

Medical Coverage Policy



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Colorectal Cancer Screening and Surveillance

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Overview

This Coverage Policy addresses screening and surveillance testing regimens for colorectal cancer.

Coverage Policy

In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

For an average-risk individual age 50 years and older, the following colorectal cancer (CRC) screening testing regimens are considered medically necessary:

- annual fecal occult blood test (FOBT) or fecal immunochemical test (FIT)
- flexible sigmoidoscopy every five years
- double-contrast barium enema (DCBE) every five years
- colonoscopy every 10 years
- computed tomographic colonography (CTC)/virtual colonoscopy every five years
- stool-based deoxyribonucleic acid (DNA) (i.e., Cologuard) testing every one to three years

For an increased- or high-risk individual who fits into any of the categories listed below, more intensive colorectal cancer screening, surveillance or monitoring are considered medically necessary:

- personal history of adenoma or adenomatous polyps found on colonoscopy
- familial history of adenoma or adenomatous polyp found at colonoscopy in a first-degree relative
- personal or family history of colorectal cancer
- personal history of inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease)
- personal or inherited risk of a colorectal cancer (e.g., familial adenomatous polyposis [FAP], attenuated FAP, hereditary nonpolyposis colorectal cancer [HNPCC], MYH polyposis)

Chromoendoscopy is considered medically necessary for colorectal cancer surveillance for patients at increased risk based on personal history of inflammatory bowel disease (IBD).

The following are considered experimental, investigational, or unproven for any indication including, but not limited to, the screening, diagnosis or surveillance of colorectal cancer:

- fiberoptic polyp analysis, narrow band imaging, and confocal fluorescent endomicroscopy}
- chromoendoscopy for any other indication
- urine-based test for detection of adenomatous polyps (e.g., PolypDX)

General Background

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide and the third leading cause of cancer deaths in the United States. Age-specific incidence and mortality rates show that most cases are diagnosed after age 54 years and 78.7% of cases occur in patients aged 55 years and older; about 15% of CRC cases occur in patients aged 45 to 54 years (National Cancer Institute [NCI], 2020).

The etiology of CRC is heterogeneous and may be influenced by both the environment and genetics. There are groups with a higher incidence of CRC. These include those with hereditary CRC conditions, a personal or family history of CRC and/or polyps, or a personal history of chronic inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease). In addition there are several factors that are considered to be modifiable. These include: obesity, physical inactivity, smoking, heavy alcohol consumption, diet high in red or processed meat and inadequate intake of fruits and vegetables (ACS, 2018b).

Hereditary CRC conditions include the following:

- Familial adenomatous polyposis (FAP) and attenuated FAP (AFAP) which are caused by changes to the APC gene.
- MYH-associated polyposis (MAP), which is caused by biallelic germ line mutations in the MutY human homolog (MYH) gene.
- Hereditary nonpolyposis CRC (HNPCC), or Lynch syndrome which is associated with mutations in DNA mismatch repair genes, MLH1, MSH2, MSH6, MS2, and EPCAM/TACSTD1

Risk Stratification

The population has been stratified into risk categories for the potential development of CRC. These groups include: average risk, increased risk with a personal history, increased risk with a family history and increased/high risk due to hereditary conditions. Guidelines for CRC screening, surveillance and monitoring have been developed based on these categories.

The National Comprehensive Cancer Network® (NCCN®) includes in definition of these groups (NCCN, 2020a):

- average risk: individuals 50 years or older with no history of adenoma, sessile serrated polyps (SSP) or colorectal cancer, and inflammatory bowel disease and a negative family history
- increased risk: individuals with personal history of adenomatous polyps/sessile serrated polyps (SSP), CRC, or inflammatory bowel disease (IBD) as well as those with a positive family history of CRC or advanced adenomatous polyps

- hereditary/high risk: individuals who have had CRC before the age of 50 years; those with family history of multiple cases of CRC or HNPCC related cancers; personal or family history of polyposis; or individuals with HNPCC/Lynch syndrome, Cowden syndrome/PTEN hamartoma tumor syndrome, L-Fraumeni syndrome.

The ACS definitions of these groups include (ACS, 2020b; Wolf, et al., 2018):

Individuals are considered to be at average risk if they do not have:

- A personal history of colorectal cancer or certain types of polyps
- A family history of colorectal cancer
- A personal history of inflammatory bowel disease (ulcerative colitis or Crohn's disease)
- A confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC)
- A personal history of getting radiation to the abdomen or pelvic area to treat a prior cancer

Increased or high risk for developing CRC includes:

- individuals with history of adenomatous polyps
- a personal history of CRC
- a family history of CRC or adenomatous polyps diagnosed in a relative before age 60 years
- a personal history of inflammatory bowel disease
- a confirmed or suspected hereditary CRC syndrome
- a history of abdominal or pelvic radiation for a previous cancer

Screening is defined by the ACS as the search for disease, such as cancer, in people without symptoms. Surveillance is considered to be the screening of individuals known to be at an increased risk. Monitoring is the follow-up after a diagnosis or treatment.

Tests and Procedures for CRC Screening/Surveillance/Monitoring

The objective of cancer screening is to reduce mortality through a reduction in incidence of advanced disease. It is thought that CRC screening can reach this goal through the detection of early-stage adenocarcinomas and with the detection and removal of adenomatous polyps, which are generally accepted as the nonobligate precursor lesions.

There is a range of options for CRC screening for average-risk individuals. The choices fall into two general categories:

- Stool tests: These include tests for occult blood or exfoliated DNA. These tests are appropriate for the detection of cancer, although they may deliver positive findings for some advanced adenomas. Testing options in this group include:
 - annual guaiac-based fecal occult blood test with high test sensitivity for cancer
 - annual fecal immunochemical test with high test sensitivity for cancer
 - stool-based DNA testing every three years
- Structural exams: These exams can reach the dual goals of detecting adenocarcinoma as well as identifying adenomatous polyps. Testing options in this group include:
 - flexible sigmoidoscopy every five years
 - colonoscopy every ten years
 - double-contrast barium enema (DCBE) every five years
 - computed tomographic colonography (CTC) every five years

At times tests are used alone or may be used in combination to improve sensitivity or when the initial test cannot be completed. A choice of screening option may be made based on individual risk, personal preference and access. There has been a change in patterns noted in the proportion of adults utilizing various tests, with sigmoidoscopy rates declining, colonoscopy rates increasing, use of stool blood tests remaining fairly constant and the use of DCBE for screening purposes becoming very uncommon (Levin, et al., 2008).

Fecal Occult Blood Testing (FOBT) and Fecal Immunochemical Testing (FIT): The sensitivity and specificity of diagnostic screening with FOBT has been reported to be extremely variable. This may vary due to the brand or variant of the test, specimen collection technique, number of samples collected per test and whether or not the stool specimen is rehydrated and variations in interpretation, screening interval and other factors. Positive reactions on guaiac-impregnated cards, the most common form of FOBT testing, can signal the presence of bleeding from premalignant adenomas and early-stage CRC. FOBT testing can also report false-positives caused by the ingestion of foods containing peroxidases, gastric irritants such as salicylates and other anti-inflammatory agents (Eskew, 2001). Small adenomas and colorectal malignancies that bleed only intermittently or not at all can be missed. The correct use of stool blood tests requires annual testing that consists of collecting specimens (two or three depending on the product) from consecutive bowel movements. Guidelines from the ACS, the U.S. Preventive Services Task Force (USPSTF) and the NCCN include recommendations that annual screening of patients using the standard take-home multiple sample FOBT. A positive test should be followed up with a colonoscopy. FOBT is the only CRC screening test where there is published evidence of efficacy from prospective, randomized controlled trials (Levin, et al., 2008). The repeated use of FOBT as a screening method in a properly-implemented screening program has proven its effectiveness (Levin, et al., 2008; NCI, 2020; NCCNa, 2020).

Limitations of this test include (Levin, et al., 2008):

- The test is commonly performed in the physician's office as a single-panel test following a digital rectal exam. This method has been noted to have a low accuracy and cannot be recommended as a method of CRC screening.
- The use of FOBT is inadequate for follow-up of a positive test. A survey revealed high rates of repeat office FOBT after a positive FOBT. In addition a substantial number reported referral for sigmoidoscopy after positive FOBT rather than a colonoscopy.

Fecal immunochemical test kits have been developed that can be used as an alternative to the standard guaiac FOBT. Examples of these include, but are not limited to:

- InSure™ (Enterix Inc., Edison, NJ)
- Instant-View™ Fecal Occult Blood Rapid Test (Alpha Scientific Designs, Inc., Poway, CA).

The main advantage of FIT over FOBT is that it detects human globin, a protein that along with heme constitutes human hemoglobin. Unlike the guaiac FOBT tests, these do not require a fecal smear. Samples for testing can be obtained by taking a brush sample of toilet bowl water.

The published peer-reviewed literature indicates that annual screening with FIT can detect a majority of prevalent CRC in an asymptomatic population and that this is an acceptable option for CRC screening in average-risk adults aged 50 or older (Levin, et al., 2008). Similar to FOBT, a positive test should be followed up with a colonoscopy.

Double-Contrast Barium Enema (DCBE): DCBE, also referred to as air-contrast barium enema, examines the colon in its entirety by coating the mucosal surface with high-density barium and distending the colon with air introduced through a flexible catheter that is inserted into the rectum. If there are findings of polyps ≥ 6 mm on DCBE, then a colonoscopy should be performed. There have been no randomized controlled trials evaluating the efficacy of DCBE as a primary screening modality to reduce incidence or mortality from CRC in average-risk adults, and there also are no case-control studies evaluating the performance of DCBE (Levin, et al., 2008). In addition it is noted that the literature describing the test performance of DCBE is limited by study designs that are retrospective and commonly do not report findings from an asymptomatic or average-risk population (Levin, et al., 2008).

In general, DCBE is included as a screening option because it offers an alternative means to examine the entire colon. It is widely available, and it detects about half of large polyps, which are most likely to be clinically important. A five-year interval between DCBE examinations is recommended because DCBE is less sensitive than colonoscopy in detecting colonic neoplasm.

Sigmoidoscopy: Flexible sigmoidoscopy is an endoscopic procedure that examines the lower half of the colon lumen. It is generally performed without sedation and with a more limited bowel preparation than standard

colonoscopy (Levin, et al., 2008). The use of this test for CRC screening is supported by high-quality case-control and cohort studies. In average-risk individuals, flexible sigmoidoscopy is generally recommended every five years beginning at age 50. A five-year interval between screening examinations is recommended. The interval is shorter than for colonoscopy since the flexible sigmoidoscopy is less sensitive than colonoscopy even in the area examined because of the technique and quality of bowel preparation, the varied experience of the examiners performing the procedure, and the effect patient discomfort and spasm may have on depth of sigmoidoscope insertion and adequacy of mucosal inspection. The test may be combined with the FOBT and FIT performed annually. Positive test findings will need to be followed up with a colonoscopy.

Colonoscopy: colonoscopy allows direct mucosal inspection of the entire colon along with same session biopsy sampling or polypectomy in case of pre-cancerous polyps and some early-stage cancers (Levin, et al., 2008). Preparation involves adopting a liquid diet one or more days before the examination, followed by either ingestion of oral lavage solutions or saline laxatives to stimulate bowel movements. Patients generally receive a mild sedative prior to procedure. There are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from CRC in people at average risk. However, several lines of evidence support the effectiveness of screening colonoscopy. Colonoscopy was an integral part of the clinical trials of FOBT screening that showed that screening reduced CRC mortality. Colonoscopy permits detection and removal of polyps and biopsy of cancer throughout the colon. However, colonoscopy involves greater risk and inconvenience to the patient than other screening tests, and not all examinations visualize the entire colon. Significant risks include postpolypectomy bleeding and perforation of the colon. Beginning at age 50, colonoscopy is recommended in average-risk individuals every 10 years (ACS, 2020b; NCCNa, 2020).

Computed Tomographic Colonography (CTC)/Virtual Colonoscopy: Computed tomographic colonography (CTC) uses data from computed tomography (CT) to generate two- and three-dimensional images of the colon and rectum. This procedure is also been referred to as virtual colonoscopy. It is a minimally-invasive procedure that requires no intravenous administration of sedatives or analgesics. The day before the procedure, bowel cleansing is performed, similar to requirements for a colonoscopy. Colonic perforation is extremely low with this test since it is minimally invasive (Levin, et al., 2008).

Use of this procedure has been proposed as an alternative to existing screening tests (e.g., colonoscopy) for CRC, and for surveillance and diagnostic purposes in patients with contraindications for the use of conventional colonoscopy. A traditional colonoscopy is still needed in order to biopsy or remove any lesion/polyp that is found (Torres, 2007; Doubeni, 2020). CTC has been included in the 2008 joint guidelines for screening and surveillance for the early detection of CRC and polyps from the ACS, the US Multi-Society Task Force (USMTF) on Colorectal Cancer and the American College of Radiology (ACR). Beginning at age 50, CTC is recommended for average-risk individuals every 5 years (Levin, et al., 2008).

Currently, there are no prospective, randomized, controlled clinical trials that are initiated or planned that demonstrate the efficacy of CTC in reducing mortality from CRC, rather studies have focused on the detection of advanced neoplasia (Levin, et al., 2008). The consensus guidelines note that, "In terms of detection of colon cancer and advanced neoplasia, which is the primary goal of screening for CRC and adenomatous polyps, recent data suggest CTC is comparable to OC (optical colonoscopy) for the detection of cancer and polyps of significant size when state-of-the-art techniques are applied.

Several meta-analyses have been performed that demonstrate that CTC compared to colonoscopy, CT-colonography has a high sensitivity for adenomas ≥ 10 mm. For adenomas ≥ 6 mm sensitivity is somewhat lower (de Haan, et al., 2011; Pickhardt, et al., 2011; Chaparro, et al., 2009; Rosman and Korsten, 2007).

Stool-Based DNA Testing: Molecular genetic screening analysis of deoxyribonucleic acid (DNA) in stool has been proposed as an alternate, noninvasive screening tool for CRC (Pignone, et al., 2002; Ahlquist, et al., 2002). Detecting CRC by testing stool for DNA is based on identifying the oncogene mutations characteristic of colorectal neoplasia that are detectable in exfoliated epithelial cells in the stool. While neoplastic bleeding is intermittent, epithelial shedding is continual, potentially making stool-based DNA testing (i.e., also known as fecal DNA [f-DNA] and stool DNA [sDNA]) testing more sensitive than other methods. Early studies of molecular stool screening primarily focused on single mutations (i.e., Kirsten rat sarcoma [K-ras] oncogene). Colorectal neoplasms are varied in nature; however, no single mutation has been identified as being expressed universally.

Cologuard® (Exact Sciences Corp., Madison, WI) is a stool DNA test. According to the product website, the test is a multitarget stool DNA test combined with a fecal immunochemical test (FIT) test. The DNA test includes amplification and detection of methylated target DNA (NDRG4, BMP3), KRAS point mutations, and ACTB (a reference gene for quantitative estimation of the total amount of human DNA in each sample) with a hemoglobin immunoassay. The results from the DNA and hemoglobin testing are integrated during analysis with an algorithm to determine a Cologuard positive or negative result. Any positive result from the testing should be followed by a diagnostic colonoscopy. The manufacturer, Exact Science Corp., recommends a three year interval for Cologuard.

U.S. Food and Drug Administration (FDA)—August 2014, the FDA granted premarket application (PMA) approval for the Cologuard test. In the PMA approval the FDA notes that, “Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.”

September 2019, the FDA approved a PMA supplement for the Cologuard test. The supplement notes: “Approval to expand the indicated age range for Cologuard Stool DNA-Based Colorectal Cancer Screening Test from 50 years or older to 45 years or older.”

Literature Review—Stool-Based DNA Testing:

Berger et al. (2016) reported on a clinical effectiveness modeling that compared test intervals of one, three, or five years on CRC incidence and related mortality to help inform screening guidelines. A clinical effectiveness modeling was used to project decreases in CRC incidence and related mortality associated with multitarget stool DNA (mt-sDNA) test screening and interval setting. The Archimedes model (Archimedes Inc., San Francisco, CA) was used to conduct a five-arm, virtual, clinical screening study of a population of 200,000 virtual individuals to compare the clinical effectiveness of mt-sDNA screening at one, three and five-year intervals compared with colonoscopy at 10-year intervals and no screening for a 30- year period. Study endpoints were decrease in CRC incidence and related mortality of each strategy versus no screening. Cost-effectiveness ratios (of mt-sDNA intervals were calculated versus no screening. The modeling indicated that compared with 10-year colonoscopy, annual mt-sDNA testing produced similar reductions in CRC incidence (65% vs. 63%) and related mortality (73% vs. 72%). mt-sDNA testing at three-year intervals reduced the CRC incidence by 57% and CRC mortality by 67%, and mt-sDNA testing at 5-year intervals reduced the CRC incidence by 52% and CRC mortality by 62%. The authors concluded that the data suggest that screening every 3 years using a mt-sDNA test provides reasonable performance at acceptable cost.

Redwood et al. conducted a prospective, cross-sectional study to assess the accuracy of a multitarget stool DNA test (MT-sDNA) compared with fecal immunochemical testing for hemoglobin (FIT) for detection of screening-relevant colorectal neoplasia (SRN). The study included 661 asymptomatic Alaska Native adults aged 40-85 years and older undergoing screening or surveillance colonoscopy. Overall, SRN detection by MT-sDNA (49%) was higher compared to FIT (28%; $P<.001$); in the screening group, SRN detection rates were 50% and 31%, respectively ($P=.01$). Multitarget stool DNA testing detected 62% of adenomas 2 cm or larger vs 29% by FIT ($P=.05$). Sensitivity by MT-sDNA increased with adenoma size (to 80% for lesions ≥ 3 cm; $P=.01$ for trend) and substantially exceeded FIT sensitivity at all adenoma sizes. For sessile serrated polyps larger than 1 cm ($n=9$), detection was 67% by MT-sDNA vs 11% by FIT ($P=.07$). For CRC ($n=10$), detection was 100% by MT-sDNA vs 80% by FIT ($P=.48$). Specificities were 93% and 96%, respectively ($P=.03$). The sensitivity of MT-sDNA for cancer and larger polyps was higher than that of FIT, while specificity was slightly higher with FIT.

Imperiale et al. (2014) reported on a large-scale study in a screening population that compared a noninvasive, multitarget stool DNA test with a fecal immunochemical test (FIT) in persons at average risk for colorectal cancer. The study included 12,776 participants at 90 sites, with 9989 participants fully evaluated. Inclusion criteria included asymptomatic individuals age 50 to 84 years considered to be at average risk for colorectal cancer and scheduled to undergo screening colonoscopy. The participants were required to provide a stool specimen and undergo screening colonoscopy within 90 days. The comparator was a commercially available

fecal immunochemical test (FIT). The primary outcome was the ability of the DNA test to detect colorectal cancer (adenocarcinoma). The secondary outcome was the performance of the DNA test for the detection of advanced precancerous lesions, including advanced adenomas (high-grade dysplasia or with $\geq 25\%$ villous histologic features or measuring ≥ 1 cm in the greatest dimension) and sessile serrated polyps measuring 1 cm or more in diameter. A total of 65 participants were found to have colorectal cancer on colonoscopy and of these, 60 had screening-relevant (stage I to III) cancers. A total of 757 participants had advanced precancerous lesions (prevalence 7.6%). The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT. The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT. The rate of detection of polyps with high-grade dysplasia was 69.2% with DNA testing and 46.2% with FIT. The specificity of DNA testing was 86.6% and with FIT 94.9% among participants with nonadvanced or negative findings. The specificity was 89.8% for DNA testing and 96.4% with FIT among those with negative results on colonoscopy. The stool DNA test was found to have a greater sensitivity when compared with FIT for colorectal cancer and for precancerous lesions.

A comparative effectiveness review for fecal DNA testing in screening for colorectal cancer in average-risk adults was performed for Agency for Healthcare Research and quality (AHRQ) by the Oregon Evidenced-based Practice Center (Lin, et al., 2012). Three studies were included that examined the test accuracy of fecal DNA testing in screening populations. Two fair-quality diagnostic accuracy studies ($n=5004$) evaluating a multi-marker fecal DNA found differing sensitivities to detect CRC (25 percent [95% CI, 5–57%] versus 51.6%, [95% CI, 34.8–68.0]). Sensitivity for advanced adenomas was similarly low in both studies. Another small study and a subset analysis of one of the larger studies were both poor quality and evaluated different tests. There were no studies found that addressed clinical utility, intervals of screening, or specific harms of screening. Three poor-quality, analytic validity studies demonstrated that technological advances appear to improve the analytic sensitivity of assays; however, it is unclear if these advances are applicable to the currently available test. Six fair-to poor-quality studies that examined acceptability found that fecal DNA testing is generally acceptable, although an important test attribute for acceptability appears to be the test's accuracy which is unknown. There were no studies found that evaluated the relative acceptability of fecal DNA tests to FIT tests. The report concluded that, "Fecal DNA tests have insufficient evidence about its diagnostic accuracy to screen for colorectal cancer in asymptomatic, average-risk patients. There is also insufficient evidence for the harms, analytic validity, and acceptability of testing in comparison to other screening modalities. Existing evidence has little or no applicability to currently available fecal DNA testing."

Professional Societies/Organizations—Colorectal Cancer Screening and Surveillance

American Cancer Society (ACS): the ACS published updated guidelines for colorectal cancer screening. The guideline update focuses on CRC screening in average-risk adults and does not address screening or surveillance in persons at increased or high risk for developing CRC. These include individuals with history of adenomatous polyps, a personal history of CRC, a family history of CRC or adenomatous polyps diagnosed in a relative before age 60 years, a personal history of inflammatory bowel disease, a confirmed or suspected hereditary CRC syndrome, or a history of abdominal or pelvic radiation for a previous cancer (ACS, 2020b; Wolf, et al., 2018).

Recommendations include:

- Adults aged 45 years and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on non-colonoscopy screening tests should be followed up with timely colonoscopy.
 - The recommendation to begin screening at age 45 years is a qualified recommendation.
 - The recommendation for regular screening in adults aged 50 years and older is a strong recommendation.
- Average-risk adults in good health with a life expectancy of greater than 10 years continue CRC screening through the age of 75 years (qualified recommendation).
- Clinicians individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history (qualified recommendation).

- Clinicians discourage individuals over age 85 years from continuing CRC screening (qualified recommendation).

The options for testing include:

Stool-based tests:

- Highly sensitive fecal immunochemical test (FIT) every year
- Highly sensitive guaiac-based fecal occult blood test (gFOBT) every year
- Multi-targeted stool DNA test (MT-sDNA) every 3 years

Visual (structural) exams of the colon and rectum:

- Colonoscopy every 10 years
- CT colonography every 5 years
- Flexible sigmoidoscopy (FSIG) every 5 years

The guidelines note that for screening, people are considered to be at average risk if they do not have (ACS, 2020b; Wolf, et al., 2018):

- A personal history of colorectal cancer or certain types of polyps
- A family history of colorectal cancer
- A personal history of inflammatory bowel disease (ulcerative colitis or Crohn's disease)
- A confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC)
- A personal history of getting radiation to the abdomen or pelvic area to treat a prior cancer

A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening.

Qualified recommendations indicate there is clear evidence of benefit (or harm) of screening but less certainty about the balance of benefits and harms or about patients' values and preferences, which could lead to different decisions about screening.

American College of Physicians (ACP): published guidelines for screening for colorectal cancer. The guidelines include the following recommendations (Qaseem, et al., 2012):

- clinicians perform individualized assessment of risk for colorectal cancer in all adults
- clinicians screen for colorectal cancer in average-risk adults starting at the age of 50 years and in high-risk adults starting at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer
- Use a stool-based test, flexible sigmoidoscopy, or optical colonoscopy as a screening test in patients who are at average risk. Recommend using optical colonoscopy as a screening test in patients who are at high risk. Clinicians should select the test based on the benefits and harms of the screening test, availability of the screening test, and patient preferences.
- clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years

American College of Obstetricians and Gynecologists (ACOG): ACOG published a committee opinion for colorectal cancer (CRC) screening strategies (ACOG, 2014). The following conclusions and recommendations are included in the guidelines:

- CRC screening for average-risk women should begin at age 50 years.
- CRC screening for African American women should begin at age 45 years.
- Supports stopping routine screening at age 75 years.
- Recommends colonoscopy every 10 years as the most effective screening modality.
- CRC screening methods should be discussed with patients to identify the method they are most likely to accept and complete.
- Tests that detect early colorectal cancer and adenomatous polyps, the most effective of which is colonoscopy, should be encouraged.

- Abnormalities found with any other screening method necessitate referral for diagnostic colonoscopy.
- Digital rectal examination for in-office single-stool guaiac fecal occult blood testing (gFOBT) for colorectal cancer screening is ineffective and not recommended.
- Every screening method has advantages and limitations, which ultimately depend on the quality of the screening test, patient adherence, screening guidelines, and access to timely and appropriate follow-up.

American Society of Colon and Rectal Surgeons (ASCRS): ASCRS published clinical practice guidelines for the surveillance of patients after curative treatment of colon and rectal cancer (Steele, et al., 2015). The guidelines include this recommendation for surveillance colonoscopy:

- Surveillance colonoscopy is recommended at one year after curative resection for patients with surgically treated stage I to IV colorectal cancer. Subsequent colonoscopy should be performed every three to five years depending on the findings at the first postoperative examination. In cases of incomplete colon evaluation before surgery, the initial colonoscopy should be performed within three to six months or upon the completion of adjuvant therapy. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

American Society of Clinical Oncology (ASCO): ASCO published resource-stratified guidelines for detection for colorectal cancer (Lopes, et al., 2019). The target population of guidelines is for people who are asymptomatic, are ages 50 to 75 years, with no family history of colorectal cancer, are at average risk, and are in settings with high incidence of colorectal cancer or for adult patients with symptoms suspicious for colorectal cancer. A multinational, multidisciplinary expert panel was convened to develop clinical practice guideline recommendations based on a systematic review of existing guidelines and a formal consensus process.

Key Recommendation Summaries

Screening: asymptomatic, average-risk population, high-incidence areas, age 50 to 75 years

- Basic setting options include the following: should receive highly sensitive guaiac fecal occult blood test (gFOBT) every one (preferred) to two years if resources are available (Evidence quality: high; Strength of recommendation: strong) or may receive fecal immunochemical testing (FIT), if available, every one (preferred) to two years (Evidence quality: intermediate; Strength of recommendation: moderate)
- Limited setting options include the following: should receive highly sensitive gFOBT annually (Evidence quality: high; Strength of recommendation: strong) or may receive FIT annually (Evidence quality: intermediate; Strength of recommendation: moderate) or should receive flexible sigmoidoscopy every five years (Evidence quality: high; Strength of recommendation: strong) or may receive flexible sigmoidoscopy every ten years plus FIT (or, if FIT not available, then FOBT) every year (Evidence quality: intermediate; Strength of recommendation: strong)
- Enhanced setting options include the following: should receive highly sensitive gFOBT annually (Evidence quality: high; Strength of recommendation: strong) or may receive FIT annually (Evidence quality: intermediate; Strength of recommendation: moderate) or should receive flexible sigmoidoscopy every 5 years (Evidence quality: high; Strength of recommendation: strong) or may receive flexible sigmoidoscopy every ten years plus FIT every year (Evidence quality: intermediate; Strength of recommendation: strong) or may receive colonoscopy every ten years (Evidence quality: low; Strength of recommendation: weak)
- Maximal setting options include the following: should receive highly sensitive gFOBT annually (Evidence quality: high; Strength of recommendation: strong) or may receive FIT annually (Evidence quality: intermediate; Strength of recommendation: moderate) or should receive flexible sigmoidoscopy every 5 years (Evidence quality: high; Strength of recommendation: strong) or may receive Flexible sigmoidoscopy every 10 years plus FIT every year (Evidence quality: intermediate; Strength of recommendation: strong) or may receive colonoscopy every 10 years (Evidence quality: low; Strength of recommendation: weak) or may receive computed tomography (CT) colonography (Evidence quality: low; Strength of recommendation: weak) or may receive FIT DNA (Evidence quality: low; Strength of recommendation: weak)

Reflex testing:

If patients have a positive result from colorectal cancer screening:

- Basic/limited: then clinicians should refer patients to colonoscopy (first choice) or sigmoidoscopy (second choice and the only option for basic) if available; however, since endoscopy is not available in most basic settings, clinicians should perform or refer patients to reflex testing with double contrast barium enema (If a patient's barium enema results are positive, refer to colonoscopy, if available; otherwise, refer the patient to surgery; Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).
- Enhanced/maximal: If patients have a positive result from a noncolonoscopy colorectal cancer screening, then clinicians should perform or refer patients to a colonoscopy. (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

For people with positive premalignant polyps or other abnormal screening results—pedunculated, enhanced/maximal, overarching—refer patients to endoscopy if available and feasible; otherwise, refer to surgery.

- Colonoscopy should be performed always with therapeutic intent (Evidence quality: insufficient; Strength of recommendation: strong), and it should be performed by endoscopist with training in polypectomy (Evidence quality: low; Strength of recommendation: strong).
- Lesions should be removed with polypectomy (Evidence quality: intermediate; Strength of recommendation: strong).
- Patients with large premalignant lesions not suitable for endoscopic resection should be referred for surgical resection (Evidence quality: insufficient; Strength of recommendation: strong).
- If lesion cannot be removed or if large lesion has a high likelihood of malignancy (Type: informal consensus), mucosal tattooing may be performed (Evidence quality: insufficient; Strength of recommendation: weak).
- Removed lesions should be retrieved for histologic exam; confirm negative borders of resection (Evidence quality: insufficient; Strength of recommendation: strong).
- Referral to surgery: Only patients with lesions that cannot be removed endoscopically should be referred to surgery (Evidence quality: insufficient; Strength of recommendation: strong).

For nonpedunculated, enhanced/maximal (term used to define sessile and flat colonic lesions):

- Colonoscopy should be performed by endoscopists with training in large complex polyps (Evidence quality: low; Strength of recommendation: weak) always with therapeutic intent; endoscopic resection is first-line therapy for large nonpedunculated colorectal polyps with no suspicion of malignancy (Intent, Evidence quality: insufficient; Strength of recommendation: strong; Resection, Evidence quality: intermediate; Strength of recommendation: strong).
- Lesions should be removed with polypectomy; removal of lesions is dependent on the low likelihood of malignancy (Evidence quality: intermediate, Strength of recommendation: strong).
- Endoscopic assessment of lesion using enhanced endoscopy methods (if available, may include chromoendoscopy); clinicians should follow the British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland (BSGACGB) guideline (Evidence quality: insufficient; Strength of recommendation: strong).
- If lesion cannot be removed (in BSGACGB guideline) or if large lesion has a high likelihood of malignancy, mucosal tattooing should be performed. For patients with polyps that are completely removed, clinicians may perform tattooing for surveillance purposes (Evidence quality: insufficient; Strength of recommendation: strong).
- Removed lesions should be retrieved for histologic exam; confirm negative borders of resection (Evidence quality: insufficient; Strength of recommendation: strong).
- Referral to surgery: Only patients with lesions that cannot be removed endoscopically should be referred to surgery (Evidence quality: insufficient; Strength of recommendation: strong).

Optimal strategy for workup/diagnosis for those with symptoms:

- Basic/limited: physical exam with digital rectal examination (DRE; Type: informal consensus; Evidence quality: insufficient), Double contrast barium enema (Type: informal consensus; Evidence quality: insufficient); colonoscopy with biopsy if no contraindications and available. If contraindications to

colonoscopy, then flexible sigmoidoscopy with biopsy barium enema (Evidence quality: low; Strength of recommendation: weak)

- Limited: see basic/limited recommendations. Also, if incomplete colonoscopy, barium enema (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong)
- Enhanced: colonoscopy with biopsy if no contraindications; if contraindications to colonoscopy, flexible sigmoidoscopy with biopsy, if no contraindication, with full visualization of the colon (barium enema or CT colonography; Evidence quality: low; Strength of recommendation: weak); CT colonography if contraindications to both of the endoscopy options or double contrast enhanced barium enema (Evidence quality: high, Strength of recommendation: moderate)
- If incomplete colonoscopy, a double contrast enhanced barium enema or CT colonography (for colonography, if the local radiology service can demonstrate competency in this technique) (Evidence quality: intermediate; Strength of recommendation: strong)
- Maximal: physical exam with DRE (Type: informal consensus; Evidence quality: insufficient); colonoscopy with biopsy if no contraindications and available; flexible sigmoidoscopy with biopsy, if no contraindication, with full visualization of the colon (barium enema or CT colonography; Evidence quality: low; Strength of recommendation: weak); CT colonography if contraindications to both of the endoscopy options or double contrast enhanced barium enema (Evidence quality: high; Strength of recommendation: moderate)
- Repeat colonoscopy: If not feasible, the next tier would be one of the two following options: CT colonography (if the local radiology service can demonstrate competency in this technique) or barium enema (Evidence quality: intermediate, Strength of recommendation: strong).

National Comprehensive Cancer Network® (NCCN®): The NCCN Colorectal Cancer Screening Clinical Practice Guidelines™ include recommendations for screening and surveillance (NCCN, 2020a; NCCN, 2020c).

Average-risk individual, age 50 or greater, with no personal history of adenoma, sessile serrated polyps (SSP), colorectal cancer, or inflammatory bowel disease and a negative family history should have screening with one of these modalities:

- Colonoscopy every 10 years
- Flexible sigmoidoscopy every five-ten years
- Computed tomographic colonography (CTC) every five years
- High sensitivity guaiac-based testing annually
- Fecal immunochemical test (FIT) annually
- Stool DNA test (which includes high-sensitivity fecal immunochemical test [FIT]) every three years

Recommendation Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

The guidelines include recommendations for increased-risk individuals with personal history of adenoma(s), sessile serrated polyp(s) (SSP), traditional serrated adenoma (TSA), or large (≥ 1 cm) hyperplastic polyps found at colonoscopy:

- Low risk adenoma (tubular adenoma) (≤ 2 polyps, ≤ 1 cm)—repeat colonoscopy between five-ten years. If negative, then repeat in ten years. If positive for adenoma or SSP, repeat colonoscopy according to clinical findings.
- Low risk SSP (SSP without dysplasia) (≤ 2 polyps, < 1 cm)—repeat colonoscopy in 5 years, if negative, repeat colonoscopy in 10 years. If positive for adenoma or SSP, repeat colonoscopy according to clinical findings.
- High risk (advanced or multiple polyps) (TSAs, high-grade dysplasia or SSP, adenoma or any SSP ≥ 1 cm, villous or tubulovillous histology, between three and ten adenomatous polyps and/or SSPs, or large [≥ 1 cm] hyperplastic polyps)—repeat colonoscopy in three years. If negative for adenoma or SSP \pm low-risk polyps, then repeat in five years. If positive for adenoma or SSP, repeat colonoscopy according to clinical findings.
- More than 10 cumulative adenomatous polyps: individual management and consider a polyposis syndrome.

- Incomplete or piecemeal polypectomy or polypectomy of large non-pedunculated polyps—refer to NCCN guidelines for colorectal cancer screening.
- Malignant polyp: refer to NCCN guidelines for colon and rectal cancer.

The guidelines for increased risk based on personal history of inflammatory bowel disease (IBD) include the recommendations for surveillance:

Personal history of ulcerative colitis, Crohn's colitis: eight years after onset of symptoms:

- Colonoscopy
 - Chromoendoscopy with targeted biopsy, including extensive sampling of strictures or masses (high-definition colonoscopy is suggested, if available)*
 - Consider two biopsies in every bowel segment (placed in separate specimen jars) to document microscopic disease activity and extent of disease involvement
 - Additional extensive sampling of strictures and masses
- OR
- High-definition white light endoscopy (HD-WLE) **
 - Random 4-quadrant biopsies every 10 cm with ≥32 total samples
 - Additional extensive sampling of strictures and masses

* Endoscopy should be performed during quiescent disease. Targeted biopsies improve detection of dysplasia, and should be considered for surveillance colonoscopies in patients with ulcerative colitis where expertise is available.

** If using standard-definition (SD)-WLE, performing colonoscopy in conjunction with chromoendoscopy is recommended. If HD-WLE or chromoendoscopy is not available, refer to institutions with expertise in these modalities.

Recommendation Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

U.S. Multi-Society Task Force of Colorectal Cancer (MSTF) (represents the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy). These organizations published updated joint guidelines for the screening and surveillance for the early detection of CRC and adenomatous polyps (Rex, et al., 2017). The guidelines focus on the needs of screening for average-risk adults.

The approach to screening includes the following recommendations:

- Clinicians offer CRC screening beginning at age 50 (strong recommendation, high-quality evidence). (See below for adjustments in recommended age for onset of screening based on race and family history.)
- Sequential offers of screening tests, offering multiple screening options, and risk-stratified screening are all reasonable approaches to offering screening (weak recommendation, low-quality evidence).

The screening tests recommended include:

- Colonoscopy every 10 years or annual FIT as first-tier options for screening the average-risk persons for colorectal neoplasia (strong recommendation; moderate-quality evidence).
- Those physicians performing screening colonoscopy measure quality, including the adenoma detection rate (strong recommendation, high-quality evidence).
- That physicians performing FIT monitor quality (strong recommendation, low-quality evidence).
- CT colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low-quality evidence) or flexible sigmoidoscopy every 5 to 10 years (strong recommendation, high-quality evidence) in patients who refuse colonoscopy and FIT.
- Capsule colonoscopy (if available) is an appropriate screening test when patients decline colonoscopy, FIT, FIT-fecal DNA, CT colonography, and flexible sigmoidoscopy (weak recommendation, low-quality evidence).

- Suggest against Septin9 for CRC screening (weak recommendation, low-quality evidence).

For average risk individuals, the recommendations include tiered testing:

- Colonoscopy every 10 years or annual FIT as first-tier options for screening the average-risk persons for colorectal neoplasia (strong recommendation; moderate quality evidence).
- Physicians performing screening colonoscopy measure quality, including the adenoma detection rate (strong recommendation, high-quality evidence).
- Physicians performing FIT monitor quality (strong recommendation, low-quality evidence).
- Recommended quality measurements for FIT programs are detailed in a prior publication.

Regarding age of screening, recommendations include the following:

- Screening begins in non-African American average-risk persons at age 50 years (strong recommendation; moderate-quality evidence).
- Screening begins in African Americans at age 45 years (weak recommendation, very-low-quality evidence).
- Adults age <50 years with colorectal bleeding symptoms (hematochezia, unexplained iron deficiency anemia, melena with a negative upper endoscopy) undergo colonoscopy or an evaluation sufficient to determine a bleeding cause, initiate treatment, and complete follow-up to determine resolution of bleeding (strong recommendation, moderate-quality evidence).
- Those persons who are up to date with screening and have negative prior screening tests, particularly colonoscopy, consider stopping screening at age 75 years or when life expectancy is less than 10 years (weak recommendation, low-quality evidence).
- Those persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities (weak recommendation, low-quality evidence).

Regarding screening for individuals with family history of CRC and/or adenoma include:

- Persons with one first-degree relative with CRC or a documented advanced adenoma diagnosed at age <60 years or with two first-degree relatives with CRC and/or documented advanced adenomas undergo colonoscopy every five years beginning 10 years younger than the age at which the youngest first-degree relative was diagnosed or age 40, whichever is earlier (weak recommendation, low-quality evidence).
- Persons with one first-degree relative diagnosed with CRC or a documented advanced adenoma at age ≥60 years begin screening at age 40. The options for screening and the recommended intervals are the same as those for average-risk persons (weak recommendation, very-low quality evidence).
- Persons with one or more first-degree relatives with a documented advanced serrated lesion (SSP or traditional serrated adenoma ≥10 mm in size or an SSP with cytologic dysplasia) should be screened according to above recommendations for persons with a family history of a documented advanced adenoma (weak recommendation, very-low-quality evidence).
- Persons with one or more first-degree relatives with CRC or documented advanced adenomas, for whom we recommend colonoscopy, should be offered annual FIT if they decline colonoscopy (strong recommendation, moderate-quality evidence).

Rating of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

US Multi-Society Task Force on Colorectal Cancer (USMSTF): This organization published joint consensus guidelines for fecal immunochemical testing (FIT) to screen for colorectal neoplasia. The guidelines include the recommendations (Robertson, et al., 2017):

- With one-time application, FIT tests are approximately 80% sensitive for cancer detection and approximately 20%–30% sensitive for advanced neoplasia detection. To enhance advanced adenoma

detection, repeated applications of FIT are required. Therefore, it is recommended repeated testing to maximize the effectiveness of cancer detection and prevention with this modality. Individuals choosing FIT should understand the need for recurring testing and for colonoscopy to evaluate a positive FIT result. Programs to track cycles of testing are encouraged to facilitate completion.
Strong recommendation; moderate-quality evidence.

- Given the high positive predictive value of FIT for cancer detection, colonoscopy is recommended when the test is positive, not repeat FIT.
Strong recommendation; moderate-quality evidence.

Rating of evidence:

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

US Multi-Society Task Force on Colorectal Cancer (USMSTF): This organization published joint consensus guidelines for colonoscopy surveillance after cancer resection (Kahi, et al., 2016). These guidelines include the following recommendations:

- Patients with CRC undergo high-quality perioperative clearing with colonoscopy. The procedure should be performed preoperatively, or within a three to six-month interval after surgery in the case of obstructive CRC. The goals of perioperative clearing colonoscopy are detection of synchronous cancer and detection and complete resection of precancerous polyps.
Strong recommendation, low-quality evidence
- Patients who have undergone curative resection of either colon or rectal cancer receive their first surveillance colonoscopy one year after surgery (or one year after the clearing perioperative colonoscopy).
Strong recommendation, low-quality evidence
- After the one-year colonoscopy, the interval to the next colonoscopy should be three years (i.e., four years after surgery or perioperative colonoscopy) and then five years (i.e., nine years after surgery or perioperative colonoscopy). Subsequent colonoscopies should occur at five-year intervals until the benefit of continued surveillance is outweighed by diminishing life expectancy. If neoplastic polyps are detected, the intervals between colonoscopies should be in accordance with published guidelines for polyp surveillance intervals. These intervals do not apply to patients with Lynch syndrome.
Strong recommendation, low-quality evidence
- Patients with localized rectal cancer who have undergone surgery without total mesorectal excision, those who have undergone transanal local excision (i.e., transanal excision or transanal endoscopic microsurgery), or endoscopic submucosal dissection, and those with locally advanced rectal cancer who did not receive neoadjuvant chemoradiation and then surgery using total mesorectal excision techniques, are at increased risk for local recurrence. In these situations, suggest local surveillance with flexible sigmoidoscopy or EUS every three-six months for the first two-three years after surgery. These surveillance measures are in addition to recommended colonoscopic surveillance for metachronous neoplasia.
Weak recommendation, low-quality evidence

Alternatives and adjuncts to colonoscopy:

- In patients with obstructive CRC precluding complete colonoscopy, we recommend CTC as the best alternative to exclude synchronous neoplasms. Double-contrast barium enema is an acceptable alternative if CTC is not available.
Strong recommendation, moderate-quality evidence
- There is insufficient evidence to recommend routine use of FIT or fecal DNA for surveillance after CRC resection.

Rating of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

US Multi-Society Task Force on Colorectal Cancer (USMSTF): The USMSTF updated their prior consensus guidelines for follow-up after colonoscopy and polypectomy (Gupta, et al., 2020). The recommendations in the guidelines include:

- Risk for Incident and Fatal Colorectal Cancer After Normal Colonoscopy and After Polyp Removal
 - Normal colonoscopy is associated with sustained reduced risk for incident and fatal CRC. (High quality of evidence)
 - Incremental effectiveness of repeat colonoscopy after baseline normal colonoscopy for further reducing CRC incidence and mortality is uncertain. (Insufficient evidence)
 - Risk for incident and fatal CRC after baseline adenoma removal is uncertain. (Low quality of evidence)
 - Surveillance colonoscopy after baseline removal of adenoma with high-risk features (e.g., size ≥ 10 mm) may reduce risk for incident CRC, but impact on fatal CRC is uncertain. (Low quality of evidence)
 - Incremental impact of surveillance colonoscopy after baseline removal of adenoma with low-risk features (such as 1–2 adenomas < 10 mm) on risk for incident and fatal CRC is uncertain. (Low quality of evidence)
 - Risk for incident and fatal CRC among individuals with baseline SSP is uncertain. (Very low quality of evidence)
- Recommended Post-Colonoscopy Surveillance Strategies for Reducing Colorectal Cancer Risk
 - For patients with normal, high-quality colonoscopy, repeat CRC screening in 10 years. (Strong recommendation, high quality of evidence)
 - For patients with 1–2 tubular adenomas < 10 mm in size completely removed at a high-quality examination, repeat colonoscopy in 7–10 years. (Strong recommendation, moderate quality of evidence)
 - For patients with 3–4 tubular adenomas < 10 mm in size completely removed at a high-quality examination, repeat colonoscopy in 3–5 years. (Weak recommendation, very low quality of evidence)
 - For patients with 5–10 tubular adenomas < 10 mm in size completely removed at a high-quality examination, repeat colonoscopy in 3 years. (Strong recommendation, moderate quality of evidence)
 - For patients with 1 or more adenomas ≥ 10 mm in size completely removed at high-quality examination, repeat colonoscopy in 3 years. (Strong recommendation, high quality of evidence)
 - For patients with adenoma containing villous histology completely removed at high-quality examination, repeat colonoscopy in 3 years. (Strong recommendation, moderate quality of evidence)
 - For patients with adenoma containing high-grade dysplasia completely removed at high-quality examination, repeat colonoscopy in 3 years. (Strong recommendation, moderate quality of evidence)
 - For patients with > 10 adenomas completely removed at high-quality examination, repeat colonoscopy in 1 year. (Weak recommendation, very low quality of evidence)
 - For patients with ≤ 20 HPs < 10 mm in size in the rectum or sigmoid colon removed at a high-quality examination, repeat CRC screening in 10 years. (Strong recommendation, moderate quality of evidence)
 - For patients with ≤ 20 HPs < 10 mm in size proximal to the sigmoid colon removed at a high-quality examination, repeat colonoscopy in 10 years. (Weak recommendation, very low quality of evidence)
 - For patients with 1–2 SSPs < 10 mm in size completely removed at high-quality examination, repeat colonoscopy in 5–10 years. (Weak recommendation, very low quality evidence)
 - For patients with TSA completely removed at a high-quality examination, repeat colonoscopy in 3 years. (Weak recommendation, very low quality of evidence)
 - For patients with 3–4 SSPs < 10 mm at high-quality examination, repeat colonoscopy in 3–5 years. (Weak recommendation, very low quality of evidence)
 - For patients with any combination of 5–10 SSPs < 10 mm at high-quality examination, repeat colonoscopy in 3 years. (Weak recommendation, very low quality of evidence)

- For patients with SSP ≥ 10 mm at a high-quality examination, repeat colonoscopy in 3 years. (Weak recommendation, very low quality of evidence)
- For patients with HP ≥ 10 mm, repeat colonoscopy in 3–5 years. A 3-year follow-up interval is favored if concern about pathologist consistency in distinguishing SSPs from HPs, quality of bowel preparation, or complete polyp excision, whereas a 5-year interval is favored if low concerns for consistency in distinguishing between SSP and HP by the pathologist, adequate bowel preparation, and confident complete polyp excision. (Weak recommendations, very low quality of evidence)
- For patients with SSP containing dysplasia at a high-quality examination, repeat colonoscopy in 3 years. (Weak recommendation, very low quality of evidence)
- For patients with history of baseline adenoma removal and 1 subsequent colonoscopy, recommendations for subsequent surveillance should take into account findings at baseline and first surveillance (Table 7). (Weak recommendation, low quality of evidence)
- There is insufficient evidence to recommend use of currently published prediction models for polyp surveillance recommendations. (Weak recommendation, very low quality of evidence)
- Evidence is insufficient to recommend differential management for patients with proximal adenoma. (Weak recommendation, very low quality of evidence)
- For patients with piecemeal resection of adenoma or SSP > 20 mm, repeat colonoscopy in 6 months. (Strong recommendation, moderate quality of evidence)

Rating of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: Any estimate of effect is very uncertain

U.S. Preventive Services Task Force (USPSTF): The USPSTF published updated evidenced-based recommendations for screening for colorectal cancer (USPSTF, 2016; Lin, et al., 2016). The recommendations include the following:

- Adults aged 50 to 75 years: The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary. Refer to the Clinical Considerations section and the Table** for details about screening strategies. Grade A*
- Adults aged 76 to 85 years: The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history.
 - Adults in this age group who have never been screened for colorectal cancer are more likely to benefit.
 - Screening would be most appropriate among adults who are healthy enough to undergo treatment if colorectal cancer is detected and do not have comorbid conditions that would significantly limit their life expectancy.
 Grade C*

*Grade definitions:

Grade A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial.

Grade C: The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.

****Table Characteristics of Colorectal Cancer Screening Strategies^a (USPSTF, 2016)**

Screening Method	Frequency ^b	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (e.g., Hemoccult SENSА) have superior test performance characteristics than older tests (e.g., Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT ^c	Every year	Test characteristic studies: Improved accuracy compared with gFOBT Can be done with a single specimen	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 years ^d	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test Improved sensitivity compared with FIT per single screening test	There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test
Direct Visualization Tests			
Colonoscopy ^c	Every 10 years	Prospective cohort study with mortality end point	Requires less frequent screening. Screening and diagnostic followup of positive results can be performed during the same examination.
CT colonography ^e	Every 5 years	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 years	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT ^c	Flexible sigmoidoscopy every 10 years plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy

Abbreviations: FIT=fecal immunochemical test; FIT-DNA=multitargeted stool DNA test; gFOBT=guaiac-based fecal occult blood test; RCT=randomized clinical trial.

^a Although a serology test to detect methylated *SEPT9* DNA was included in the systematic evidence review, this screening method currently has limited evidence evaluating its use (a single published test characteristic study met inclusion criteria, which found it had a sensitivity to detect colorectal cancer of <50%). It is therefore not included in this table.

^b Applies to persons with negative findings (including hyperplastic polyps) and is not intended for persons in surveillance programs. Evidence of efficacy is not informative of screening frequency, with the exception of gFOBT and flexible sigmoidoscopy alone.

^c Strategy yields comparable life-years gained (i.e., the life-years gained with the noncolonoscopy strategies were within 90% of those gained with the colonoscopy strategy) and an efficient balance of benefits and harms in CISNET modeling.

^d Suggested by manufacturer.

^e Strategy yields comparable life-years gained (i.e., the life-years gained with the noncolonoscopy strategies were within 90% of those gained with the colonoscopy strategy) and an efficient balance of benefits and harms in CISNET modeling when

lifetime number of colonoscopies is used as the proxy measure for the burden of screening, but not if lifetime number of cathartic bowel preparations is used as the proxy measure.

In Vivo Analysis of Colorectal Polyps

Several technologies of in vivo analysis of polyps are being researched for the purpose of improving the analysis of lesions and detection of changes in walls of colon. These methods are intended to be used as an adjunct to endoscopic procedures. These methods include chromoendoscopy, fiberoptic analysis, narrow band imaging (NBI) and confocal endomicroscopy. A conventional colonoscopy utilizes white light which has a limited ability to distinguish between benign or neoplastic lesion during the procedure. During a colonoscopy, the standard procedure is to remove all visualized lesions and submit these to histopathology. It is proposed that these technologies may allow for in vivo analysis of the polyps, possibly avoiding unnecessary biopsies and increasing detection of difficult to visualize lesions (e.g., flat lesions). Some of the devices are also utilized during other endoscopic procedures including gastroscopy.

Chromoendoscopy, or chromoscopy, involves the topical application of dye (e.g., indigo carmine or methylene blue) to enhance mucosal irregularities and facilitate targeted biopsies. It may be applied with a spray-catheter to stain the full colon (panchromoendoscopy) or a segment can be sprayed directly through the working channel to assess a specific area of interest (Hazewinkel, et al., 2011).

Fiberoptic analysis has been proposed to assist the physician in determining if potential cancerous changes are present within the colon. Positive findings would be suggestive of the need for potential biopsy of the area. The WavSTAT™ Optical Biopsy System (SpectraScience™, Minneapolis, MN) contains a laser, electronic components that collect the emitted fluorescent signals, and a computer that operates the system and analyzes the tissue. The device is intended for the evaluation of polyps that are less than one centimeter that the physician has not already elected to remove. Use of this device is only to assist in deciding whether such polyps should be removed and submitted for histological examination. It is intended to be used as an adjunct during a sigmoidoscopy or colonoscopy.

Narrow band imaging (NBI) utilizes short wavelength (essentially blue) endoscopic light which penetrates the mucosa only superficially and is mainly absorbed by hemoglobin—this will highlight mucosal surface patterns and microvascular details. It is theorized that this will improve the detection of small and subtle mucosal lesions. It is also thought that there is potential for endoscopic differentiation of lesions with use of NBI, which would enable on-table decisions to be made (van den Brock, et al., 2009). Olympus EVIS EXERA II™ (Olympus, Tokyo, Japan; Center Valley, PA) is NBI device that is used with colonoscope as well as other endoscopy devices.

Confocal fluorescent endomicroscopy, or confocal laser endomicroscopy is based on tissue illumination with a low-power laser with subsequent detection of the fluorescence light reflected from the tissue through a pinhole (ASGE, 2014). Confocal refers to the alignment of both illumination and collections systems in the same focal plane. Confocal endomicroscopy based on tissue fluorescence uses a local and/or intravenous contrast agent and generates a high-quality image that may be comparable with traditional histological examination. Cellvizio® (Mauna Kea Technologies, Newtown, PA) is a probe-based Confocal Laser Endomicroscopy (pCLE) device that is compatible with flexible video-endoscopes. According to the vendor website the device can magnify a polyp by a factor of 1,000 which may assist a physician in detecting cellular-level features that differentiate adenomatous from non-adenomatous colorectal polyps during the colonoscopy procedure in real time.

U.S. Food and Drug Administration (FDA)—In Vivo Analysis of Colorectal Polyps

The Optical Biopsy System received premarket approval (PMA) as a Class III device from the FDA in November 2000. In 2001 the name was changed to WavStat Optical Biopsy System.

The Olympus EVIS EXERA II device received FDA approval as a class II device through the 510 (k) process in 2006.

Confocal Laser Endomicroscopy received FDA approval as a class II device through the 510 (k) approval process in 2006.

Literature review—In Vivo Analysis of Colorectal Polyps

Chromoendoscopy

Resende et al. (2020) conducted a systematic review and meta-analysis with the aim to review all randomized clinical trials (RCTs) available and compare the efficacy of different endoscopic methods of surveillance for dysplasia in patients with ulcerative colitis (UC) and Crohn's disease (CD). It was estimated the risk difference (RD) for dichotomous outcomes (number of patients diagnosed with one or more dysplastic lesions, total number of dysplastic lesions diagnosed and number of dysplastic lesions detected by targeted biopsies) and mean difference for continuous outcomes (procedure time). The study included 17 RCTs (2,457 patients). There was superiority of dye-spraying chromoendoscopy (DCE) when compared to standard-definition white light endoscopy (SD-WLE). When compared with high-definition (HD) WLE, no difference was observed in all outcomes (number of patients with dysplasia (RD 0.06; 95 % CI [-0.01, 0.13])). Comparing other techniques, no difference was observed between DCE and virtual chromoendoscopy (VCE - including narrow-band imaging [NBI], i-SCAN and flexible spectral imaging color enhancement). In all outcomes except procedure time (mean difference, 6.33 min; 95 % CI, 1.29, 11.33). DCE required a significantly longer procedure time compared with WLE (mean difference, 7.81 min; 95 % CI, 2.76, 12.86). The authors concluded that dye-spraying chromoendoscopy detected more patients and dysplastic lesions than SD-WLE. The study noted that although no difference was observed between DCE and HD-WLE or narrow-band imaging, the main outcomes favored numerically dye-spraying chromoendoscopy, except for procedure time.

Alexandersson et al. (2020) performed a prospective, randomized study of 305 patients with ulcerative colitis or Crohn's colitis referred for surveillance colonoscopy. Patients were randomly assigned to a group that received high-definition chromoendoscopy with indigo carmine (HD-CE; n=152), collection of 32 random biopsies, and targeted biopsies or polypectomies or to a group that received high-definition white light endoscopy (HD-WLE; n = 153), collection of 32 random biopsies, and targeted biopsies or polypectomies. The primary endpoint was number of patients with dysplastic lesions. Dysplastic lesions were detected in 17 patients with HD-CE and seven patients with HD-WLE (P=.032). Dysplasias in random biopsies (n= 9760) were detected in nine patients: six (3.9%) in the HD-CE group and three (2.0%) in the HD-WLE group (P=.72). Of the nine patients with dysplasia, three patients (33%) had primary sclerosing cholangitis—only 18% of patients (54/305) included in the study had primary sclerosing cholangitis. The number of dysplastic lesions per ten minutes of withdrawal time was 0.066 with HD-CE and 0.027 with HD-WLE (P=.056). The authors concluded that they found HD-CE with collection of random biopsies to be superior to HD-WLE with random biopsies for detection of dysplasia per colonoscopy and that the results support the use of chromoendoscopy for surveillance of patients with inflammatory bowel diseases.

Iannone et al. (2017) performed a systematic review of randomized trials comparing chromoendoscopy vs other endoscopic techniques for dysplasia surveillance in inflammatory bowel diseases. The review included ten randomized trials (n=1500 participants). The review found that there was a higher likelihood of detecting patients with dysplasia with chromoendoscopy compared with other techniques (RR, 1.37; 95% CI, 1.04-1.79). Subgroup analyses confirmed this effect only if chromoendoscopy was compared with standard-definition white-light endoscopy (RR, 2.12; 95% CI, 1.15-3.91). Chromoendoscopy required a significantly longer procedural time compared with other techniques (mean difference, 8.91 min; 95% CI, 1.37-16.45). There was no difference in the likelihood of detecting dysplastic subtypes and dysplasia by targeted biopsies between groups. Test sensitivity and specificity were similar between groups. The authors concluded that in surveillance of inflammatory bowel diseases, chromoendoscopy identifies more patients with dysplasia only when compared with standard-definition white-light endoscopy and it is associated with longer procedural time with no direct evidence of effect on preventing all-cause/cancer-specific mortality or time to interval cancer.

Brown et al. (2016) reported on a Cochrane review determine whether the use of chromoscopy enhances the detection of polyps and neoplasia during endoscopic examination of the colon and rectum, an update of a 2010 review. The review included prospective, randomized trials that compared chromoscopic with conventional endoscopic examination of the whole of the colon and rectum. The review excluded studies of people with inflammatory bowel disease or polyposis syndromes and any studies that combined chromoscopy with additional interventions. Seven trials (2727 participants) were included in the update. It was noted that all the trials had some methodological drawbacks and the study classified all evidence as low quality. When results were combined, it was noted that there was a significant difference in favor of chromoscopy for all detection outcomes. Chromoscopy appeared likely to yield significantly more people with at least one neoplastic lesion (odds ratio (OR) 1.53, 95% confidence interval (CI) 1.31 to 1.79; 7 trials; 2727 participants), and at least one diminutive

neoplastic lesion (OR 1.51, 95% CI 1.19 to 1.92; 4 trials; 1757 participants). There was no report of adverse events related to the use of the contrast dye. Limitations of the study included that study designs of this type do not allow blinding of the examiner; subtle variations in study design (e.g., time spent examining the colon was standardized in some studies for both those undergoing chromoscopy and those with conventional colonoscopy, whereas in other studies it was not; potential causes of variation included the different points of randomization of participants; and varied reasons for undergoing colonoscopy (e.g., taking part in a general screening program may have smaller and less easily detected polyps than those presenting with symptoms).

Wu et al. (2011) reported on a meta-analysis of six randomized, controlled trials (1528 patients) that examined diagnostic accuracy of chromoendoscopy for dysplasia in ulcerative colitis. The use of chromoendoscopy with histological diagnosis was performed. Methylene blue was used in three studies and indigo carmine in the other three studies. The results indicate higher diagnostic precision with a pooled sensitivity and specificity of 0.833 (95% CI, 0.359–0.996) and 0.913 (95% CI, 0.438–1.000) for chromoendoscopy using dye spray and targeted biopsies compared with conventional colonoscopy. Subgroup analysis suggested that chromoendoscopy using indigo carmine as the dye spray appeared to achieve better sensitivity (0.93 vs 0.74) although it had a decreased specificity (0.91 vs 0.92) compared with methylene blue. It is noted that it is not clear if this was due to differences in the experience of the endoscopist. Further studies are needed to assess the cost-effectiveness, tolerance and application of this technique in clinical practice.

Subramanian et al. (2011) conducted a meta-analysis of studies to compare the diagnostic yield of dysplastic lesions in patients with inflammatory bowel disease (IBD) undergoing surveillance colonoscopy between chromoendoscopy and standard white light endoscopy. The review included six studies with 1277 patients: two randomized, one prospective non-randomized, and four prospective cohort studies. The analysis found a difference in the yield of dysplasia between chromoendoscopy and while light endoscopy of 7% on a per person analysis with a number need to treat of 14.3. The difference in proportion of lesion detected by targeted biopsies was 44% and flat lesions were 27% in favor of chromoendoscopy. The authors note that while chromoendoscopy increases detection of dysplasia the majority of lesions detected were low grade dysplasia and there is still debate regarding treatment of patients with these lesions. This could lead to unnecessary resection or surgery. Limitations include small sample size in the studies and heterogeneity several factors including relative proportion of patients with dysplasia included in each study, differences in application technique, dye contact time, operator experience, and interpretation of staining. It is not clear if the results will patient outcome.

Kahi et al. (2010) conducted a multicenter, randomized trial that compared high-definition chromocolonoscopy with high-definition white light colonoscopy for the detection of colorectal adenomas. Six hundred sixty average-risk patients referred for screening colonoscopy were randomized to either high-definition chromocolonoscopy (321) or high-definition white light colonoscopy (339). The primary outcome was a comparison between the two groups of patients with at least one adenoma and the number of adenomas per patient. The secondary outcome was patients with flat or depressed neoplasms. Overall the mean number of adenomas per patient was 1.2 ± 2.1 ; mean number of flat polyps per patient was 1.4 ± 1.9 , and the mean number of flat adenomas per patient was 0.5 ± 1.0 . The number of patients with at least one adenoma, and the number of adenomas per patient were marginally higher in the chromocolonoscopy group. There were no significant differences in the number of advanced adenomas per patient and the number of advanced adenomas <10 mm per patient. Two invasive cancers were found, one in each group; neither was a flat neoplasm. Chromocolonoscopy detected significantly more flat adenomas per patient (0.6 ± 1.2 vs. 0.4 ± 0.9 , $p=0.01$), adenomas < 5 mm in diameter per patient (0.8 ± 1.3 vs. 0.7 ± 1.1 , $p=0.03$), and non-neoplastic lesions per patient (1.8 ± 2.3 vs. 1.0 ± 1.3 , $p<0.0001$). The authors concluded that high-definition chromocolonoscopy marginally increased overall adenoma detection and yielded modest increase in flat adenoma and small adenoma detection compared with white-light colonoscopy. The yield for advanced neoplasm was similar for the two methods. The authors note that the findings do not support the routine use of high-definition chromocolonoscopy for CRC screening in average-risk patients.

Fiberoptic Polyp Analysis: A prospective, non-randomized, multicenter study was conducted by SpectraScience regarding the Optical Biopsy System. Results of this study were not published but were available to the FDA for their review. One hundred and one patients underwent a colonoscopy that included the use of this device in comparing polyps that a physician would determine should be removed versus those detected through the use of the “spectral measures.” The physician was blinded to the spectral measures that were taken during this study, and a total of 135 specimens were elevated by two pathologists who were also

blinded to the “spectral measures.” The researchers reported the device sensitivity and specificity as 79.0 and 55.6%, respectively. The physician’s visual assessment was measured as having 82.7% sensitivity and 50% specificity. When the results were combined, the sensitivity rose to 96.3% with a specificity of 33.3%. The researchers reported that the outcomes obtained through the combination of colonoscopy and OBS were statistically significant. It is unclear how the use of this device during a colonoscopy would improve patient health outcomes, if a polyp is not removed and submitted for histological analysis, the potential increases for precancerous lesions to go undetected, and an actual increase in CRC to occur.

Confocal Fluorescent Endomicroscopy: Lord et al. (2018) conducted a systematic review and meta-analysis for the diagnostic accuracy of in vivo lesion characterization in colonic inflammatory bowel disease (IBD), using optical imaging techniques, including virtual chromoendoscopy (VCE), dye-based chromoendoscopy (DBC), magnification endoscopy and confocal laser endomicroscopy (CLE). The review included 22 studies (retrospective and prospective cohorts, randomized controlled trials) with 1,491 patients; 4,674 polyps, of which 539 (11.5%) were neoplastic. Real-time CLE had a pooled sensitivity of 91% (95%CI: 66%-98%), specificity of 97% (95%CI: 94%-98%), and an AUSROC of 0.98 (95%CI: 0.97-0.99). Magnification endoscopy had a pooled sensitivity of 90% (95%CI: 77%-96%) and specificity of 87% (95%CI: 81%-91%). VCE had a pooled sensitivity of 86% (95%CI: 62%-95%) and specificity of 87% (95%CI: 72%-95%). DBC had a pooled sensitivity of 67% (95%CI: 44%-84%) and specificity of 86% (95%CI: 72%-94%). The authors concluded that real-time CLE is a highly accurate technology for differentiating neoplastic from non-neoplastic lesions in patients with colonic IBD; however, most CLE studies were performed by single expert users within tertiary centers, which potentially confounds the results.

Su et al. (2012) reported on a meta-analysis of the efficacy of confocal laser endomicroscopy (CLE) for discriminating colorectal neoplasms from non-neoplasms. The study included 15 studies with eligibility criteria including: clinical trials on the diagnostic efficacy of CLE for the diagnosis of colorectal neoplasms including real-time assessment with the knowledge of macroscopic endoscopy images, and blinded off-line assessment based on CLE videos; adults with indications for screening or surveillance colonoscopy such as colorectal polyps, Crohn’s disease, chronic ulcerative colitis (> 8 years), etc.; diagnosis of colorectal neoplasms using histological biopsy as a standard criterion and the WHO classification or Vienna pattern as reference criteria; and, studies presenting data to enable calculation of sensitivity and specificity. Meta-analysis of the 15 eligible studies showed that the summary sensitivity was 0.94 (95% confidence intervals [CI] 0.88–0.97), and the summary specificity was 0.95 (95% CI 0.89–0.97). The sensitivity was moderately inconsistent (66.2%), and the specificity was extremely inconsistent (92.6%). Limitations of the review included the relatively high heterogeneity presented across the 15 enrolled studies. The authors note that CLE cannot substitute for conventional biopsy histopathology. Further prospective, randomized studies are needed to obtain unbiased results on the effectiveness and cost-effectiveness of CLE along with standardization of the procedure and a comparison between this strategy and conventional colonoscopy.

Buchner et al. (2009) conducted a study with the aim to compare sensitivity and specificity of probe-based confocal laser endomicroscopy (pCLE) to virtual chromoendoscopy for classification of colorectal polyps using histopathology as a gold standard. Colonoscopy was performed with high-resolution colonoscopies, then the surface pit pattern was determined with narrow band imaging (NBI) or Fujinon intelligent color enhancement (FICE) in all patients. The confocal images were recorded and subsequently analyzed offline, while blinded to the endoscopic characteristics and histopathology. Polyps were diagnosed as benign or neoplastic based on confocal features according to modified Mainz criteria. A total of 119 polyps (81 neoplastic, 38 hyperplastic) from 75 patients was considered. The pCLE was found to have higher sensitivity compared to virtual chromoendoscopy when considering histopathology as gold standard (91% vs 77%; $p=.010$) and modified gold standard (88% vs 76%; $p=.037$). No statistically significant difference in specificity was noted between pCLE and virtual chromoendoscopy when considering histopathology or modified gold standard.

Narrow Band Imaging (NBI): There have been several published studies that compare the use of NBI with white light colonoscopy. The studies have reported variable and at times conflicting results regarding detection of adenomas with NBI.

Riu Pons et al. (2020) conducted a randomized, cross-over trial to examine if narrow-band imaging (NBI) could be more effective than high-definition white-light endoscopy (HD-WLE) in detecting serrated lesions in patients

with prior serrated lesions > 5 mm not completely fulfilling serrated polyposis syndrome (SPS) criteria. The study included 41 patients with prior detection of at least one serrated polyp ≥ 10 mm or ≥ 3 serrated polyps larger than 5 mm, both proximal to the sigmoid colon. Five experienced endoscopists performed same-day tandem colonoscopies, with the order being randomized 1:1 to NBI-HD-WLE (n=20) or HD-WLE-NBI (n=21). No differences were observed in the serrated lesion detection rate of NBI versus HD-WLE: 47.4% versus 51.9% (OR 0.84, 95% CI: 0.37-1.91) for the first and second withdrawal, respectively. Equally, no differences were found in the polyp miss rate of NBI versus HD-WLE: 21.3% versus 26.1% (OR 0.77, 95% CI: 0.43-1.38). Follow-up colonoscopy in nine patients (22%) allowed them to be reclassified as having SPS. The authors concluded that in patients with previous serrated lesions, the serrated lesion detection rate was similar with NBI and HD-WLE. The study was limited by the small number of patients.

Lv et al. (2019) conducted a systematic review and meta-analysis to compare NBI versus other endoscopic techniques in surveillance of IBD basing on current evidences. The review included a total of ten studies involving with 938 participants. Statistically significant differences were not found in the likelihood of detecting patients with dysplastic lesions [RR, 1.11; 95% confidence interval (CI), 0.83-1.48] nor in the likelihood of detecting dysplastic lesions by targeted biopsies (RR, 0.76; 95% CI, 0.51-1.12) between NBI and other techniques, and there was also no difference in the likelihood of detecting dysplastic subtypes. NBI required shorter procedural time compared with other techniques (MD, -10.23; 95% CI, -11.53 to -8.92). The sensitivity and specificity of NBI to differentiate neoplastic lesions from non-neoplastic lesions were 0.64 (95% CI, 0.50-0.77) and 0.74 (95% CI, 0.69-0.79), respectively, and the area under the curve (AUC) was 0.7626. The authors concluded that although a shorter procedural time is needed, the clinical application of NBI for both dysplasia detection and neoplasia differentiation in IBD is not superior to other endoscopic techniques.

Singh et al. (2017) reported on a randomized, controlled trial that compared high definition white light endoscopy and bright narrow band imaging for colon polyps' detection rates. The study included 1006 patients that were randomized to high definition white light endoscopy (HD-WLE) (n=511) or the bright narrow band imaging (bNBI) (n=495) during withdrawal of the colonoscope. The polyps identified in either mode were characterized using bNBI with dual focus (bNBI-DF) according to the Sano's classification. The primary outcome was to compare adenoma detection rates (ADRs) between the two arms. The secondary outcome was to assess the negative predictive value (NPV) in differentiating adenomas from hyperplastic polyps for diminutive rectosigmoid lesions. The mean of adenoma per patient was 1.62 and 1.84, respectively. The ADRs in bNBI and HD-WLE group were 37.4% and 39.3%, respectively. When adjusted for withdrawal time (OR = 1.19, 95%CI: 1.15-1.24, $P < 0.001$), the use of bNBI was associated with a reduced ADR (OR = 0.69, 95%CI: 0.52-0.92). The sensitivity (Sn), specificity (Sp), positive predictive value and NPV in differentiating adenomatous from non-adenomatous polyps of all sizes were 95.9%, 87.2%, 94.0% and 91.1% respectively. The NPV in differentiating an adenoma from hyperplastic polyp using bNBI-DF for diminutive rectal polyps was 91.0%. The authors concluded that ADRs did not differ between bNBI and HD-WLE; however HD-WLE had higher ADR after adjustment of withdrawal time.

Visovan et al. (2017) reported on a randomized trial to investigate the diagnostic yield of narrow band imaging (NBI) colonoscopy for polyp detection compared with standard colonoscopy. The study randomized 505 patients into two groups: 226 patients in NBI group and 279 in non-NBI group (standard colonoscopy). Primary endpoints were polyp detection rate (PDR) and adenoma detection rate (ADR). Polyps detected with NBI technique were characterized according to the NBI International Colorectal Endoscopic (NICE) classification. The total number of polyps detected in NBI group was higher compared with non-NBI group (325 polyps in 226 patients versus 189 polyps in 279 patients, respectively). PDR in NBI group was 55.3%, versus 43.3% in non-NBI group. ADR in NBI group was higher compared with non-NBI group (35.3% versus 20%, respectively). The proportion of detected adenomas in the left-sided colon was higher in NBI group (72.8% versus 61.06% in non-NBI group), which was related to an increased number of small adenomas detected in NBI group. In the NBI group, a significant number of flat adenomas were detected (28 versus 9 in non-NBI group). A total of 147 (45.2%) polyps were classified according to the NICE classification, and showed a good correlation with histological analysis. The authors note that the results in this study may be due to several reasons, including: experience of endoscopist, exclusion of patients with poor bowel preparation, and withdrawal time of more than 8 minutes.

Nagorni et al. (2012) conducted a Cochrane review to compare standard or high definition white light colonoscopy with narrow band imaging colonoscopy for detection of colorectal polyps. The review included eight randomized trials with 3,673 participants. The study found no statistically significant difference between white

light colonoscopy (standard definition and high definition pooled) and NBI for the detection of patients with colorectal polyps (six trials), patients with colorectal adenomas (eight trials), or patients with colorectal hyperplastic polyps (two trials). The authors concluded that NBI colonoscopy was not better than high definition white light colonoscopy for the detection of patients with colorectal polyps; it was found that there was weak evidence that narrow band imaging colonoscopy might be better than conventional white light colonoscopy for detection of patients with colorectal polyps. It was noted that more randomized trials with a greater number of participants are needed to further clarify the role of NBI for detection of colorectal polyps.

Dinesen et al. (2012) reported on a meta-analysis of narrow-band imaging (NBI) compared to standard white-light colonoscopy (WLC) for adenoma detection. The review included seven prospective, randomized studies with a total of 2936 patients. Studies were excluded that utilized spray chromoendoscopy and studies of inflammatory bowel disease and polyposis syndromes. The results of the analysis indicated that there was no statistically significant difference in the overall adenoma detection rate with use of NBI or WLC and there no statistically significant difference in polyp detection rate with use of NBI or WLC. It was also noted that there was no difference seen regarding the mean number of flat adenomas per person between NBI and WLC.

Kobayashi et al (2011) reported on a meta-analysis that compared diagnostic performance of chromoendoscopy and narrow band imaging for colonic neoplasms. The review included 27 studies. The pooled sensitivity for chromoendoscopy and NBI was 0.94 (95% CI, 0.92–0.95) and 0.94 (0.91–0.97), and specificity was 0.82 (0.77–0.88) and 0.86 (0.83–0.89), respectively. There were no differences in sensitivity ($p=0.99$) or specificity ($p=0.54$) between the two methods. In the secondary analysis, pooled sensitivity for chromoendoscopy and NBI was 0.93 (95% CI, 0.90–0.97) and 0.96 (0.93–0.99) and specificity was 0.80 (0.73–0.87) and 0.85 (0.78–0.92), respectively. The pooled false-negative rate was 0.057 (95% CI, 0.040–0.73) for chromoendoscopy and 0.057 (95% CI, 0.028–0.085) for NBI. The authors concluded that chromoendoscopy and NBI had similar diagnostic test characteristics in the assessment of colonic neoplasms; however, the false-negative rate for both methods of 5.7% is an unacceptably high rate therefore, neither method is ready for general use.

Sabbagh et al. (2011) reported on a randomized, controlled trial (RCT) ($n=482$) that compared narrow-band imaging to conventional colonoscopy. A systematic review of RCTs was also performed. Most patients presented for diagnostic colonoscopy (75.3%). The overall rate of polyp detection was found to be significantly higher in the conventional group as compared to the NBI group (risk ratio [RR] 0.75, 95% CI 0.60–0.96). However, no significant differences were found in the mean number of polyps (MD -0.1; 95% CI -0.25–0.05), and the mean number of adenomas (weighted mean difference [WMD] 0.04 95%CI -0.09 to 0.17). the meta-analysis of studies (regardless of indication) did not find any significant differences in the mean number of polyps (5 RCT, 2479 participants; WMD -0.07 95% CI -0.21–0.07; I² 68%), the mean number of adenomas (8 RCT, 3517 participants; WMD -0.08 95% CI -0.17; 0.01–I² 62%) and the rate of patients with at least one adenoma (8 RCT, 3512 participants, RR 0.96 95% CI 0.88–1.04; I² 0%). The authors concluded that NBI does not improve detection of colorectal polyps when compared to conventional colonoscopy.

Adler et al. (2009) conducted prospective, randomized, multicenter trial of 1256 patients. The patients were randomized to screening colonoscopy with either NBI or white-light imaging on instrument withdrawal. The primary outcome measurement was the adenoma detection rate. The study found no difference between the two groups in terms of the general adenoma detection rate (0.32 vs 0.34); the total number of adenomas (200 vs 216), or in the detection in subgroups of adenomas. These findings were in light of a minimal, but significantly longer, withdrawal time in the NBI group (8.5 vs 7.9 min; $p<.05$). Hyperplastic polyps were found more frequently in the NBI group ($p=.03$).

Ignjatovic et al. (2009) reported on a prospective, cohort study that aimed to assess whether diagnosis of small polyps with non-magnifying NBI is feasible and safe in routine clinical practice (DISCARD trial). The study included 130 patients referred for surveillance colonoscopy or who had positive fecal occult blood testing. Polyp histology using optical diagnosis with high definition white light was predicted, followed by narrow-band imaging without magnification and chromoendoscopy. The primary outcome was accuracy of polyp characterization using optical diagnosis compared with histopathology, the current gold standard. There were 278 polyps smaller than 10mm that had both optical and histopathological diagnosis. With histology—198 of these polyps were adenomas and 80 were non-neoplastic lesions (62 hyperplastic). Optical diagnosis accurately diagnosed 186 of 198 adenomas (sensitivity 0.94; 95% CI 0.90–0.97) and 55 of 62 hyperplastic polyps (specificity 0.89; 0.78–

0-95), with an overall accuracy of 241 of 260 for polyp characterization. Using optical diagnosis alone, 82 of 130 patients could be given a surveillance interval immediately after colonoscopy, and the same interval was found after formal histopathology in 80 patients (98%) using British guidelines and in 78 patients (95%) using US multi-society guidelines.

Adler et al (2008) conducted a prospective study of 401 patients who were randomly assigned to undergo wide-angle colonoscopy using either conventional imaging or NBI during instrument withdrawal. The primary outcome measurement was the difference between adenoma detection rate with the two techniques. The study found more frequent detection of adenomas in the NBI group (23%) than in the control group (17%) with the difference found not to be statistically significant ($p=0.129$). The two techniques were then compared in consecutive subgroups of 100 study patients—adenoma rates in the NBI group remained fairly stable, whereas these rates steadily increased in the control group (8%, 15%, 17%, and 26.5%, respectively). The significant differences in the first 100 cases (26.5% versus 8%; $p=0.02$) were not maintained in the last 100 cases (25.5% versus 26.5%, $p=0.91$). It was theorized by the authors that the increase might be the result of a form of learning effect resulting from the NBI contrast-enhancement technique.

Rex et al (2007) reported on a randomized controlled trial comparing colonoscopy withdrawal in white light with NBI in 434 patients. It was found that there was no difference in the percent of patients with ≥ 1 adenoma for the entire cohort in white light (67%) versus NBI (65%) ($p=.61$) or in the subset of 257 patients with indication screening (58% vs 57%; $p=.91$). The authors report that the prevalence of adenomas and the numbers of adenomas per colonoscopy are the highest ever reported in colonoscopy studies—the high prevalence rates of adenomas were accounted for by detection of large numbers of adenomas, including flat adenomas, which were ≤ 5 mm.

Professional Societies/Organizations—In Vivo Analysis of Colorectal Polyps

American Society for Gastrointestinal Endoscopy (ASGE) and American Gastroenterological Association (AGA): these organizations published the SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease (Laine, et al., 2018). The statement includes the following recommendations:

Detection of dysplasia on surveillance colonoscopy

- When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition (strong recommendation, low-quality evidence).
- When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy (strong recommendation, moderate-quality evidence).
- When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy (conditional recommendation, low-quality evidence).
- When performing surveillance with standard-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy (conditional recommendation, low-quality evidence).
- When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy (conditional recommendation, moderate-quality evidence).
- When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy (conditional recommendation, moderate-quality evidence).

Management of dysplasia discovered on surveillance colonoscopy

- After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy (strong recommendation, very low-quality evidence).
- After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy (conditional recommendation, very low-quality evidence).
- For patients with endoscopically invisible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy (conditional recommendation, very low-quality evidence).

The guidelines note regarding chromoendoscopy for detection of dysplasia on surveillance colonoscopy that potential barriers to the use of chromoendoscopy were considered and include the additional preparation and time required for chromoendoscopy, need to train endoscopists in this technique, need to develop quality measures and assess performance after training, procedure-related costs.

The strength of recommendation, provided for each recommendation, reflects the level of confidence that desirable effects of an intervention outweigh undesirable effects:

- Strong recommendations mean panelists are confident that the desirable effects outweigh the undesirable effects; therefore, most informed patients would choose the recommended management, and clinicians would provide the intervention to most patients.
- Conditional recommendations mean the desirable and undesirable effects of the intervention are closely balanced or appreciable uncertainty exists regarding the balance; therefore, informed patients' choices will vary according to their values and preferences, with many not wanting the intervention, and clinicians must ensure that patients' care is in keeping with their values and preferences.

Multi-Society Task Force on Colorectal Cancer (USMSTF): In an update to joint consensus guidelines for colonoscopy surveillance after polypectomy, the USMSTF includes the following regarding the role of chromoendoscopy, magnification endoscopy, narrow band imaging, in postpolypectomy surveillance (Lieberman, et al., 2012):

- The role of new endoscopic technologies has not been studied in surveillance cohorts.
- The technical endoscopic enhancements may increase the likelihood of detecting small polyps.
- Chromoendoscopy and narrow band imaging may enable endoscopists to accurately determine if lesions are neoplastic, and if there is a need to remove them and send material to pathology.
- At this point, these technologies do not have an impact on surveillance intervals.

American Society for Gastrointestinal Endoscopy (ASGE): The ASGE published a technology status evaluation report regarding electronic chromoendoscopy (ASGE, 2015a). The report notes that the term electronic chromoendoscopy refers to endoscopic imaging technologies that provide detailed contrast enhancement of the mucosal surface and blood vessels. The technologies offer an alternative to dye-based chromoendoscopy and include narrow-band imaging (NBI) (Olympus Medical Systems Tokyo, Japan), flexible spectral imaging color enhancement (FICE) (Fujinon, Fujifilm Medical Co, Saitama, Japan), and i-SCAN (PENTAX Endoscopy, Tokyo, Japan).the report identifies several areas pertaining to these technologies that deserve further study:

- Further studies evaluating the cost-effectiveness of these technologies relative to the standard of care and whether enhanced imaging accuracy decreases the need for biopsy.
- Ongoing development of validated teaching modules for NBI, FICE, and i-SCAN.
- Identification of optimal FICE and i-SCAN settings on the basis of location and lesion(s) of interest.
- The next generation of electronic chromoendoscopy technologies has just started being evaluated in clinical trials. There is an ongoing need to evaluate new technologies as they develop.
- Consensus and validation of disease-specific classification systems in multicenter trials in academic and nonacademic settings.

The report concludes that although strides have been made in standardization of image characterization, especially with NBI, further image-to-pathology correlation and validation are required. Further community-based studies are needed before development of a resect and discard policy for diminutive adenomas by using electronic chromoendoscopy is adopted. In addition, further validated training tools for these technologies will also be required for the use of these techniques to become widespread.

American Society for Gastrointestinal Endoscopy (ASGE): ASGE published a technology status evaluation report regarding confocal laser endomicroscopy (CLE) (ASGE, 2014). The report notes that an evolving application of the technology includes differentiation of colorectal polyps, inflammatory, bowel diseases, gastric diseases, and pancreatic cysts. Regarding the studies for colorectal polyps it is noted that the studies are heterogeneous and difficult to compare due to differing primary objectives and the modality of CLE used. The studies suggest that CLE may have the potential to reach ASGE PIVI (Preservation and Incorporation of

Valuable endoscopic Innovations) thresholds; however, the generalizability of the results obtained in academic settings to community practice is unknown. The limitations of CLE include the high cost of the equipment and probes, the lack of proven efficacy compared with other widely available advanced imaging techniques, and the need for either intravenous or topical fluorescent contrast agents. The report notes that before the technology can be widely accepted, many further studies are needed to determine its clinical efficacy and evaluate its cost-effectiveness and its utilization in both academic and community settings.

Urine-Based Test for Detection of Colon Polyps (e.g., PolypDx)

PolypDx™ (Metabolomic Technologies Inc, Edmonton, AB, Canada) is a urine-based test that test for metabolites using liquid chromatography–mass spectrometry (LC-MS) technology. The test is based on the analysis of key metabolomic biomarkers in urine, with the biomarker measurement data interpreted by a proprietary algorithm which generates the PolypDx test result. It is proposed by the vendor to be used for colorectal cancer screening. The results indicate if there is a strong or low likelihood of a polyp being present. If there is a strong likelihood the patient is referred for colonoscopy.

U.S. Food and Drug Administration (FDA): PolypDx is not currently FDA approved. PolypDx is currently available as a laboratory developed test (LDT) through Clinical Laboratory Improvement Amendments (CLIA) certified laboratories.

Literature review PolypDx: Deng et al. (2019) conducted a prospective study to identify a urine metabolomic-based biomarker panel for the detection of CRC that has potential for global population-based screening. Prospective urine samples were collected from study participants. The study included 342 participants (CRC, 171; healthy controls, 171) from two study sites. Targeted liquid chromatography-mass spectrometry was performed to quantify 140 highly valuable metabolites in each urine sample. Potential biomarkers for CRC were identified by comparing the metabolomics profiles from CRC versus controls. Multiple models were constructed leading to a good separation of CRC from controls. A panel of 17 metabolites was identified as possible biomarkers for CRC. Using only two of the selected metabolites, namely diacetylspermine and kynurenine, a predictor for detecting CRC was developed with an AUC of 0.864, a specificity of 80.0% and a sensitivity of 80.0%. the authors concluded that this represents a potentially “universal” metabolomic biomarker panel for CRC independent of cohort clinical features based on a North American population, however further research is needed to confirm the utility of the profile in a prospective, population-based CRC screening trial.

Erben et al. (2018) conducted a systematic review of biomarkers for the early detection of colorectal neoplasms in easy-to-collect human bio-fluids. Information on study design and performance characteristics for diagnostic accuracy was extracted. Forty-one 41 studies were included in the analysis investigating biomarkers in different bio-fluids (blood, urine, and feces). Although single metabolites mostly had limited ability to distinguish people with and without colorectal neoplasms, promising results were reported for metabolite panels, especially amino acid panels in blood samples, as well as nucleosides in urine samples in several studies, however, validation of the results is limited. The authors concluded that panels of metabolites consisting of amino acids in blood and nucleosides in urinary samples might be useful biomarkers for early detection of advanced colorectal neoplasms; however, to make metabolomic biomarkers clinically applicable, future research in larger studies and external validation of the results is required.

Deng et al. (2017) reported on a study with the aim to develop a clinically scalable (high throughput, low cost, and high sensitivity) mass spectrometry (MS)-based urine metabolomic test for the detection of adenomatous polyps. Urine and stool samples were collected from 685 participants enrolled in a colorectal cancer screening program to undergo colonoscopy. Statistical analysis was performed on 69 urine metabolites measured by one-dimensional nuclear magnetic resonance spectroscopy to identify key metabolites. A targeted MS assay was then developed to quantify the key metabolites in urine. A MS-based urine metabolomic diagnostic test for adenomatous polyps was established using 67% samples (un-blinded training set) and validated using the remaining 33% samples (blinded testing set). The MS-based urine metabolomic test identifies patients with colonicadenomatous polyps with an AUC of 0.692, outperforming the nuclear magnetic resonance spectroscopy (NMR) based predictor with an AUC of 0.670. This study is a preliminary validation and needs further clinical trials to determine clinical utility.

Wang et al. (2014) reported on a study with the aim to develop a highly accurate, prototypic, proof-of-concept, spot urine-based diagnostic test using metabolomic technology to distinguish persons with adenomatous polyps from those without polyps. Prospective urine and stool samples were collected from 876 participants undergoing colonoscopy examination in a colon cancer screening program. Colonoscopy reference standard identified 633 participants with no colonic polyps and 243 with colonic adenomatous polyps. A urine metabolomic diagnostic test for colonic adenomatous polyps was established using 67% of the samples (un-blinded training set) and validated using the other 33% of the samples (blinded testing set). The urine metabolomic diagnostic test's specificity and sensitivity were compared with those of fecal-based tests. With a two-component, orthogonal, partial least-squares model of the metabolomic profile, the un-blinded training set identified patients with colonic adenomatous polyps with 88.9% sensitivity and 50.2% specificity. Validation using the blinded testing set confirmed sensitivity and specificity values of 82.7% and 51.2%, respectively. Sensitivities of fecal-based tests to identify colonic adenomas ranged from 2.5 to 11.9%. The study is preliminary and needs further study to determine clinical utility.

Professional Societies/Organizations- PolypDx

Professional organization guidelines for colorectal cancer screening do not include recommendations for urine-based testing for detection of colon polyps.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

The ABIM includes the following statements:

AMDA – The Society for Post-Acute and Long-Term Care Medicine™:

Don't recommend screening for breast, colorectal or prostate cancer if life expectancy is estimated to be less than 10 years.

American College of Surgeons:

Avoid colorectal cancer screening tests on asymptomatic patients with a life expectancy of less than 10 years and no family or personal history of colorectal neoplasia.

American Gastroenterological Association:

Do not repeat colorectal cancer screening (by any method) in average risk individuals for 10 years after a high-quality colonoscopy that does not detect neoplasia.

Do not repeat surveillance colonoscopy for at least five years for average-risk patients who have one or two small (<1cm) adenomatous polyps, without high-grade dysplasia or villous histology, completely removed via a high-quality colonoscopy.

American Geriatrics Society:

Don't recommend screening for breast, colorectal, prostate or lung cancer without considering life expectancy and the risks of testing, overdiagnosis and overtreatment.

American Society for Clinical Pathology

Only order Methylated Septin 9 (SEPT9) to screen for colon cancer on patients for whom conventional diagnostics are not possible.

Society of Surgical Oncology

Don't obtain routine blood work (e.g., CBC, liver function tests) other than a CEA level for surveillance for colorectal cancer.

Use Outside of the US

Asia Pacific Consensus on Colorectal Cancer (CRC): This organization published consensus recommendations on colorectal cancer screening, an update to their 2008 guidelines (Sung, et al., 2014).

The recommendations for colorectal cancer screening include:

- Population screening for colorectal cancer is recommended in those Asia Pacific regions where the incidence of CRC is high. In both genders, subjects aged 50–75 years are the target for CRC screening. Quality of evidence: II-2; Classification of recommendation: B.
- In the Asia Pacific region, age, male gender, family history, smoking and obesity are risk factors for CRC and advanced neoplasia. Quality of evidence: II-2; Classification of recommendation: A.

- Stool-based occult blood test:
 - Stool-based occult blood testing is of proven value for CRC screening. Quality of evidence: I; Classification of recommendation: A.
 - Guaiac-based stool testing should be replaced by quantitative fecal immunochemical test (FIT). Quality of evidence: I; Classification of recommendation: A.
- Fecal immunochemical test identifies individuals who should be referred for colonoscopy. Quality of evidence: II-2; Classification of recommendation: A.
- Flexible sigmoidoscopy is effective for CRC screening. Quality of evidence: I; Classification of recommendation: A.
- Colonoscopy:
 - Colonoscopy is effective for CRC screening. Quality of evidence: II-2; Classification of recommendation: B.
 - Colonoscopy is the preferred choice of CRC screening in increased risk individuals. Quality of evidence: II-2; Classification of recommendation: B.
- CT colonography (CTC): CTC is not recommended for colorectal cancer screening. It may be used in cases when total colonoscopy is not possible. Quality of evidence: II-2; Classification of recommendation: B.
- Capsule endoscopy: A role for capsule endoscopy in CRC screening is not defined. It may be used in cases when total colonoscopy is not possible. Quality of evidence: II-2; Classification of recommendation: B.
- First-degree relatives of patients with sporadic CRC diagnosed at age <50 are at an increased risk of colorectal neoplasm and early screening is warranted. Quality of evidence: II-2; Classification of recommendation: B.
- The surveillance interval for colonoscopy should be tailored to risk for colorectal neoplasia. Quality of evidence: II-1; Classification of recommendation: A.
- Right-sided lesions and sessile serrated polyps can be difficult to detect and contribute to interval cancers. Quality of evidence: II-2; Classification of recommendation: A.
- Colonoscopy: Good quality colonoscopy is key to success of a screening program and quality of colonoscopy should be audited. Quality of evidence: II-2; Classification of recommendation: A.
- Colonoscopy: Ancillary methods with the exception of chromoendoscopy have not proven to be superior to high-definition white light endoscopy in identifying adenoma. Quality of evidence: I; Classification of recommendation: A.

Quality of evidence:

I Evidence obtained from at least one RCT

II-1 Evidence obtained from well-designed control trials without randomization

II-2 Evidence obtained from well-designed cohort or case-control study

Classification of recommendation:

A There is good evidence to support the statement

B There is fair evidence to support the statement

European Society of Gastrointestinal Endoscopy (ESGE): ESGE published guidelines for advanced imaging for detection and differentiation of colorectal neoplasia (Bisschops, et al., 2019). The guidelines includes these recommendations:

- ESGE suggests that high definition endoscopy, and dye or virtual chromoendoscopy, as well as add-on devices, can be used in average risk patients to increase the endoscopist's adenoma detection rate. However, their routine use must be balanced against costs and practical considerations. Weak recommendation, high quality evidence.
- ESGE recommends the routine use of high definition systems in individuals with Lynch syndrome. Strong recommendation, high quality evidence.
- ESGE recommends the routine use, with targeted biopsies, of dye-based pancolonic chromoendoscopy or virtual chromoendoscopy for neoplasia surveillance in patients with long-standing colitis. Strong recommendation, moderate quality evidence.
- ESGE suggests that virtual chromoendoscopy and dye-based chromoendoscopy can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive ($\leq 5\text{mm}$) colorectal polyps and

can replace histopathological diagnosis. The optical diagnosis has to be reported using validated scales, must be adequately photo-documented, and can be performed only by experienced endoscopists who are adequately trained, as defined in the ESGE curriculum, and audited. Weak recommendation, high quality evidence.

- ESGE recommends the use of high definition white-light endoscopy in combination with (virtual) chromoendoscopy to predict the presence and depth of any submucosal invasion in nonpedunculated colorectal polyps prior to any treatment. Strong recommendation, moderate quality evidence.
- ESGE recommends the use of virtual or dye-based chromoendoscopy in addition to white-light endoscopy for the detection of residual neoplasia at a piecemeal polypectomy scar site. Strong recommendation, moderate quality evidence.
- ESGE suggests the possible incorporation of computer aided diagnosis (detection and characterization of lesions) to colonoscopy, if acceptable and reproducible accuracy for colorectal neoplasia is demonstrated in high quality multicenter in vivo clinical studies. Possible significant risks with implementation, specifically endoscopist deskilling and over-reliance on artificial intelligence, unrepresentative training datasets, and hacking, need to be considered. Weak recommendation, low quality evidence.

ESGE Strength of recommendation:

Strong: Benefits clearly outweigh risks and burden, or vice versa. Usually stated as “we recommend.”

Weak: Benefits closely balanced with risks and burden. Usually stated as “we suggest.”

ESGE Evidence Level:

High quality: One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: RCTs with important limitations (i. e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case – control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Observational studies would typically be rated as low quality because of the risk for bias.¹ This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.

Very low quality: Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

National Institute for Health and Clinical Excellence (NICE) (United Kingdom): NICE (2011) published recommendations for colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. The guidelines include the following:

Inflammatory Bowel Disease:

- Offer colonoscopic surveillance to people with inflammatory bowel disease (IBD) whose symptoms started 10 years ago and either of the following:
 - Ulcerative colitis (but not proctitis alone)
 - Crohn's colitis involving more than one segment of colon
- Offer a baseline colonoscopy with chromoscopy and targeted biopsy of any abnormal areas to people with IBD who are being considered for colonoscopic surveillance to determine their risk of developing colorectal cancer
- Offer colonoscopic surveillance to people with IBD as defined in the recommendation above based on their risk of developing colorectal cancer, determined at the last complete colonoscopy:
 - Low risk: offer colonoscopy at 5 years.
 - Intermediate risk: offer colonoscopy at 3 years.
 - High risk: offer colonoscopy at 1 year.

- For people with IBD who have been offered colonoscopic surveillance, continue to use colonoscopy with chromoscopy as the method of surveillance.
- Offer a repeat colonoscopy with chromoscopy if any colonoscopy is incomplete. Consider whether a more experienced colonoscopist is needed.

Adenomas:

- Consider colonoscopic surveillance for people who have had adenomas removed and are at low risk of developing colorectal cancer
- Offer colonoscopic surveillance to people who have had adenomas removed and are at intermediate or high risk of developing colorectal cancer:
 - Low risk: consider colonoscopy at 5 years:
 - If the colonoscopy is negative (that is, no adenomas are found) stop surveillance.
 - If low risk, consider the next colonoscopy at 5 years (with follow-up surveillance as for low risk).
 - If intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk).
 - If high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk).
 - Intermediate risk: offer colonoscopy at 3 years:
 - If the colonoscopy is negative, offer the next colonoscopy at 3 years. Stop surveillance if there is a further negative result.
 - If low or intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk).
 - If high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk).
 - High risk: offer colonoscopy at 1 year:
 - If the colonoscopy is negative, or low or intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk).
 - If high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk).
- consider CTC as a single examination if colonoscopy is not clinically appropriate (e.g., because of comorbidity or because colonoscopy cannot be tolerated)
- consider double contrast barium enema as a single examination if CTC is not available or not appropriate
- consider CTC or double contrast barium enema for ongoing surveillance if colonoscopy remains clinically inappropriate, with a discussion of the risks and benefits

NICE (2005) conducted a review of the literature and published recommended indications for use of CTC. The authors stated that conventional colonoscopy and double-contrast barium enema are the main methods currently used for examining the colon. It was indicated that CTC may be used:

- for the examination of the colon and rectum to detect abnormalities such as polyps and cancer
- in asymptomatic patients with a high risk of developing CRC
- as an alternative procedure to barium enema in frail and elderly patients as a diagnostic tool to detect tumors

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3)	2015
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.

- 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Colorectal Cancer Screening, Surveillance, or Monitoring

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
45330	Sigmoidoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
45331	Sigmoidoscopy, flexible; with biopsy, single or multiple
45333	Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
45338	Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
45346	Sigmoidoscopy, flexible; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
45378	Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
45380	Colonoscopy, flexible; with biopsy, single or multiple
45381	Colonoscopy, flexible; with directed submucosal injection(s), any substance
45384	Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
45385	Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
45388	Colonoscopy, flexible; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
45390	Colonoscopy, flexible; with endoscopic mucosal resection
74263	Computed tomographic (CT) colonography, screening, including image postprocessing
74270	Radiologic examination, colon; contrast (eg, barium) enema, with or without KUB
74280	Radiologic examination, colon; air contrast with specific high density barium, with or without glucagon
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result
82270	Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided 3 cards or single triple card for consecutive collection)
82274	Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations

HCPCS Codes	Description
G0104	Colorectal cancer screening; flexible sigmoidoscopy
G0105	Colorectal cancer screening; colonoscopy on individual at high risk
G0106	Colorectal cancer screening; alternative to G0104, screening sigmoidoscopy, barium enema
G0120	Colorectal cancer screening; alternative to G0105, screening colonoscopy, barium enema
G0121	Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
G0122	Colorectal cancer screening; barium enema
G0328	Colorectal cancer screening; fecal-occult blood test, immunoassay, 1-3 simultaneous determinations
G9936	Surveillance colonoscopy - personal history of colonic polyps, colon cancer, or other malignant neoplasm of rectum, rectosigmoid junction, and anus
S0285	Colonoscopy consultation performed prior to a screening colonoscopy procedure

Considered Medically Necessary when used to report chromoendoscopy for colorectal cancer surveillance for patients at increased risk based on personal history of inflammatory bowel disease (IBD):

CPT®* Codes	Description
44799	Unlisted procedure, intestine
45399	Unlisted procedure, colon
45999	Unlisted procedure, rectum

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0002U	Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps

Considered Experimental/Investigational/Unproven when used to report in vivo analysis of colorectal polyps (e.g., chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, confocal fluorescent endomicroscopy):

CPT®* Codes	Description
44799	Unlisted procedure, intestine
45399	Unlisted procedure, colon
45999	Unlisted procedure, rectum
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

***Current Procedural Terminology (CPT®) ©2019 American Medical Association: Chicago, IL.**

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