Cigna Medical Coverage Policy

Subject **Colorectal Cancer Screening and Surveillance**

Effective Date **6/15/2014**
Next Review Date **6/15/2015**
Coverage Policy Number **0148**

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Coverage Policy

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

Coverage of colorectal cancer screening is generally subject to the terms, conditions and limitations of a preventive services benefit as described in the applicable benefit plan's schedule of copayments. Please refer to the applicable benefit plan document and schedules to determine benefit availability and the terms, conditions and limitations of coverage.

If coverage for colorectal cancer screening is available, the following conditions apply.

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

- 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

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

- 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)

Cigna does not cover stool-based deoxyribonucleic acid (DNA) testing for the screening or surveillance of colorectal cancer, as its use is experimental, investigational, or unproven.

Cigna does not cover in vivo analysis of colorectal polyps (e.g., chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, and confocal fluorescent endomicroscopy) for any indication including, but not limited to, the screening, diagnosis or surveillance of colorectal cancer, as its use is experimental, investigational, or unproven.

Cigna does not cover the following tests for any indication including, but not limited to, the screening, diagnosis or surveillance of colorectal cancer, because each is considered experimental, investigational, or unproven:

- methylated Septin 9 testing (e.g., Abbott RealTime mS9 Colorectal Cancer assay, Colovantage™ , Septin 9 [SEPT9])
- ColonSentry®

General Background

Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women and the second leading cause of deaths from cancer in the United States. CRC primarily affects men and women aged 50 years or older. Age-specific incidence and mortality rates show that most cases are diagnosed in individuals over age 50 (National Cancer Institute [NCI], 2013a). Incidence rates for CRC have been decreasing for most of the last two decades. This decline has been greater over the most recent time period which is considered to be partly due to an increase in screening, which can result in the detection and removal of colorectal polyps before they progress to cancer (American Cancer Society [ACS], 2013a).

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, 2013b).

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®) and ACS definitions of these groups include (NCCN, 2013; ACS, 2013b):

Risk	NCCN	ACS
average risk	individuals 50 years or older with no history of adenoma or colorectal cancer, and inflammatory bowel disease and a negative family history	individuals with no first-degree relatives having a history of CRC or adenomatous polyps and has not experienced these problems personally
increased risk	individuals with personal history of adenomatous polyps/sessile serrated polyps (SSP), CRC, colorectal cancer, or inflammatory bowel disease as well as those with a positive family history of CRC or advanced adenomatous polyps	individuals who have a personal history of CRC or adenomas, a family history of CRC or adenomas diagnosed in any first-degree relative before age 50, or in two or more first-degree relatives diagnosed at any age (if not a hereditary syndrome). According to the ACS, individuals who have a personal history of CRC or adenomatous polyp require regular surveillance, not screening.
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	individuals who have a personal history of CRC or adenomas, a family history of CRC or adenomas diagnosed in any first-degree relative before age 50, or in two or more first-degree relatives diagnosed at any age (if not a hereditary syndrome). According to the ACS, individuals who have a personal history of CRC or adenomatous polyp require regular surveillance, not screening.

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 (Levin, et al., 2008):

- 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
- 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 (Levin, et al., 2008), the U.S. Preventive Services Task Force (USPSTF) and the NCCN strongly recommend the 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, 2013a; NCCN, 2013).

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.

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 that 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 (ACS 2013c). 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 (Levin, et al., 2008).

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 exanimation, 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, 2013c; Rex, 2006; NCCN, 2013). Choice of a 10-year interval between screening examinations for average-risk people (if the preceding examination is negative) is based on estimates of the sensitivity of colonoscopy and the rate at which advanced adenomas develop.

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).

Beginning at age 50, DCBE is included in the recommendations for screening in average-risk individuals (ACS, 2013c). 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.

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; Itzkowitz, 2010). 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., Kirstan rat sarcoma [K-ras] oncogene). Colorectal

neoplasms are varied in nature; however, no single mutation has been identified as being expressed universally. For this reason, multiple target assay panels currently being studied have the potential to attain higher detection rates than current screening methods. This test requires the entire stool specimen (30g minimum) to ensure an adequate sample of stool for evaluation (Levin, et al., 2008).

PreGen-Plus™ (EXACT Sciences Corporation, Maynard, MA; Laboratory Corporation of America [LabCorp], Burlington, NC), is no longer being marketed. This test has not received FDA premarket (PMA) approval. In Oct 2007, EXACT Science received a warning letter from FDA that states the FDA believes that the commercial PreGen-Plus assay is a medical device requiring pre-market approval or clearance (FDA, 2007).

ColoSure™ (Laboratory Corporation of America [LabCorp], Burlington, NC) is no longer commercially available. It is a fecal DNA test that utilizes a methylation-specific PCR and gel electropheresis technique to detect aberrant methylation in the vimentin gene. Aberrant methylation of exon-1 sequences within the nontranscribed region of the vimentin gene is associated with CRC.

There are currently no commercially available tests or tests that have received FDA clearance for stool-based DNA testing for colorectal cancer screening. There may be laboratories that perform this testing with in-house developed tests. These tests are not subject to FDA premarket approval, but are regulated by Clinical Laboratory Improvement Amendments (CLIA).

The joint guidelines from the ACS, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology (Levin, et al., 2008) include stool-based DNA testing as an acceptable option for CRC screening in their guidelines; however, it is noted that there is insufficient data to support this interval and further research is needed to determine the interval between negative tests. The appropriate interval for this testing is uncertain at this time. The ACS current guidelines that are published at their website, note that "Although stool DNA tests have been used for colorectal screening in the past, they are no longer available in the US." (ACS, 2013d).

Literature Review—Stool-Based DNA Testing: 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)/US Multi-Society Task Force on Colorectal Cancer (USMSTF)/American College of Radiology (ACR): Joint guidelines from these organizations for the screening and surveillance for the early detection of CRC and adenomatous polyps were published in 2008 (Levin, et al., 2008). The USMSTF includes representation from the American College of Gastroenterology (ACG), American Gastroenterological Association (AGA), and American Society for Gastrointestinal Endoscopy (ASGE). The guidelines focus on the needs of screening for average-risk adults. The screening tests for CRC fall into two general categories:

- Stool tests: 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 FOBT with high test sensitivity for cancer
  - Annual FIT with high test sensitivity for cancer

    - Stool DNA test with high sensitivity for cancer, interval uncertain
- 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
    - DCBE every five years
    - CTC every five years

Regarding the noninvasive fecal testing the guidelines make the following comments:

- Collection of fecal samples for blood or DNA testing can be performed at home, without bowel preparation.
- Limitations and requirements of these noninvasive tests include:
    - These tests are less likely to prevent cancer compared with the invasive tests.
    - These tests must be repeated at *regular* intervals to be effective.
    - If the test is abnormal, an invasive test (colonoscopy) will be needed.
- If patients are not willing to have repeated testing or have colonoscopy if the test is abnormal, these programs will not be effective and should not be recommended.

The guidelines note that colon cancer prevention should be the primary goal of CRC screening. The testing that is intended to detect both early cancer and adenomatous polyps should be encouraged if patients are willing to undergo an invasive test. These tests include colonoscopy, sigmoidoscopy, DCBE and CTC. These tests require bowel preparation, an office or hospital visit and involve various levels of risk to patients. In regards to sigmoidoscopy, DCBE, and CTC, if there are significant positive findings a colonoscopy will be required.

American Cancer Society (ACS)/US Multi-Society Task Force on Colorectal Cancer (USMSTF): These organizations published joint consensus guidelines for colonoscopy surveillance after cancer resection (Rex, et al., 2006; Brooks, et al., 2008). These guidelines include the following:

- Patients with colon and rectal cancer should undergo high quality perioperative clearing. In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, CTC with intravenous contrast or double contrast barium enema can be used to detect neoplasms in the proximal colon. In these cases, a colonoscopy to clear the colon of synchronous disease should be considered 3 to 6 months after the resection if no unresectable metastases are found during surgery. Alternatively, colonoscopy can be performed intraoperatively.
- Patients undergoing curative resection for colon or rectal cancer should undergo a colonoscopy 1 year after the resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease). This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors.
- If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years.
- Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of hereditary nonpolyposis CRC or if adenoma findings warrant earlier colonoscopy.
- Periodic examination of the rectum for the purpose of identifying local recurrence usually performed at 3- to 6-month intervals for the first 2 or 3 years, may be considered after low anterior resection of rectal cancer. The techniques utilized are typically rigid proctoscopy, flexible proctoscopy, or rectal endoscopic ultrasound. These examinations are independent of the colonoscopic examinations described above for detection of metachronous disease.

American Cancer Society (ACS): in addition to the above recommendations for colonoscopy surveillance after polypectomy and colonoscopy surveillance after cancer resection patients, the ACS includes the following screening and surveillance recommendations for increased- and high-risk individuals (ACS, 2013c):
Increased risk—patients with a family history:

- CRC or adenomatous polyps in any first-degree relative before age 60, or in two or more first-degree relatives at any age (if not hereditary syndrome): colonoscopy age at age 40, or 10 years before the youngest case in the immediate family, whichever is earlier

- CRC or adenomatous polyps in any first-degree relative aged 60 or higher, or in at least 2 second-degree relatives at any age: surveillance starting at age 40, with same options and same interval as for those at average risk.

High risk:

- FAP diagnosed by genetic testing or suspected FAP without genetic testing: flexible sigmoidoscopy to look for signs of FAP starting at age 12
- HNPCC, or at increased risk of HNPCC based on family history without genetic testing: start at age 20 to 25 years, or 10 years before the youngest case in immediate family; colonoscopy every one to two years
- Inflammatory bowel disease (i.e., chronic ulcerative colitis, Crohn's disease): colonoscopy every one to two years with biopsies for dysplasia

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 Gastroenterology (ACG): ACG published guidelines for CRC screening which includes the following recommendations (Rex, et al., 2009)**:**

Preferred CRC screening recommendations:

- Cancer prevention tests should be offered first. The preferred CRC prevention test is colonoscopy every 10 years, beginning at age 50. (Grade 1B*) Screening should begin at age 45 years in African Americans (Grade 2C*)
- Cancer detection test. This test should be offered to patients who decline colonoscopy or another cancer prevention test. The preferred cancer detection test is annual FIT for blood (Grade 1B*)

Alternative CRC prevention tests:

- Flexible sigmoidoscopy every 5–10 years (Grade 2B*)
- CT colonography every 5 years (Grade 1C*)

Alternative cancer detection tests:

- Annual Hemoccult Sensa (Grade 1B*)
- Fecal DNA testing every 3 years (Grade 2B*)

Recommendations for screening when family history is positive but evaluation for HNPCC considered not indicated:

- Single first-degree relative with CRC or advanced adenoma diagnosed at age ≥ 60 years–recommended screening: same as average risk (Grade 2B*)
- Single first-degree with CRC or advanced adenoma diagnosed at age < 60 years or two first-degree relatives with CRC or advanced adenomas–recommended screening: colonoscopy every 5 years beginning at age 40 years or 10 years younger than age at diagnosis of the youngest affected relative (Grade 2B*)

FAP:

- Patients with known FAP or who are at risk of FAP based on family history (and genetic testing has not been performed) should undergo annual flexible sigmoidoscopy or colonoscopy, as appropriate, until such time as colectomy is deemed by physician and patient as the best treatment (Grade 2B*)
- Patients with retained rectum after subtotal colectomy should undergo flexible sigmoidoscopy every 6–12 months (Grade 2B*)

HNPCC:

- Those with positive genetic testing, or those at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every 2 years beginning at age 20 – 25 years, until age 40 years, then annually thereafter (Grade 2B*)

*Grading recommendations
1A: Strong recommendation, high-quality evidence
1B: Strong recommendation, moderate quality evidence
1C: Strong recommendation, low-quality or very low-quality evidence
2A: Weak recommendation, high-quality evidence
2B: Weak recommendation, moderate quality evidence
2C: Weak recommendation, low-quality or very low-quality evidence

American Society of Clinical Oncology (ASCO): ASCO recommends additional surveillance for follow-up after primary therapy for stage II and III CRC based on the outcomes of three meta-analyses reviewed from 1999 to 2005 (Desch, et al., 2005). The ASCO panel surveillance guidelines include the following:

- Computed tomography (CT) — annual of the chest and abdomen for three years after primary therapy for patients who are at higher risk of recurrence and who could be candidates for surgery with curative intent.
- Pelvic CT —should be considered for rectal cancer surveillance, especially for patients who have not been treated with radiation.
- Colonoscopy —at three years after operative treatment; if results normal, every five years thereafter
- Flexible proctosigmoidoscopy —every six months for five years for rectal cancer patients who have not been treated with radiation

Institute for Clinical Systems Improvement (ICSI): ICSI (2010a) published updated guidance for the screening of CRC, based on a review of the current literature. CRC screening is recommended for average-risk patients 50 years of age and older, age 45 and older for African Americans, using one of the following methods, based on joint decision-making by patient and provider:

- Stool testing:
  - Guaiac-based fecal occult blood testing (gFOBT) annually
  - Fecal immunochemical testing (FIT) annually
  - Stool DNA testing (sDNA) interval unknown
- 60 cm flexible sigmoidoscopy every five years with or without stool test for occult blood annually
- Double-contrast barium enema every five years
- CT colonography every five years
- Colonoscopy every 10 years

National Comprehensive Cancer Network® (NCCN®): The NCCN Colorectal Cancer Screening Clinical Practice Guidelines™ include recommendations for screening and surveillance (NCCN, 2013). Average-risk individual, age 50 or greater, with no personal history of adenoma or inflammatory bowel disease and a negative family history should have screening with one of these modalities:

- Guaiac-based or immunohistochemical-based testing annually.
- Flexible sigmoidoscopy (60 centimeter scope or longer)–every five years
- Colonoscopy–every 10 years. Available evidence suggests that colonoscopy may be the preferred method.

The guidelines include the following:

- Stool DNA test: while it has been shown that there is increasing evidence as a reasonably accurate screening test, there is limited data to determine a screening interval. This testing is not considered a first line screening test.
- There is no consensus on the use of CTC as a primary screening modality and it is evolving with regards to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra-colonic lesions. The available data suggests, that if CTC is negative with no polyps, then CTC should be repeated in five years and if positive/polyps, colonoscopy should be performed.

The guidelines include recommendations for increased-risk individuals with personal history of adenoma(s)/sessile serrated polyp(s) (SSP) found at colonoscopy:

- Low risk adenoma (≤ 2 polyps, <1cm, tubular)–repeat colonoscopy within five years. If normal, then repeat every five to ten years. If positive/polyp, repeat depending on endoscopic and pathologic findings.
- Advanced or multiple adenomas (high-grade dysplasia/carcinoma in situ, larger than 1 cm, villous (>25% villous), between three and ten polyps–repeat colonoscopy within three years. If normal, then repeat within five years. If abnormal, repeat depending on endoscopic and pathologic findings.
- Incomplete or piecemeal polypectomy or polypectomy of large sessile polyps–repeat colonoscopy within 2–6 months (timing dependent on endoscopic and pathologic findings)

Increased-risk individual with personal history:

- Following curative intent resected CRC: follow-up with a colonoscopy after one year, (within three to six months if there was none or an incomplete preoperative colonoscopy):
  - Normal surgical pathology results: repeat colonoscopy in two to three years, then repeat colonoscopy in every three to five years based on findings
  - Adenoma/SSP findings: repeat colonoscopy in one to three years

Increased-risk Individual with personal history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) then colonoscopy performed every one to two years:

- when clinically quiescent, four quadrant biopsies every 10cm with >30 samples
- additional extensive sampling of strictures and masses
- endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia

Increased/high-risk screening based on positive family history:

- Positive family history of CRC:
  - Individuals with a first-degree relative (i.e., full sibling, parent, child) age <50 years with CRC, or two first-degree relatives with CRC at any age—colonoscopy should begin at age 40 or 10 years before earliest diagnosis of CRC and repeat colonoscopy every three to five years depending on individual family history.
  - Individuals with a first-degree relative with CRC ≥50 years—colonoscopy should begin at age 50 or 10 years before earliest diagnosis of CRC and repeat colonoscopy every five years
  - Individual with one second degree relative with CRC <50 years—colonoscopy should begin at age 50 and repeat colonoscopy per colonoscopy findings.
  - First-degree relatives with advanced adenoma— colonoscopy should begin at age 50 or age of onset, whichever is first, then repeat colonoscopy per colonoscopy findings.

- Personal or inherited risk of polyposis syndromes:
  - Family history of familial adenomatous polyposis (FAP):
    - Individual is a genetic carrier:
      - annual flexible sigmoidoscopy or colonoscopy, beginning at age 10 to 15
    - Genetic status is unknown:
      - annual flexible sigmoidoscopy or colonoscopy, beginning at age 10 to 15, until age 24 then:
      - repeat every two years until age 34
      - repeat every three years until age 44
      - then every three to five years thereafter
    - Individual is not a carrier: average-risk screening should occur

  - Family history of attenuated FAP (AFAP):
    - Individual is a genetic carrier:
      - annual colonoscopy beginning in late teens, then every two to three years
    - Genetic status is unknown:
      - colonoscopy every two to three years beginning in late teens; if adenomas are found, annual colonoscopy
    - Individual is not a carrier: average-risk screening should occur

- For MYH-associated polyposis (MAP):
    - Unaffected family member and family mutation known; with biallelic MUTYH mutation positive or not tested:
        - Begin colonoscopy at age 25–30, and then every two to three years if negative.
        - Consider upper endoscopy and side viewing duodenoscopy starting at age 30-35 years
    - For personal history of MAP with small adenoma burden: colonoscopy and polypectomy every one to two years.

- For Lynch syndrome:
    - MLH1 and MSH2 mutation carriers (Lynch syndrome): colonoscopy age 20 to 25, or 2-5 years prior to the earliest colon cancer if it is diagnosed before age 25 years and repeat one to two years
    - MSH6 and PMS2 mutation carriers (Lynch syndrome): colonoscopy age 30-35 years and every two to three years and then after age 40, every one to two years.

US Multi-Society Task Force on Colorectal Cancer (USMSTF): The USMSTF updated their 2008 consensus guidelines for colonoscopy surveillance after polypectomy (Lieberman, et al., 2012; Brooks, et al., 2008; Winawer, et al., 2006). The organization is comprised of three gastroenterology professional organizations: American College of Gastroenterology, American Gastroenterological Association Institute, and American Society for Gastrointestinal Endoscopy. The report includes statements that summarize new, relevant literature since 2005. This is followed by recommendations for surveillance based on the most advanced finding of the baseline colonoscopy examination. The guidelines note that there are no high-quality randomized controlled trials of polyp surveillance performed in the past 6 years. All studies are either retrospective or prospective observational, cohort, population-based, or case-control studies. The organizations utilized a rating of evidence that relies on expert consensus about whether new research is likely to change the confidence level of the recommendation*. The guidelines include the following recommendations:

- No polyps: recommended surveillance interval is ten years. Moderate quality of evidence, stronger than found in 2006.
- Small rectal hyperplastic polyps (<10mm): recommended surveillance interval is ten years. No change in recommendation, moderate evidence.
- One to two small (<10 mm) tubular adenomas: next follow-up colonoscopy in 5 to 10 years. Moderate quality of evidence, stronger than found in 2008.
- Three to ten tubular adenomas: next follow-up colonoscopy in three years. Moderate quality of evidence, stronger than found in 2006.
- More than 10 adenomas: should be examined at a shorter (<3 years) interval established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome. Moderate evidence.
- One or more tubular adenomas ≥10 mm: recommended surveillance internal three years. High level of evidence, stronger than found in 2006.
- One or more villous adenomas: recommended surveillance internal three years. Moderate level of evidence, stronger than found in 2006.
- Adenoma with high-grade dysplasia (HGD): recommended surveillance internal three years: moderate level of evidence.
- Serrated lesions:
    - Sessile serrated polyp(s) <10mm with no dysplasia: recommended surveillance internal five years: low level of evidence.
    - Sessile serrated polyp(s) ≥10 mm, sessile serrated polyp with dysplasia, or traditional serrated adenoma: recommended surveillance interval three years: low level of evidence.
- Serrated polyposis syndrome: recommended surveillance interval one year: moderate level of evidence.

*Rating of evidence and impact of potential further research:
High quality: Very unlikely to change confidence in the estimate of effect
Moderate quality: Likely to have an important impact on confidence and may change estimate of effect
Low quality: Very likely to have an important impact on 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, 2008, Whitlock, et al., 2008). The recommendations include the following findings:

- For fecal occult blood testing, flexible sigmoidoscopy, and colonoscopy to screen for colorectal cancer, there is high certainty that the net benefit is substantial for adults age 50 to 75 years.
- For adults, age 76 to 85 years, there is moderate certainty that the net benefits of screening are small.
- For adults older than age 85 years, there is moderate certainty that the benefits of screening do not outweigh the harms.
- There is insufficient evidence to assess the sensitivity and specificity of fecal DNA testing for colorectal neoplasia, and that therefore the balance of benefits and harms cannot be determined for this test.
- For CTC, evidence to assess the harms related to extracolonic findings is insufficient, and the balance of benefits and harms cannot be determined.

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.

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, 2009). Confocal refers to the alignment of both illumination and collections systems in the same focal plane. Confocal endomicroscopy based on tissue fluorence 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.

Chromoendoscopy, or chromoscopy, involves staining of mucosa with dyes, frequently methylene blue or indigo carmine, to enhance the superficial structure of lesions. 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).

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: 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 man 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.

Brown et al. (2010) conducted a Cochrane review to determine whether the use of chromoscopy enhances detection of polyps and neoplasia during endoscopic examination of the colon and rectum. Secondary endpoints examined the implications of chromoendoscopy in terms of extra time taken to perform the procedure properly and potential increased morbidity of more biopsies. The review included five prospective, randomized trials that

compared chromoscopic with conventional endoscopic examination of the lower gastrointestinal tract and excluded studies with inflammatory bowel disease or polyposis syndromes. Although there were some methodological drawbacks and differences in study design, the study found that combining the results showed a significant difference in favor of chromoscopy for all detection outcomes. In particular, it was found that chromoscopy is likely to yield significantly more patients with at least one neoplastic lesion and significantly more patients with three or more neoplastic lesions. The withdrawal times were significantly slower for the chromoscopy group.

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: 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 WTO 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.

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 met-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 trail). 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
In an update to joint consensus guidelines for colonoscopy surveillance after polypectomy, the US Multi-Society Task Force on Colorectal Cancer (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) published a technology status evaluation report regarding narrow band imaging (NBI). In the report, it is noted that NBI may enhance the diagnosis and characterization of mucosal lesions in the GI tract, in particular as an adjunct to magnification endoscopy; however, standardization of image characterization, further image pathology correlation and validation, and the impact of these technologies on patient outcomes are necessary before endorsing the use of NBI in the routine practice of gastrointestinal endoscopic procedures (ASGE, 2008).

The ASGE published a report on emerging technology regarding confocal laser endomicroscopy (ASGE, 2009). The report notes that this method is an examiner-dependent technology and the interobserver and intraobserver variability of the technique has not been adequately studied. The review notes that, “In recent years, confocal laser endomicroscopy rapidly moved from the bench to the bedside. It is being analyzed as a potentially valuable addition to conventional endoscopy as a means of in vivo optical biopsy enabling real-time histological examination of the superficial layer of the GI tract. How this will affect the practice of screening, surveillance, and early diagnosis of benign, premalignant, and malignant lesions of the GI tract requires further study.”

The ASGE published a technology status evaluation report regarding chromoendoscopy (ASGE, 2007). The report notes that, “Chromoendoscopy is inexpensive, safe, and relatively easy to perform, although the method is not standardized for several stains and the staining patterns are subject to observer interpretation. There is a need to build consensus on the staining techniques and terminology of the mucosal patterns for most applications, in addition to proving efficacy and reproducibility in high-quality, randomized, controlled trials before chromoendoscopy can be incorporated into routine clinical practice.”

Summary for In Vivo Analysis of Colorectal Polyps: Due to insufficient published studies involving these technologies within the peer-reviewed published literature, the use as an adjunct to colonoscopy remains unproven.

Methylated Septin 9 Testing
Methylated Septin 9 is a plasma-based blood test intended to detect circulating methylated DNA from the SEPT9 gene. The test has been proposed as a biomarker for CRC and that it has potential for use in CRC screening. It is suggested by the vendors that a physician may order the test for screen-eligible patients who have previously avoided established CRC screening methods. It is theorized that a patient whose test is positive may be at risk for CRC and further evaluation may be considered. According to a vendor, Quest Diagnostics, the test is 70% sensitive for CRC detection at specificity of 89%. Several case-control studies have indicated that detection of SEPT9 may be a biomarker for CRC (Toth, et al., 2012; Warren, et al., 2011; Tanzer, et al., 2010; deVos, et al., 2009; Grutzman, et al., 2008). There is a need for these findings to be confirmed in larger studies, along with studies that evaluate the clinical utility of this test.

Methylated septin 9 testing is available from several laboratories including but not limited to the following:

- Abbott RealTime mS9 Colorectal Cancer assay (Abbott Laboratories. Abbott Park, Illinois)
- Colovantage™ (methylated Septin 9) (Quest Diagnostics, Madison, NJ)
- Septin 9 (SEPT9), Methylated DNA Detection by Real-Time PCR (ARUP Laboratories, Salt Lake City, Utah)

ColonSentry
ColonSentry® (Innovative Diagnostic Lab, Richmond, VA) is a test that measures the expression of seven gene biomarkers in the blood that are proposed to be early warning signs of colon cancer. The risk for colorectal cancer then calculated based on the expression of these genes. There is insufficient evidence to demonstrate the clinical utility of this test for colon cancer screening.

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

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.

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

Singapore Ministry of Health: The Singapore Ministry of Health published guidelines for cancer screening. Regarding colorectal cancer screening, the guidelines include (2010):

- For average-risk individuals, screening for colorectal cancer has been shown to improve survival and is recommended. Grade A, Level 1^{++}
- For average-risk individuals, screening for colorectal cancer should begin at age 50 years. Grade B, Level 2^{++}
- For individuals at increased risk or high risk, screening by colonoscopy is indicated. Grade B, Level 2^{++}

1^{++}: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
2^{++}: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

Grade A: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1^{++} and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
Grade B: A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1^{++} or 1^{+}

Summary
Detection and removal of polyps through colorectal cancer (CRC) screening provides an opportunity to reduce the occurrence of CRC. In addition, early detection of CRC can provide an opportunity for reducing the case fatality rate of those individuals with previously undetected CRC. The American Cancer Society (ACS), American College of Gastroenterology (ACG), American Society of Colorectal Surgeons (ASCR), American Society for Gastrointestinal Endoscopy (ASGE), National Cancer Institute (NCI), National Comprehensive Cancer Network (NCCN) and the U.S. Preventative Services Task Force (USPSTF), and the US Multi-Society Task Force on Colorectal Cancer all support age- and risk-appropriate population screening for the early detection of CRC. The literature and patient morbidity and mortality measures support the ongoing use of preventative screening, early diagnosis and close surveillance of individuals for CRC.

Due to the lack of well-designed, randomized controlled trials within the published peer-reviewed literature, there is insufficient evidence to support the use of in vivo analysis of colorectal polyps (e.g., chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, and confocal fluorescent endomicroscopy), methylated Septin 9 testing, stool-based deoxyribonucleic acid (DNA) testing for the screening, diagnosis or surveillance of colorectal cancer.

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

Covered when medically necessary:

CPT®* Codes	Description
45330	Sigmoidoscopy, flexible; diagnostic, with or without collection of specimen(s) by brushing or washing
45331	Sigmoidoscopy, flexible with biopsy, single or multiple
45338	Sigmoidoscopy, flexible with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
45339	Sigmoidoscopy, flexible with ablation of tumor(s), polyp(s), or other lesions(s) not amenable to removal by hot forceps, bipolar cautery or snare technique
45378	Colonoscopy, flexible, proximal to splenic flexure; diagnostic, with or without collection of specimen(s) by brushing or washing, with or without colon decompression (separate procedure)
45380	Colonoscopy, flexible, proximal to splenic flexure; with biopsy, single or multiple
45381	Colonoscopy, flexible, proximal to splenic flexure; with directed submucosal injection(s), any substance
45383	Colonoscopy, flexible, proximal to splenic flexure; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
45384	Colonoscopy, flexible, proximal to splenic flexure; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
45385	Colonoscopy, flexible, proximal to splenic flexure; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
74263	Computed tomographic (CT) colonography, screening including image postprocessing
74270	Radiologic examination, colon; barium enema, with or without KUB
74280	Radiologic examination, colon; air contrast with specific high density barium, with or without glucagon
82270	Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces 1-3 simultaneous determinations
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

Stool-Based Deoxyribonucleic Acid (DNA) Testing

Experimental/Investigational/Unproven/Not Covered:

HCPCS Codes	Description
S3890	DNA analysis, fecal, for colorectal cancer screening

In Vivo Analysis of Colorectal Polyps

Experimental/Investigational/Unproven/Not Covered 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
45999	Unlisted procedure, rectum

Methylated Septin 9 Testing

Experimental/Investigational/Unproven/Not Covered when used to report methylated Septin 9 testing (e.g. ColoVantage™):

CPT®* Codes	Description
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • SEPT9 (Septin 9) (eg, colon cancer), methylation analysis

ColonSentry

Experimental/Investigational/Unproven/Not Covered when used to report ColonSentry:

CPT®* Codes	Description
81479	Unlisted molecular pathology procedure

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