisible multifocal or high-grade dysplasia on histology should prompt colectomy. For visible lesions that can be resected or if histologic dysplasia is not confirmed on a high-quality dye spray chromoendoscopy examination, continued endoscopic surveillance at frequent intervals is appropriate."
"Targeted biopsies of representative or concerning pseudopolyps is appropriate during colonoscopy. Removal and sampling of all lesions is neither required nor practical. Surgery should be a last resort to manage colorectal cancer risk in the setting of severe pseudopolyposis. Dye spray chromoendoscopy should not be used to detect flat or subtle lesions within a field of pseudopolyps."

In 2015, the American Society for Gastrointestinal Endoscopy (ASGE) and the American Gastroenterological Association (AGA) published a SCENIC consensus statement on the surveillance and management of dysplasia in patients with IBD.⁵⁶ This statement, developed by an international multidisciplinary group representing a variety of stakeholders, incorporated systematic reviews of the literature. Table 2 summarizes relevant recommendations.

Table 2. Recommendations on Surveillance and Management of Dysplasia in Patients With Inflammatory Bowel Disease

Recommendation	LOA	SOR	QOE
"When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition."	80%	Strong	Low
"When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy."	85%	Strong	Moderate
"When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy."	84%	Conditional	Low

LOA: level of agreement; QOE: quality of evidence; SOR: strength of recommendation.

Panelists did not reach consensus on the use of chromoendoscopy in random biopsies of patients with IBD undergoing surveillance.

Commentaries in 2 gastroenterology journals questioned whether the SCENIC guidelines would be accepted as the standard of care in IBD surveillance.^{57,58} Both commentaries noted that the guidelines considered the outcome of the detection of dysplasia and not disease progression or survival. Moreover, the commentators noted the lack of longitudinal data on clinical outcomes in patients with dysplastic lesions detected using chromoendoscopy. Two other articles published in 2022 comment on how the approach to dysplasia surveillance in IBD has changed significantly since the publication of the SCENIC guidelines, and therefore, updates to the recommendations are warranted based on findings from recent meta-analyses and randomized trials (discussed in this review).^{59,60}

The ASGE (2015) issued guidelines on endoscopy in the diagnosis and treatment of IBD, which made the following recommendations about chromoendoscopy: "Chromoendoscopy with pancolonic dye spraying and targeted biopsies is sufficient for surveillance in inflammatory bowel disease; consider 2 biopsies from each colon segment for histologic staging."⁶¹ The ASGE (2015) also published a systematic review and meta-analysis assessing narrow-band imaging, i-SCAN, and Fujinon Intelligent Color Enhancement for predicting adenomatous polyp histology of small or diminutive colorectal polyps to determine whether they have met previously established criteria or thresholds to incorporate into clinical practice.⁶² The ASGE assessment confirmed that: "....The thresholds have been met for narrow-band imaging with endoscopists who are experts in using these advanced imaging technologies and when assessments are made with high confidence. The ASGE Technology Committee endorsed the use of NBI [narrow band imaging] for both the 'diagnose-and-leave' strategy for diminutive (≤ 5 mm) rectosigmoid hyperplastic polyps and the 'resect-and-discard' strategy for diminutive (≤ 5 mm) adenomatous polyps."

The report addressed the "trepidation" of patients, endoscopists, and pathologists with the "diagnose-and-leave" strategy, indicating there are challenges for implementation for the use of these strategies in clinical practice.

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

In 2020, the U.S. Multi-Society Task Force issued guidelines on the endoscopic removal of colorectal lesions. Regarding lesion assessment and description, the Task Force suggested "proficiency in the use of electronic- (eg, NBI, i-SCAN, and Fuji Intelligent Chromoendoscopy, or blue light imaging) or dye (chromoendoscopy)-based image-enhanced endoscopy techniques to apply optical diagnosis classifications for colorectal lesion histology [conditional recommendation, moderate-quality evidence]."⁶³ The Task Force also suggested "careful examination of the post-mucosectomy scar site using enhanced imaging, such as dye-based (chromoendoscopy) or electronic-based methods, as well as obtaining targeted biopsies of the site. Post-resection scar sites that show both normal macroscopic and microscopic (biopsy) findings have the highest predictive value for long-term eradication [conditional recommendation, moderate-quality evidence]."

In 2012, the U.S. Multi-Society Task Force guidelines on colonoscopy surveillance after screening and polypectomy (consensus update) stated that chromoendoscopy and narrow-band imaging might enable endoscopists to accurately determine if lesions are neoplastic and if there is a need to remove them and send specimens to pathology.⁶⁴ The guidelines noted that these technologies currently do not have an impact on surveillance intervals. In 2020, the U.S. Multi-Society Task Force published updated recommendations for follow-up after colonoscopy and polypectomy (consensus update); however, there was no mention of chromoendoscopy.⁶⁵

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force** (2021) recommendations on screening for colorectal cancer do not mention chromoendoscopy.⁶⁶

Medicare National Coverage

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2012	New policy	
June 2013	Replace policy	Policy updated with literature search, No change to policy statements, References added, some renumbered or removed.
June 2014	Replace policy	Policy updated with literature review, no change in policy statements. References 10, 15, 18, and 20 added.
June 2015	Replace policy	Policy updated with literature review. Reference 11 and 13 added. Policy statements unchanged.
June 2016	Replace policy	Policy updated with literature review through October 7, 2015; references 11 and 21-23 added. Policy statements unchanged.
March 2018	Replace policy	Policy updated with literature review through September 14, 2017; reference 27 added. Policy statement changed to correct error: Chromoendoscopy and virtual chromoendoscopy considered investigational since Sept. 2012 but policy incorrectly listed chromoendoscopy as medically necessary; also not medically necessary language corrected to investigational due to 510k FDA status.
March 2019	Replace policy	Policy updated with literature review through September 14, 2018; no references added. Policy statement unchanged
March 2020	Replace policy	Policy updated with literature review through September 9, 2019; no references added. Policy statements unchanged
March 2021	Replace policy	Policy updated with literature review through October 6, 2020; references added. Policy statements unchanged.
March 2022	Replace policy	Policy updated with literature review through September 29, 2021; references added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through September 29, 2022; references added. Policy statements unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.