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## Chromoendoscopy

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**INTRODUCTION** — Chromoendoscopy involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy [1]. Several agents have been described that can broadly be categorized as absorptive (vital) stains, contrast stains, and reactive stains ([table 1](#)). Absorptive stains (eg, Lugol's solution and [methylene blue](#)) diffuse or are preferentially absorbed across specific epithelial cell membranes. Contrast stains (eg, [indigo carmine](#)) highlight surface topography and mucosal irregularities by permeating mucosal crevices. Reactive stains (eg, Congo red and phenol red) undergo chemical reactions with specific cellular constituents, resulting in a color change. The stains used for chromoendoscopy are transient, unlike the stains used to tattoo lesions. (See ["Tattooing and other methods for localizing colonic lesions", section on 'Tattooing'.](#))

Chromoendoscopy has been applied in a variety of clinical settings and throughout the gastrointestinal tract. Interest in chromoendoscopy increased with the development of technologies such as endoscopic mucosal resection and photodynamic therapy that require precise visual tissue characterization. In addition, chromoendoscopy is being used in conjunction with other advances in endoscopic imaging, such as magnification endoscopy, confocal endomicroscopy, and confocal endocytoscopy. (See ["Magnification endoscopy"](#) and ["Confocal laser endomicroscopy and endocytoscopy"](#).)

Compared with other evolving diagnostic modalities, such as fluorescence spectroscopy, fluorescence endoscopy, and optical coherence tomography, the equipment needed for chromoendoscopy is widely available. Furthermore, the techniques are simple, quick, inexpensive, and safe. However, the interpretation of the findings is not always straightforward, and, like many endoscopic techniques, the impact of chromoendoscopy on clinical outcomes relative to standard endoscopic and histologic methods has not been established in large controlled trials.

This topic will review chromoendoscopy, which generally refers to the application of stains or pigments by spraying through a catheter. Endoscopic tattooing (the injection of dye through a needle to mark a site for future identification), optical coherence tomography, narrow band imaging, magnification endoscopy, and autofluorescence endoscopy are discussed separately. (See ["Tattooing and other methods for localizing colonic lesions", section on 'Tattooing'](#) and ["Optical coherence tomography in the gastrointestinal tract"](#) and ["Barrett's esophagus: Evaluation with narrow band imaging"](#) and ["Magnification endoscopy"](#) and ["Barrett's esophagus: Evaluation with autofluorescence endoscopy"](#).)

**EQUIPMENT** — Minimal equipment is required for chromoendoscopy, and the reagents used are generally widely available. The procedure is carried out using standard endoscopic equipment. In addition, a special spray catheter (such as the Olympus PW-5L) is essential, since it delivers a fine mist to the mucosa ([movie 1](#)). The catheters are reusable and last several years, even when used frequently. A new biopsy channel cap is

preferable to minimize the amount of stain that leaks out.

Stains that are used for chromoendoscopy include Lugol's solution, [methylene blue](#), toluidine blue, Congo red, phenol red, and [indigo carmine](#). In order to choose the appropriate stain, the endoscopist needs to be familiar with the characteristics of the individual stains and the staining features of specific tissues ([table 1](#)).

**GENERAL TECHNIQUE** — The technique for staining is simple and easy to learn. Certain staining techniques require specific tissue preparations, which are described below. Once that has been accomplished, application of the stain is generally straightforward. The endoscope and catheter tip should be directed toward the mucosa using a combination of rotational clockwise-counterclockwise movements, while simultaneously withdrawing the endoscope tip. [Atropine](#) or [glucagon](#) can be administered immediately prior to staining to minimize contractility and thereby facilitate staining.

## SPECIFIC DYES

**Lugol's solution** — Lugol's solution contains potassium iodine and iodine, which have an affinity for glycogen in non-keratinized squamous epithelium. The stock solution needs to be diluted to 1 to 4 percent (usually 2 to 3 percent strength works best) followed by spraying of 20 to 50 mL through a spray catheter. Normal squamous epithelium stains black, dark brown, or green-brown after a few minutes ([picture 1](#)).

An abnormal staining pattern (absence of dye uptake) is associated with conditions that result in depletion of glycogen in squamous cells, such as inflammatory change (eg, reflux esophagitis), dysplasia, or early malignancy. Staining with Lugol's solution is particularly helpful in patients at increased risk for squamous cell carcinoma (such as those who abuse alcohol) and in those with head and neck cancer [[2-7](#)]. As a result, it is most commonly used in the esophagus for detection of squamous dysplasia and early squamous cell carcinoma ([picture 1](#)). Because it can help in revealing the extent and delineation of a lesion, it can be used to guide endoscopic mucosal resection of early squamous cell carcinomas. (See "[Overview of endoscopic resection of gastrointestinal tumors](#)".)

Lugol's is also used to differentiate regenerating squamous epithelium from small areas of residual Barrett's mucosa in patients who have undergone mucosal ablation (eg, after photodynamic therapy or multipolar electrocoagulation). The residual areas of Barrett's esophagus will not stain, but the regenerating squamous islands and normal squamous epithelium will appear dark brown or black ([picture 2](#)) [[8](#)].

**Efficacy of Lugol's staining** — For the detection of squamous lesions, staining with Lugol's solution has a sensitivity of 91 to 100 percent and a specificity of 40 to 95 percent [[9](#)].

The value of Lugol's staining has been demonstrated in studies looking at the detection and evaluation of esophageal squamous neoplasia:

- One study that included 158 patients at high risk for squamous cell cancer (because of a history of smoking and alcoholism) demonstrated that Lugol's staining improved the evaluation of the extent of lesions [[10](#)]. Twelve of the patients had cancerous lesions detected by endoscopy before Lugol's staining, with one additional patient with cancer being identified after staining. There was a significant difference in the size of the lesions detected before and after staining. The dye-free surfaces (suggestive of malignancy) after staining averaged 11.6 cm<sup>2</sup> compared with the endoscopically measured mucosal involvement before staining of 1.4 cm<sup>2</sup>.
- In a series of 225 patients, Lugol's staining increased the identification of both moderate and severe dysplasia, but not of cancer [[9](#)]. Of 31 patients with moderate dysplasia, 17 (55 percent) were identified only after staining with Lugol's solution. Of the 35 patients with severe dysplasia, eight (23 percent) were

identified only after staining. In addition, 88 percent of the high-grade dysplasia and cancerous lesions were larger or more clearly defined after staining.

**Safety of Lugol's staining** — Lugol's staining may lead to a transient retrosternal discomfort. A controlled trial suggested that the application of a [sodium thiosulfate](#) solution (20 mL of a 5 percent solution) following staining was associated with a significant reduction in discomfort 30 minutes after the procedure [11]. Patients with a history of iodine allergy should not undergo Lugol's staining. Severe allergic reactions have been reported [12], as have cases of chemical esophagitis [13] and gastritis [14].

**Methylene blue** — [Methylene blue](#) is a vital stain taken up by actively absorbing tissues such as small intestinal and colonic epithelium. It does not stain nonabsorptive epithelia such as squamous or gastric mucosa.

[Methylene blue](#) staining has been studied in the esophagus, stomach, and small and large intestines. In the small intestine and colon, a lack of staining suggests metaplastic, neoplastic, or inflammatory change, whereas in other areas of the gastrointestinal tract it is used to identify metaplastic absorptive mucosa (eg, Barrett's mucosa).

[Methylene blue](#) staining is used to:

- Aid in the detection of Barrett's esophagus and associated dysplasia and/or early cancer.
- Improve the diagnosis of early gastric cancer, either alone [15] or in combination with Congo red dye [16].
- Identify metaplastic absorptive epithelium, such as intestinal-type metaplasia in the stomach [17]. In addition, because it only stains absorptive epithelium, it can identify metaplastic nonabsorptive epithelium (such as ectopic gastric metaplasia) in areas that have background staining, such as the small bowel.
- Highlight subtle mucosal changes in the small intestine (eg, celiac disease [18]).
- Detect colonic neoplasia (flat adenomas and carcinomas) [19].
- Detect the extent of inflammatory changes and aid in the detection of intraepithelial neoplasia in patients with chronic ulcerative colitis [20].
- Act as a contrast agent for confocal laser endomicroscopy and endocytoscopy. (See "[Confocal laser endomicroscopy and endocytoscopy](#)".)

**Methylene blue application** — [Methylene blue](#) staining involves the application of a mucolytic, followed by dye, followed by washing off excess dye. Surface mucus must be removed by applying a mucolytic agent to increase the uptake of the dye into epithelial cells. The original technique for staining reported by Japanese endoscopists involved ingestion of a proteolytic enzyme solution (proteinase or Pronase) followed by methylene blue in a capsule [15,21]. The Japanese technique was adapted for use in the United States by substituting a 10 percent solution of N-acetylcysteine for Pronase and a 0.5 percent solution of methylene blue for the capsule [17].

The reagents are sequentially sprayed onto the mucosa using a washing catheter ([picture 3](#)). Excess dye is then vigorously washed off with syringes. The endpoint of staining is subjective and is the most difficult part to learn. As a general rule, washing should continue until the staining pattern is stable. The most common mistake is failure to adequately rinse the mucosa following dye application. Positive staining is defined as the presence of blue-stained mucosa that persists despite vigorous water irrigation.

**Staining patterns** — As noted above, [methylene blue](#) is taken up by actively absorbing cells, such as small intestine or colonic epithelium, or ectopic intestinal mucosa. It does not stain non-absorptive epithelia. Thus, staining in the small intestine or colon will normally lead to diffuse background absorption of the dye. Abnormal areas, such as inflamed or neoplastic tissue, will not stain. On the other hand, in the case of metaplastic intestinal mucosa, as is seen in Barrett's esophagus, the abnormal absorptive mucosa will appear blue, while the normal background mucosa will not take up the stain.

In patients with Barrett's esophagus, staining may be focal ([picture 4](#)) or diffuse (>75 percent of Barrett's mucosa stains blue) [[22](#)]. Most patients with long-segment Barrett's esophagus have diffuse staining because specialized intestinal metaplasia comprises the majority of the columnar mucosa [[22](#)]. The pattern of [methylene blue](#) staining is important because dysplastic and malignant Barrett's esophagus behave differently from nondysplastic epithelium [[23](#)]. Increasing grades of dysplasia are associated with focal areas of decreased stain intensity and/or increased stain heterogeneity (ie, increasing proportion of light blue or pink unstained mucosa compared with dark blue mucosa). This results from the differential absorption of methylene blue dye into dysplastic cells that have varying degrees of goblet cell loss and decreased cytoplasm (the sites where the dye is absorbed). High-grade dysplasia and endoscopically inapparent adenocarcinomas in Barrett's esophagus can be diagnosed by sampling the heterogeneously stained or light blue/unstained epithelium ([picture 5](#)).

Abnormal [methylene blue](#) staining can be helpful in delineating dysplastic or malignant areas for endoscopic therapy, such as endoscopic mucosal resection [[24](#)] or photodynamic therapy [[25](#)]. The addition of magnification endoscopy to methylene blue staining may aid in the detection of Barrett's esophagus by classifying its histologic features ([picture 6](#)) [[26,27](#)]. (See "[Magnification endoscopy](#)".)

[Methylene blue](#) staining has also been used to detect colonic dysplasia. Pit patterns, which are highlighted by the methylene blue, have been described that correlate with neoplastic lesions. (See '[Colonic dysplasia](#)' below.)

### Efficacy of methylene blue staining

**Barrett's esophagus** — The most extensive experience with [methylene blue](#) staining in the United States, Europe, Asia, and Latin America has been in the evaluation of patients with Barrett's esophagus ([picture 2](#)). Multiple reports have been published in final form or as abstracts that have shown discrepant results [[22,23,25,28-41](#)]. The discrepancies appear to be related to the learning curve for this staining technique; investigators with experience and studies with large sample sizes have reported the best results [[22-26,28-31,42](#)]. Perhaps because of these issues, a meta-analysis of nine studies with heterogeneous study designs, methods, and study populations concluded that methylene blue chromoendoscopy did not significantly increase the yield of detection of specialized intestinal metaplasia and dysplasia compared with random biopsies [[43](#)].

The potential to improve the detection of intestinal metaplasia was illustrated in a study of 975 patients with areas in the distal esophagus that were macroscopically conspicuous for Barrett's esophagus [[42](#)]. All patients underwent conventional biopsies, after which the distal esophagus was sprayed with [methylene blue](#); additional targeted biopsies were obtained based upon the staining pattern. All patients with documented intestinal metaplasia underwent a repeat endoscopy within one year to assess the reproducibility of the method.

A total of 3900 conventional biopsies without staining and 130 biopsies with staining were obtained. Conventional biopsies were significantly less likely to show intestinal metaplasia compared with dye-directed biopsies (1.4 versus 88 percent). The conventional biopsies diagnosed Barrett's esophagus in 16 patients (1.6

percent), whereas the dye-directed biopsies diagnosed it in 35 patients (3.5 percent), including all of the patients diagnosed with conventional biopsies. Intestinal metaplasia was confirmed on the follow-up endoscopy in all dye-positive patients.

**Colonic dysplasia** — Chromoendoscopy has been used in patients undergoing colonoscopy, including those undergoing surveillance for chronic ulcerative colitis. Using pit pattern classifications, chromoendoscopy has a sensitivity of 92 to 98 percent and a specificity of 91 to 95 percent for differentiating neoplastic from non-neoplastic lesions [44]. The Kudo pit pattern classification is most commonly used ([figure 1](#)) [45,46]. Lesions with gyrus-like pits or non-structural pits are more likely to be neoplastic than lesions with round pits or stellar pits.

One study found that when combined with high-magnification endoscopy, 0.25 percent [methylene blue](#) can aid in the visualization of aberrant crypt foci, the earliest neoplastic lesions of the colon that are precursors to adenomas and carcinomas [47]. In an examination of 97 biopsy samples, the combination of chromoendoscopy and magnification endoscopy had a sensitivity of 100 percent and a specificity of 97 percent for detecting dysplasia. (See "[Magnification endoscopy](#)".)

In a randomized trial, 174 patients with chronic ulcerative colitis were assigned to either undergo colonoscopy with chromoendoscopy using 0.1 percent [methylene blue](#) or conventional colonoscopy [44]. Magnification endoscopy was used in the chromoendoscopy arm to classify the lesions detected by chromoendoscopy based upon the pit pattern [45]. The yield of chromoendoscopy for the detection of intraepithelial neoplasia was significantly higher than that for conventional colonoscopy (32 versus 10 lesions). In addition, chromoendoscopy had a 93 percent sensitivity and specificity for differentiating neoplastic from nonneoplastic lesions. Similarly, in a preliminary report of a randomized trial comparing high-definition endoscopy using chromoendoscopy with high-definition white light endoscopy in 103 patients with ulcerative colitis, chromoendoscopy detected dysplastic lesions in more patients than white light endoscopy (22 versus 9 percent) and detected more dysplastic lesions per patient (0.26 versus 0.12) [48].

**Gastric neoplasia** — [Methylene blue](#) staining has been combined with magnification endoscopy in the evaluation of gastric neoplasia [49,50]. In a study of 136 patients, the sensitivity and specificity of magnification chromoendoscopy for intestinal metaplasia were 76 and 87 percent, and for dysplasia were 97 and 81 percent, respectively [49].

**Safety of methylene blue** — [Methylene blue](#) staining is generally considered to be safe. However, a concern has been raised regarding the potential to induce oxidative damage to DNA in tissues exposed to methylene plus white light (which is used during endoscopy) [51]. Such oxidative damage has the potential to accelerate carcinogenesis. However, this theoretical risk for increasing neoplastic transformation has not been proven by clinical studies showing increased cancers in patients who have undergone staining.

**Indigo carmine** — [Indigo carmine](#) is derived from a blue plant dye (indigo) and a red coloring agent (carmine) [1]. Unlike the vital stains (which are taken up by tissues), indigo carmine is not absorbed by gastrointestinal epithelium. It pools in crevices between epithelial cells, highlighting small or flat lesions and defining irregularities in mucosal architecture, particularly when used with high-magnification or high-resolution endoscopy.

It is used primarily in the colon for the detection and evaluation of colorectal neoplasia and is the most common form of chromoendoscopy applied in the colon. As with many other stains, [indigo carmine](#) is used to evaluate pit patterns ([figure 1](#)). These patterns can help discriminate between hyperplastic polyps (which have a typical "pit" pattern) and adenomatous polyps (which have a "groove" or "sulci" pattern) [52]. Pit patterns can also aid in the diagnosis of minute, flat, or depressed colorectal tumors and increase the detection of flat

adenomas ([picture 7](#)) [[53-57](#)]. Indigo carmine can assist in the detection of dysplastic changes in patients with ulcerative colitis undergoing surveillance colonoscopy [[58,59](#)], as well as aid in the detection of adenomas in patients with hereditary nonpolyposis colorectal cancer [[60](#)].

[Indigo carmine](#) has also been used:

- In combination with high-magnification endoscopy and Lugol's staining to diagnose the villiform appearance of Barrett's esophagus [[12,61](#)] (see "[Magnification endoscopy](#)")
- To diagnose small gastric cancers used alone [[15](#)] or in combination with acetic acid staining [[62](#)]
- To evaluate villous atrophy in patients suspected of having malabsorption from celiac disease or tropical sprue [[63](#)]
- To detect duodenal adenomas in patients with familial adenomatous polyposis [[64](#)]

There are several techniques described for [indigo carmine](#) staining. The oral route involves ingestion of a capsule or a dye-containing colonic electrolyte lavage solution. The dye (0.1 to 0.8 percent) can also be sprayed directly onto the mucosa. Indigo carmine has also been injected into the celiac artery (intra-arterial dye method) to facilitate endoscopic delineation of the size and extent of gastric cancers [[65](#)].

**Efficacy for finding colorectal neoplasia** — The use of [indigo carmine](#) in the colon has been examined in randomized controlled trials with variable results [[56,57,66-68](#)]. A meta-analysis from 2007 found a benefit from chromoendoscopy for the detection of polyps, both neoplastic and non-neoplastic [[69](#)]. The analysis found that patients who underwent chromoendoscopy were more likely to have a polyp detected (odds ratio [OR] 2.1), a benefit that persisted when only neoplastic lesions (OR 1.6) or diminutive neoplastic lesions (OR 1.7) were considered. Finally, chromoendoscopy also detected significantly more patients with three or more neoplastic lesions (OR 2.6).

Representative trials (including trials done subsequent to the meta-analysis) have demonstrated the following:

- In one trial, 660 patients were assigned to undergo either high-definition chromoendoscopy with spraying of the entire colon or high-definition white light colonoscopy [[67](#)]. Chromoendoscopy showed a trend toward higher mean rates of detection of patients with at least one adenoma (56 versus 48 percent for white light colonoscopy,  $p = 0.07$ ) and number of adenomas per patient (1.3 versus 1.1,  $p = 0.07$ ). While the absolute differences were small, chromoendoscopy detected significantly more flat adenomas per patient (0.6 versus 0.4), more adenomas less than 5 mm in diameter per patient (0.8 versus 0.7), and more non-neoplastic lesions per patient (1.8 versus 1.0). The mean procedure time was longer for chromoendoscopy (30 versus 22 minutes).
- In a second large trial, 400 patients were assigned to undergo colonoscopy with chromoendoscopy performed by an endoscopist experienced in the technique (group A,  $n = 200$ ), chromoendoscopy performed by an endoscopist who was not experienced in the technique (group B2,  $n = 100$ ), or colonoscopy without chromoendoscopy, but with a minimum withdrawal time of 10 minutes (group B1,  $n = 100$ ) [[70](#)]. After adjusting for confounders, the odds of finding a polyp were significantly lower in group B1 compared with group A (OR 0.44). There was no significant difference in polyp detection between group A and group B2. While there was not a statistically significant difference in the rate of adenoma or cancer detection between group A and group B1, flat adenomas were detected less often in patients in group B1 compared with group A (OR 0.24).
- In another trial, 259 patients were assigned to undergo either colonoscopy with spraying of the entire colon or routine colonoscopy [[56](#)]. The study found no difference in the proportion of patients with at least one adenoma or the total number of adenomas detected between the two groups, though there were

more adenomas less than 5 mm detected proximal to the sigmoid colon and more patients with three or more identified adenomas in the chromoendoscopy arm. The withdrawal time was significantly longer in the chromoendoscopy arm compared with the control arm (median 9 versus 5 minutes).

- A fourth trial compared the use of pancolonoscopic chromoendoscopy and targeted chromoendoscopy [66]. A total of 260 patients were assigned to one of the two arms. In an attempt to control for withdrawal time, a minimum withdrawal time of 8 minutes was established, and there was no difference in median withdrawal times (17 minutes in the chromoendoscopy group and 15 minutes in the control group). Significantly more adenomas were detected in the pan-chromoendoscopy group compared with the control group (57 versus 34), including more diminutive adenomas (<4 mm) and more patients with greater than three adenomas detected.
- A fifth trial included 1008 patients who were assigned to either pancolonoscopic chromoendoscopy or standard colonoscopy [68]. The proportion of patients with at least one adenoma was higher in the chromoendoscopy group compared with the control group (46 versus 36 percent). In addition, chromoendoscopy increased the per patient detection rate for adenomas overall (0.95 versus 0.66), flat adenomas (0.56 versus 0.28), and serrated lesions (1.19 versus 0.49). Mean extubation times were longer in the chromoendoscopy group (11.6 versus 10.1 minutes).

Randomized trials using tandem colonoscopy studies have also been performed to evaluate adenoma detection rates for chromoendoscopy. In a tandem colonoscopy study, a standard colonoscopy is performed, and any polyps detected are removed. A second colonoscopy is then immediately carried out with patients assigned to have the exam either with chromoendoscopy or without (in an attempt to control for the fact that some lesions that were missed on the first examination might be detected on a second examination, even without dye spraying).

Tandem colonoscopy trials have also had variable results:

- In a trial of 50 patients with a history of either colon cancer or colon adenomas, chromoendoscopy found additional adenomas in 44 percent of patients, compared with 17 percent for those who underwent a second colonoscopy with intensive inspection (inspection time of more than 20 minutes) [71]. The adenomas detected by chromoendoscopy were smaller than those detected with intensive inspection (mean 2.7 versus 3.2 mm). Chromoendoscopy took longer than intensive inspection (mean procedure time 37 versus 27 minutes). After controlling for inspection time, chromoendoscopy still detected more adenomas than intensive inspection.
- A second trial from the same group examined 54 patients with Lynch syndrome using the same protocol described above [72]. After controlling for age, number of prior colonoscopies, procedure time, and history of prior colonic resection, chromoendoscopy detected more polyps overall, but there was no difference in the adenoma detection rate. (See "[Lynch syndrome \(hereditary nonpolyposis colorectal cancer\): Clinical manifestations and diagnosis](#)".)
- There was no difference in polyp detection rate in a tandem colonoscopy trial that included 292 patients [73]. The patients in the chromoendoscopy group were also examined with structure enhancement (an electronic function that is supposed to enhance medically relevant structures). While more hyperplastic polyps were detected in the chromoendoscopy group, there was no difference between the groups with regard to the number of patients found to have adenomas or the total number of adenomas detected. The median procedure times were significantly longer in the chromoendoscopy group compared with the control group (27 versus 19 minutes).

Given mixed results with regard to the effectiveness of chromoendoscopy for adenoma detection and the increased time required to perform the procedure, the use of chromoendoscopy for the routine detection of colorectal neoplasia needs to be individualized.

**Efficacy in chronic ulcerative colitis** — A study of 100 patients undergoing surveillance colonoscopy for longstanding, extensive ulcerative colitis used tandem colonoscopies to examine whether chromoendoscopy would increase the detection of dysplasia. After undergoing a routine colonoscopy that included non-targeted four quadrant biopsies obtained every 10 cm, patients underwent a colonoscopy with pancolonic staining with [indigo carmine](#) [59]. Biopsies were obtained from any additional visible abnormalities. The 2904 non-targeted biopsies did not detect dysplasia in any patient. Biopsies obtained of visible lesions detected during routine colonoscopy identified two patients with dysplasia associated lesions/masses. Biopsies obtained using chromoendoscopy detected a total of seven dysplastic lesions in five patients. All seven lesions were considered to be adenomas. Chromoendoscopy targeted biopsies detected dysplasia in significantly more patients than non-targeted biopsies, and there was a trend toward an increased dysplasia detection rate compared with targeted biopsies obtained during standard colonoscopy ( $p = 0.06$ ).

While these data suggest that there may be a role for chromoendoscopy in patients with chronic ulcerative colitis, there is not yet enough evidence to recommend its routine use during surveillance colonoscopy. The American Gastroenterologic Association has taken the following position [74]:

- "[A]t this time, normal white light colonoscopy, using standard or high-definition colonoscopes along with multiple colon biopsies, remains a reasonable method of surveillance for patients with IBD. However, chromoendoscopy with targeted biopsies is considered an acceptable alternative to white light endoscopy for endoscopists who have experience with this technique."

**Toluidine blue** — Toluidine blue (also called tolonium chloride) is a basic dye that stains cellular nuclei. These properties make it useful for identifying malignant tissues, which have increased DNA synthesis and a high nuclear to cytoplasmic ratio [75].

Staining is accomplished by spraying 1 percent acetic acid (which acts as a mucolytic) before and after spraying a 1 percent aqueous solution of toluidine blue. The second application of acetic acid washes off excess dye. After staining, abnormal tissue appears blue, but false-positive results may occur if inflammatory or fibrotic lesions are present.

Toluidine blue staining has been applied in several clinical settings:

- Screening for early squamous esophageal cancers in alcohol and tobacco abusers [76] and patients with head and neck cancers [77,78].
- Helping to distinguish benign from malignant ulcers in the stomach [79].
- Detecting Barrett's esophagus. In one report, the sensitivity and specificity were 98 and 80 percent, respectively [80]. A limitation is that it cannot discriminate between gastric and intestinal metaplasia.

No adverse effects from toluidine blue staining have been reported.

**Cresyl violet** — Cresyl violet has been used for staining uterine cervical lesions and enhancing the endoscopic diagnosis of early malignancies. It acts by staining cell nuclei and is applied as a 0.05 to 0.2 percent solution. It has been used in the colon to highlight pit patterns [81] and has been combined with magnification endoscopy to diagnose a characteristic staining pattern of early gastric carcinomas [82].

**Crystal violet** — Crystal violet stains cell nuclei and can be used in the esophagus for the detection of

Barrett's esophagus and Barrett's associated dysplasia [83]. It has also been used to highlight pit patterns in the colon [84]. It is applied as a 0.05 to 0.1 percent solution.

A double-staining technique has been used in the esophagus and colon to aid with lesion delineation. In the esophagus, [methylene blue](#) staining is performed to delineate the lesion, followed by crystal violet staining to enhance mucosal patterns. A similar technique has been used in the colon, substituting [indigo carmine](#) for methylene blue. In one study of 1250 patients, high-magnification chromoendoscopy, using a combination of indigo carmine and crystal violet staining in the colon, predicted incomplete endoscopic mucosal resection of flat, sessile colonic lesions [85]. (See '[Methylene blue](#)' above and '[Indigo carmine](#)' above.)

**Congo red** — Congo red is a rarely used pH-sensitive indicator that changes from red to dark blue or black in acidic conditions. The staining technique involves the stimulation of acid production with 250 mcg of pentagastrin given orally. During endoscopy, a 0.5 to 5 percent [sodium bicarbonate](#) solution is sprayed prior to a 0.3 to 0.5 percent Congo red solution. A positive reaction (black color change) results within minutes, allowing acid-secreting areas (blue-black) to be distinguished from non-acid secreting areas (red).

Congo red staining has been used to map acid-producing epithelium in the stomach or in ectopic sites:

- It has primarily been used for screening for early gastric cancers and for detecting synchronous lesions when used in combination with [methylene blue](#) (which stains gastric intestinal metaplasia) [16]. Early gastric cancer will usually be identified as a "bleached" area of mucosa that did not stain with either Congo red or methylene blue [1]. In one study looking at patients with multiple gastric cancers, only 28 percent were detected by routine endoscopy, compared with 89 percent of patients who underwent staining with Congo red and methylene blue [86].
- It can also aid in the detection of intestinal metaplasia of the stomach that is accompanied by gastric atrophy and decreased or absent acid production. A study of 124 patients, for example, suggested that its sensitivity was 100 percent and its positive predictive value was 90 percent compared with gastric biopsies as the gold standard [87]. These values were significantly better than those of visual inspection alone (sensitivity and positive predictive values of 25 and 50 percent, respectively).
- It can help assess the completeness of vagotomy [88].

**Phenol red** — Like Congo red, phenol red is a pH indicator. It detects alkaline pH by a color change from yellow to red. The technique involves the administration of a proton pump inhibitor the day prior to the examination or an H2 receptor antagonist given intravenously 30 minutes prior. The patient also ingests a mucolytic agent (dimethylpolysiloxane) before the endoscopy [89]. During endoscopy, a solution of 0.1 percent phenol red and 5 percent urea is sprayed evenly over the gastric mucosal surface. A positive test consists of a color change from yellow to red [89]. Areas of gastric intestinal metaplasia will not change color [89].

A promising clinical application of phenol red is the detection of *Helicobacter pylori* infection. The urease produced by the bacterium catalyzes hydrolysis of urea to NH<sub>3</sub> and CO<sub>2</sub>, resulting in an increase in pH. As a result, *Helicobacter pylori* can be observed in red stained mucosa. Its potential value was illustrated in a study of 108 patients undergoing endoscopy who had no obvious endoscopic findings. The sensitivity and specificity of phenol red dye spraying for *H. pylori* were 100 and 85 percent, respectively, compared to biopsy as the gold standard [90]. This technique has also been used as a research tool to clarify the role of *H. pylori* in gastric carcinogenesis [89,91]. Bile reflux may lead a false-positive result.

**Acetic acid** — Acetic acid has been used to stain abnormal tissues during examination of the cervix, where it whitens immature and dysplastic cervical squamous epithelium. More recently, it has also been applied in the gastrointestinal tract. (See '[Cervical cancer screening tests: Visual inspection methods](#)'.)

Studies have suggested that the application of acetic acid may help identify areas of intestinal metaplasia in the esophagus (Barrett's esophagus) and gastric cardia ([picture 8](#) and [picture 9](#)), to detect dysplasia or early cancer in patients with Barrett's esophagus, and to visualize areas of mucosal atrophy in patients suspected of having celiac disease [\[92-102\]](#). Acetic acid has also been mixed with [indigo carmine](#) to improve the visualization of early gastric cancer [\[62\]](#) and as a mucolytic agent to enhance the visualization of the mucosal pattern with high-resolution (high-definition) endoscopy [\[103\]](#). (See "[Magnification endoscopy](#)".)

Acetic acid provides contrast enhancement of the surface epithelium. It is typically used in combination with magnification endoscopy, in which case it is referred to as enhanced magnification endoscopy (EME). Approximately 10 mL of 1.5 to 3 percent acetic acid is sprayed onto the esophageal wall. Initially, both the esophageal mucosa and the gastric mucosa turn white, but after two to three minutes, the normal esophagus remains white, whereas Barrett's mucosa and gastric columnar mucosa will turn red. The effect is transient, lasting only two to three minutes, so repeated applications of acetic acid may be required. Compared with random biopsies, targeted biopsies following acetic acid staining are associated with an increased yield for detecting Barrett's esophagus (57 versus 26 percent) [\[93\]](#). Acetic acid staining also appears to increase the detection of dysplasia and cancer in patients with Barrett's esophagus. In a retrospective study with 982 patients with Barrett's esophagus undergoing surveillance, staining with acetic acid was compared with random biopsies for detecting dysplasia or early cancer [\[101\]](#). Among those who received staining with acetic acid, dysplasia or superficial cancer was detected in 41 of 327 patients (13 percent), compared with 13 of 655 patients (2 percent) in the random biopsy group. In addition, the number of biopsies needed to detect one patient with dysplasia or early cancer was lower with acetic acid (40 versus 604).

The diagnostic accuracy of EME for Barrett's esophagus ranges from 52 to 90 percent [\[94-100\]](#), but interobserver agreement for the findings is poor ( $\kappa < 0.4$ ) [\[94,104\]](#). It has also been used to detect residual islands of Barrett's esophagus following mucosal ablative therapy [\[105\]](#).

**LIMITATIONS** — While easy to perform and readily available, there are multiple limitations to chromoendoscopy.

- Chromoendoscopy, especially in the colon, can be time-consuming.
- Many endoscopists lack training in chromoendoscopy, which can result in poor staining techniques and misinterpretation of findings (eg, failure to adequately wash following staining with [methylene blue](#), resulting in false-positive results). Interpretation of the staining patterns requires familiarity and is not always straightforward. It is also prone to interobserver variability.
  - In a study of 51 patients undergoing magnificent chromoendoscopy for detecting Barrett's esophagus, there was a high level of interobserver variability ( $\kappa < 0.4$ ) [\[94\]](#).
  - In a study of 163 small colon polyps from 104 patients, interobserver variability for interpreting pit patterns ([figure 1](#)) was low for experienced endoscopists ( $\kappa$  0.85), but high for trainees ( $\kappa$  0.40).
  - In a study of various techniques for detecting Barrett's esophagus, the interobserver variability for chromoendoscopy using [indigo carmine](#) for various findings was low, with  $\kappa$  values ranging from 0.32 to 0.46 [\[106\]](#). Chromoendoscopy with acetic acid was not significantly better ( $\kappa$  values ranging from 0.42 to 0.48). In addition, the values did not change significantly when only experts were evaluated.
- While some classification systems for chromoendoscopic findings exist (eg, the Kudo pit classification system), overall there is a lack of standardization.

- Studies have shown poor reproducibility with regard to the efficacy of chromoendoscopy (eg, as noted above, some studies have found that chromoendoscopy increases adenoma detection rates in the colon, while others have not).
- Studies looking at the impact of chromoendoscopy on patient outcomes are lacking.
- Studies comparing chromoendoscopy with other enhanced imaging technologies (such as narrow band imaging) are limited, and primarily focus on chromoendoscopy in the colon [107-110]:
  - One study randomized 114 patients to undergo magnifying colonoscopy with either computed virtual chromoendoscopy using Fujinon Intelligent Color Enhancement (FICE), which is similar to narrow band imaging (NBI), or targeted [indigo carmine](#) dye spraying for colonic lesions of 1 cm or less [107]. There was no difference in sensitivity or specificity for the FICE group compared with the chromoendoscopy group (93 versus 97 percent and 82 versus 89 percent, respectively). (See "[Barrett's esophagus: Evaluation with narrow band imaging](#)", section on 'Principles'.)
  - A study of 142 patients being screened for esophageal malignancy found that NBI performed well when compared with chromoendoscopy as the gold standard [108]. NBI had a sensitivity of 91 percent for detecting squamous cell carcinoma or high-grade intraepithelial neoplasia, with a specificity of 95 percent.
  - A study of 13 patients with familial adenomatous polyposis compared chromoendoscopy with NBI, autofluorescence endoscopy, and white light (standard) colonoscopy [109]. Chromoendoscopy detected a higher mean number of lesions per patient compared with NBI, autofluorescence, or white light colonoscopy (43 versus 20, 21, and 12 lesions, respectively). (See "[Barrett's esophagus: Evaluation with autofluorescence endoscopy](#)", section on 'Autofluorescence for distinguishing tissue types'.)

## SUMMARY AND RECOMMENDATIONS

- Chromoendoscopy involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy. Several agents have been described that can broadly be categorized as absorptive (vital) stains, contrast stains, and reactive stains ([table 1](#)). (See '[Introduction](#)' above.)
- Lugol's solution is most commonly used in the esophagus for the detection of squamous dysplasia and early squamous cell carcinoma. It is also used to differentiate regenerating squamous epithelium from small areas of residual Barrett's mucosa in patients who have undergone mucosal ablation (eg, after photodynamic therapy or multipolar electrocoagulation). It is our preferred staining method for these indications because it is readily available, easily applied, and clinically useful. It can also be combined with other mucosal enhancement techniques, such as narrow band imaging. (See '[Lugol's solution](#)' above.)
- [Methylene blue](#)'s main use is in the evaluation of Barrett's mucosa. In the stomach, it may be used with Congo red for the identification of early gastric cancer. (See '[Methylene blue](#)' above and '[Congo red](#)' above.)
- [Indigo carmine](#) is used primarily in the colon for the detection and evaluation of colorectal neoplasia. It is the most common form of chromoendoscopy applied in the colon. Indigo carmine may be used alone or with crystal violet for the detection of early colorectal cancers. (See '[Indigo carmine](#)' above and '[Crystal violet](#)' above.)

- Other stains that are used less frequently include toluidine blue, cresyl violet, phenol red, and acetic acid. (See ['Toluidine blue'](#) above and ['Cresyl violet'](#) above and ['Phenol red'](#) above and ['Acetic acid'](#) above.)
- We suggest that patients with endoscopic findings concerning for dysplastic Barrett's esophagus based upon findings from a standard endoscopy undergo chromoendoscopy using [methylene blue](#). (See ['Barrett's esophagus'](#) above.)
- We suggest that patients who have undergone ablative therapy for Barrett's esophagus have a follow-up examination using chromoendoscopy with Lugol's solution to look for residual Barrett's mucosa. (See ['Lugol's solution'](#) above.)
- We suggest that chromoendoscopy with Lugol's solution be performed prior to endoscopic mucosal resection of dysplasia or early cancer of the esophagus, using Lugol's solution for squamous lesions and [methylene blue](#) for lesions arising from Barrett's esophagus. (See ['Lugol's solution'](#) above and ['Methylene blue'](#) above.)
- We suggest against the routine use of chromoendoscopy for the detection of colorectal neoplasia in patients undergoing colonoscopy ([Grade 2B](#)). However, in patients at high risk for dysplasia or malignancy, such as those with longstanding ulcerative colitis, there may be a role for chromoendoscopy using [indigo carmine](#). (See ['Indigo carmine'](#) above.)

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## GRAPHICS

### Tissue stains used during gastrointestinal endoscopy

Stain type	What is stained	Mechanism of staining	Positive staining	Clinical uses in GI
Vital stains				
Lugol's solution (iodine + potassium iodide)	Normal glycogen containing squamous cells	Binds iodine in non-keratinized cells	Dark brown	1) Squamous cell esophageal cancer (non-staining)
				2) Columnar epithelium in the esophagus, including residual Barrett's esophagus following mucosal ablation (non-staining)
				3) Reflux esophagitis (non-staining)
Methylene blue (methylthionine chloride)	Small or large intestinal cells or intestinal metaplasia	Active absorption into cells	Blue	1) Specialized epithelium (intestinal metaplasia) in Barrett's esophagus*
				2) Intestinal metaplasia in the stomach
				3) Early gastric cancer <sup>¶</sup>
				4) Gastric metaplasia in the duodenum (non-staining)
				5) Celiac and tropical sprue
Toluidine blue (tolonium chloride or dimethylamino-toluphenazothioni-chloride)	Nuclei of columnar (gastric and intestinal-type) cells	Diffuses into cell	Blue	1) Squamous cell carcinoma of the esophagus
				2) Gastric or intestinal metaplasia in Barrett's esophagus
Reactive stains				
Congo red (biphenylene-naphthadene sulformic acid)	Acid-containing gastric cells	Acid pH <3.0 results in color change	Turns red to dark blue or black	1) Acid-secreting gastric mucosa (including ectopic locations)
				2) Gastric cancer (nonstaining); (may be combined with methylene blue to outline intestinal metaplasia)
Phenol red (phenolsulfonphthalein)	H. pylori-infected gastric cells	Alkaline pH (from hydrolysis of urea to NH3 and CO2 by urease) results in color change	Turns yellow to red	Diagnose Helicobacter pylori infection (positive color change) and map its distribution in the stomach
Contrast stain				
Indigo carmine <sup>Δ</sup>	Cells are not stained	Pools in crevices and valleys between mucosal projections	Blue (indigo)	1) Colon, gastric, duodenal, esophageal lesions
				2) Barrett's esophagus

\* Methylene blue does not stain non-specialized or gastric metaplasia; specialized columnar epithelium stains blue, but highly dysplastic or malignant specialized columnar epithelium in Barrett's esophagus generally takes up little to no dye; low grade dysplasia in Barrett's esophagus may or may not take up stain.

¶ With or without Congo red.

Δ Also used in combination with high resolution or high magnification endoscopy; may be used with or without crystal violet (for early colorectal cancers).

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Graphic 68885 Version 9.0

## Chromoendoscopy of esophageal squamous cell carcinoma

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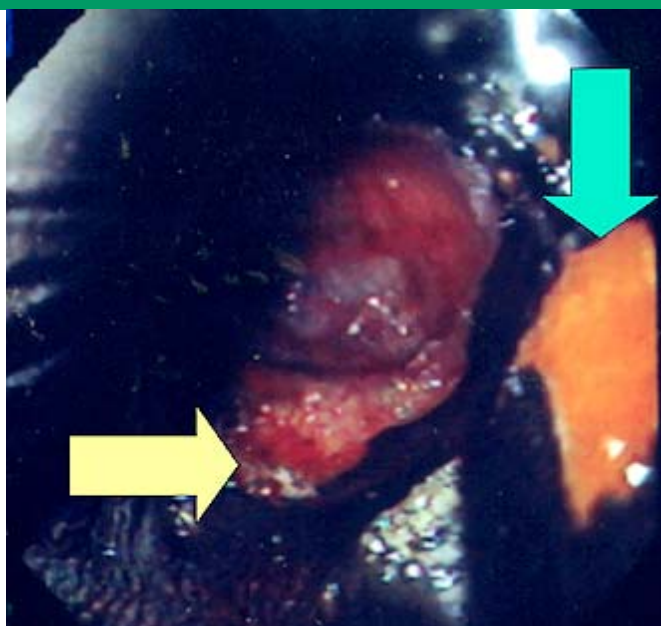


Endoscopic view of the esophagus following staining with Lugol's iodine solution showing squamous cell carcinoma, which appears as an unstained plaque (arrow). The dark brown areas are normal squamous mucosa.

*Courtesy of Marcia I Canto, MD, MHS.*

Graphic 71269 Version 2.0

## Chromoendoscopy showing residual Barrett's esophagus after photodynamic therapy

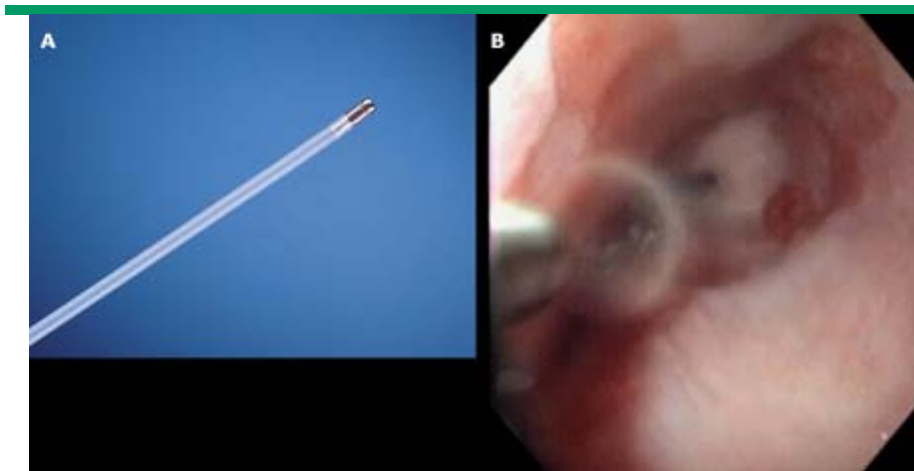


Endoscopic image after Lugol's chromoendoscopy, which shows an unstained small area of residual Barrett's esophagus following photodynamic therapy (green arrow). Note the adjacent normal black colored squamous mucosa, squamocolumnar junction, and unstained normal gastric cardiac mucosa (yellow arrow).

*Courtesy of Marcia I Canto, MD, MHS.*

Graphic 75257 Version 2.0

## Washing catheter used during chromoendoscopy

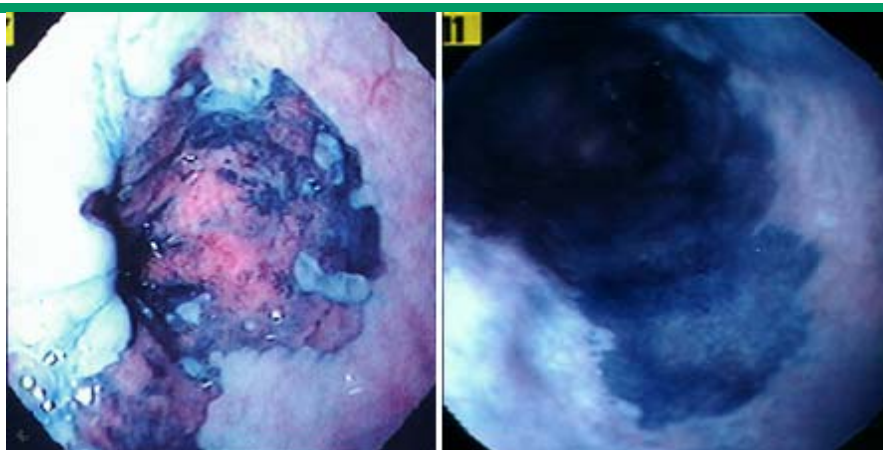


Washing catheter for chromoendoscopy (A) creates a fine mist spray (B) necessary for optimal application of reagents to the gastrointestinal mucosa.

*Courtesy of Marcia I Canto, MD, MHS.*

Graphic 66043 Version 2.0

## Chromoendoscopy of Barrett's esophagus



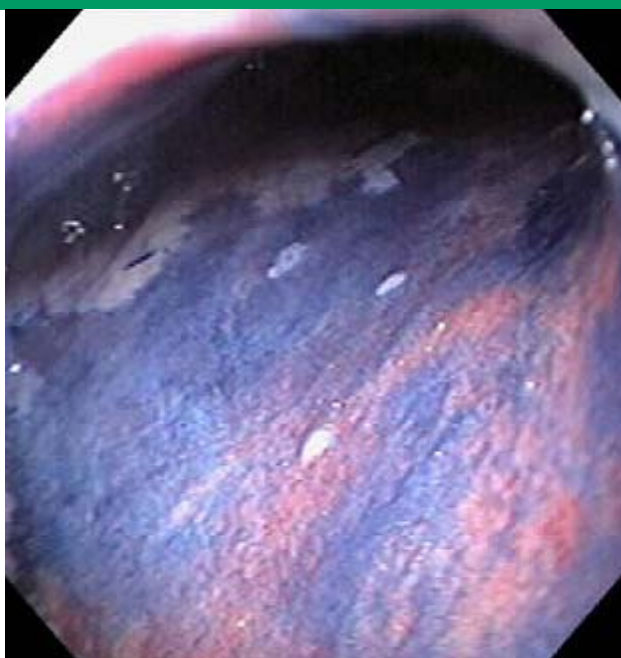
Endoscopic views of short-segment Barrett's esophagus (left panel) and long-segment Barrett's esophagus (right panel) seen after staining with methylene blue.

*Courtesy of Marcia I Canto, MD, MHS.*

Graphic 60183 Version 2.0

## Chromoendoscopy of Barrett's esophagus

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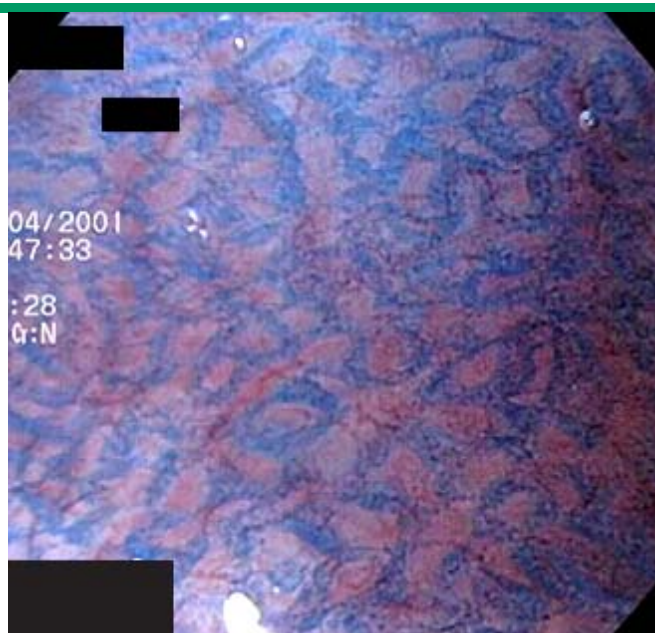


Endoscopic image of diffusely-stained, long-segment Barrett's esophagus with an area of heterogenous staining (pink or unstained mucosa) corresponding to high grade dysplasia, which was confirmed by biopsy.

*Courtesy of Marcia I Canto, MD, MHS.*

Graphic 73339 Version 3.0

## Barrett's esophagus



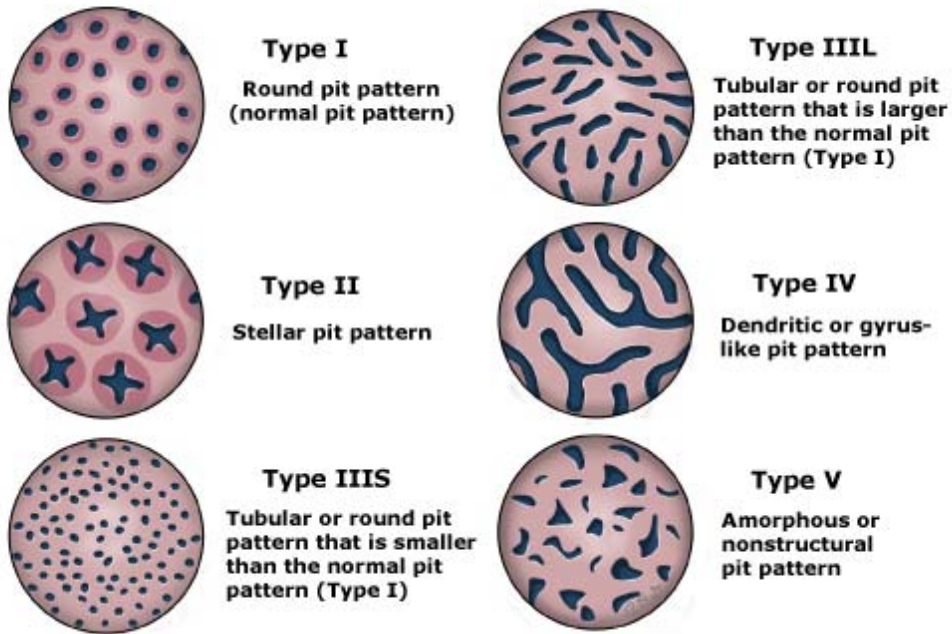
Endoscopic image of specialized intestinal metaplasia in Barrett's esophagus with a tubular pit pattern by methylene blue high magnification chromoendoscopy (Olympus 240 Z, magnified 135x).

*Courtesy of Marcia I Canto, MD, MHS.*

Graphic 71929 Version 1.0

## Kudo Pit Pattern Classification of colonic mucosal lesions

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Pit pattern classification for colonic mucosal lesions.

Graphic 69425 Version 6.0

## Chromoendoscopy with indigo carmine of a colon adenoma



High resolution endoscopic image of a small flat colon adenoma in a patient with familial adenomatous polyposis after spraying with indigo carmine. The indigo carmine is not absorbed and collects in the crevices between epithelial cells thereby enhancing the mucosal details.

*Courtesy of Francis Giardiello, MD.*

Graphic 54584 Version 2.0

## Magnification endoscopy in a patient with Barrett's esophagus

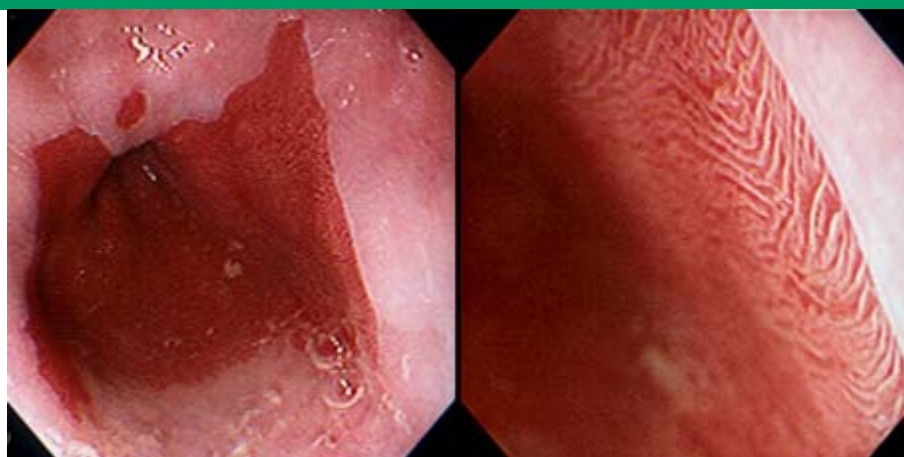


Magnification endoscopy following instillation of acetic acid in a patient suspected of having short-segment Barrett's esophagus (left panel). The magnified image (right panel) shows a reticular mucosal pattern suggestive of cardiac epithelium (rather than intestinal metaplasia), which was confirmed on pathology.

*Courtesy of Moises Guelrud, MD.*

Graphic 62055 Version 3.0

## Magnification endoscopy in a patient with Barrett's esophagus



Magnification endoscopy following instillation of acetic acid in a patient suspected of having short-segment Barrett's esophagus (left panel). The magnified image (right panel) shows a villous pattern, typical for intestinal metaplasia, which was confirmed on biopsy.

*Courtesy of Moises Guelrud, MD.*

Graphic 73908 Version 3.0

## Contributor Disclosures

**Marcia Irene Canto, MD, MHS** Nothing to disclose **John R Saltzman, MD, FACP, FACG, FASGE, AGAF** Nothing to disclose **Anne C Travis, MD, MSc, FACG, AGAF** Equity Ownership/Stock Options: Proctor & Gamble [Peptic ulcer disease/GI bleeding (omeprazole)].

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