



**BlueCross BlueShield
of Alabama**

Name of Blue Advantage Policy:
Chromoendoscopy as an Adjunct to Colonoscopy

Policy #: 494

Latest Review Date: November 2022

Category: Radiology

ARCHIVED EFFECTIVE 11/1/2023

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **chromoendoscopy** as a **non-covered benefit** and as **investigational** as an adjunct to diagnostic or surveillance colonoscopy.

Blue Advantage will treat **virtual chromoendoscopy** as a **non-covered benefit** and as **investigational** as an adjunct to diagnostic or surveillance colonoscopy.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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 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 results from dye or stain spraying.

Colonoscopy

Colonoscopy, a procedure during which colonic and rectal polyps can be identified and removed, is considered the criterion standard test for colorectal cancer (CC) screening and diagnosis of colorectal disease. However, colonoscopy is an imperfect procedure. A systematic review and meta-analysis by Zhao et al (2019) pooled findings from more than 15,000 tandem (i.e., back-to-back) colonoscopies in 43 publications and found a miss rate of 26% for adenomas, 9% for advanced adenomas, and 27% for serrated polyps. Miss rates were higher for proximal advanced adenomas (14%), serrated polyps (27%), flat adenomas (34%), and in patients at high risk for CC (33%).

Adjunctive Procedures

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 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.

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 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). 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 a family history of colorectal cancer, 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 (IBD)
- 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, procedures, (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.

KEY POINTS:

The most recent literature review was updated through September 29, 2022.

Summary of Evidence

Chromoendoscopy

For individuals who have an average risk of CC who receive chromoendoscopy, the evidence includes a meta-analysis of RCTs. Relevant outcomes are OS, 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 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 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. The relevant outcomes are OS, DSS,

test validity, and change in disease status. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies on the impact of virtual chromoendoscopy on CC incidence or 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. The relevant outcomes are OS, DSS, test validity, and change in disease status. The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies on the impact of virtual chromoendoscopy on CC incidence or 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.

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy and the 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). 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. 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. 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).

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

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.

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 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- (e.g., 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]." 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]."

The 2012 Multi-Society Task Force guidelines on colonoscopy surveillance after screening and polypectomy (consensus update) stated that chromoendoscopy and NBI might 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 these technologies currently do not have an impact on surveillance interval.

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.

KEY WORDS:

Chromoendoscopy, Chromoscopy, Chromocolonoscopy. Virtual chromoendoscopy, FICE, i-scan, NBI

APPROVED BY GOVERNING BODIES:

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.

In June 2012, the i-SCAN™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by the FDA through the 510(k) process. This is a digital image enhancement technology and is part of the Pentax EPK-i5010 Video Processor. 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.

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

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

There is no specific coding for chromoendoscopy. The additional work of the chromoendoscopy would probably be reported with the unlisted CPT code 44799 (unlisted procedure, intestine) or 78299 (unlisted gastrointestinal procedure, diagnostic nuclear medicine).

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POLICY HISTORY:

Adopted for Blue Advantage, April 2012

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Medical Policy Group, April 2013

Medical Policy Group, March 2014

Medical Policy Group, March 2015

Medical Policy Group, November 2015
Medical Policy Group, January 2017
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Medical Policy Group, November 2019
Medical Policy Group, November 2020
Medical Policy Group, November 2021
Medical Policy Group, November 2022
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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.