MEDICAL POLICY

Medical Policy Title	**Colorectal Cancer Screening and Surveillance**
Policy Number	**2.01.51**
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Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. **ANY** of the following colorectal cancer (CRC) screening modalities are considered **medically necessary** for average-risk individuals aged 45 years or older:

- A. Colonoscopy every ten (10) years;
- B. Flexible sigmoidoscopy every five (5) years;
- C. Screening computed tomography colonography (CTC)/virtual colonoscopy every five (5) years (CPT 74263);
- D. High-sensitivity guaiac fecal occult blood test (gFOBT) annually;
- E. Fecal immunochemical test (FIT) annually;
- F. Multitarget stool DNA test (sDNA-FIT/mt-sDNA) (i.e., Cologuard and Cologuard Plus) every one (1) to three (3) years.

II. A diagnostic CT colonography (CTC)/virtual colonoscopy is considered **medically appropriate** for CRC screening or surveillance of individuals at increased/higher risk of CRC (see Policy Guidelines) when the following criteria is met:

Diagnostic CTC without contrast (CPT 74261):

- A. Failed conventional colonoscopy due to known colonic lesion, structural abnormality, or technical difficulty; **or**
- B. Conventional colonoscopy is medically contraindicated (e.g., coagulopathy, intolerance to sedation, aged 80 years of age or older, or recent [within the last 60-days] myocardial infraction [MI]).

Diagnostic CTC with contrast (CPT 74262):

- C. There is a known obstructing colorectal malignancy so that staging prior to surgery can be performed, if desired; **or**
- D. There is a clearly stated indication for intravenous (IV) contrast to evaluate extra-colonic organs.

III. Any other testing modality for CRC screening or surveillance is considered **investigational,** including but not limited to:

A. Blood-based marker testing and/or gene expression profiling (e.g., methylated DNA [e.g., Epi proColon, ColoVantage], cell-free DNA [e.g., Shield], cell-free RNA, microRNA, messenger RNA, ColonSentry, BeScreened-CRC);

B. Urine-based testing (e.g., metabolite biomarker [e.g., PolypDX], microRNA);

C. Stool-based protein marker or molecular genetic testing, other than Cologuard or Cologuard Plus (e.g., ColoSense, CRCbioscreen);

D. Capsule endoscopy (refer to Corporate Medical Policy #6.01.27).

IV. The following adjunct endoscopic techniques are considered **investigational,** including:

A. Chromoendoscopy (also known as chromoscopy and chromocolonoscopy);

B. Narrow band imaging;

C. Confocal laser endomicroscopy (also known as confocal fluorescent endomicroscopy and optical endomicroscopy;

D. Fiberoptic analysis.

RELATED POLICIES

Corporate Medical Policy

2.02.60 Germline Genetic Testing for Hereditary Cancers

6.01.27 Capsule Endoscopy, for colon capsule endoscopy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. Colonoscopy is indicated if a noninvasive screening test result is abnormal (positive).

II. The U.S. Preventive Services Task Force (USPSTF) and the National Comprehensive Cancer Network (NCCN) recommend that people at average risk for CRC should undergo routine CRC screening as follows:

A. Begin screening at age 45 years and continue to age 75 years.

B. For ages 76 through 85 years, routine CRC screening is individualized and should include a discussion of the risks and benefits based on comorbidity status.

III. The NCCN Colorectal Cancer Screening Clinical Practice Guidelines (v.1.2024 February 27, 2024) recommend that individuals at an increased or higher risk of CRC begin screening at a younger age and at more frequent time intervals.

IV. Individuals at increased or higher risk of CRC include those with any of the following:

A. A personal history of colorectal cancer, adenomatous polyps, or SSP/SSL (sessile serrated polyp, sessile serrated lesion, sessile serrae adenoma are all synonymous);

B. A personal history of childhood, adolescent, or young adult cancer treated with

chemotherapy and/or radiation therapy;

C. A personal history of inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease);

D. A personal history of Cystic fibrosis;

E. A strong family history of colorectal cancer or polyps (Please refer to Description section); or

F. A personal or known family history of a hereditary colorectal cancer syndrome (i.e., polyposis syndromes [e.g., familial adenomatous polyposis (FAP), Peutz-Jeghers, juvenile polyposis, Cowden syndrome/PTEN hamartoma tumor syndrome], hereditary non-polyposis CRC [HNPCC, Lynch syndrome]).

V. NCCN (v.1.2024) recommended screening modality and schedule intervals for individuals at average risk of colorectal cancer:

Screening Test	**Recommended Testing Interval**
Colonoscopy	Every 10 years
Flexible sigmoidoscopy	Every 5 years to 10 years
CT colonography (also known as virtual colonoscopy)	Every 5 years
High-sensitivity guaiac fecal occult blood test (gFOBT)	Annually
Quantitative fecal immunochemical (FIT) (using OC-Sensor)	Annually
Quantitative fecal immunochemical (FIT) (using OC-Light)	Annually
Multi-targeted stool DNA test (mt-sDNA, sDNA-FIT)	Every 1-3 years

VI. Screening CTC (CPT 74263) for colorectal cancer is not indicated if FIT-DNA (multi-targeted stool DNA test) within the last 3 years, or colonoscopy within the last 10 years. A diagnostic CTC would be the appropriate code, if approvable, for any other reason than average risk screening. This would include surveillance for a history of colon polyps, the evaluation of a change in bowel habits, abdominal pain, bleeding, etc.

VII. CT Colonography is routinely performed without contrast, and intravenous (IV) contrast is not needed in most cases.

DESCRIPTION

Colorectal cancer (CRC) is a leading cause of cancer in both men and women in the United States. CRC screening testing is one of the most powerful strategies for identifying pre-cancer or cancer in people with no signs or symptoms. Since a colorectal polyp can take 10 to 15 years to develop into

colorectal cancer, regular screening can prevent some cases of colorectal cancer by finding and removing certain types of polyps before they can turn into cancer. Screening can also help find colorectal cancer early, when it is small, has not spread, and is easier to treat.

There are several testing options for CRC screening, divided into two main groups: stool-based tests and direct visualization exams. For individuals at increased risk, colonoscopy is the preferred method. Blood-based and urine-based testing is being investigated as screening options to detect CRC.

Colonoscopy

Colonoscopy is a screening modality that can detect colorectal polyps and cancer. A colonoscopy requires a full bowel preparation. A flexible tube with a tiny camera is inserted through the anus. The inside of the rectum and colon can be viewed for polyps, cancer, and diseases. The colonoscope is about four feet in length and allows the entire colon to be visualized. The exam takes about 30 minutes, and sedation may be necessary. Tissue samples and polyps may be removed and sent to the lab, to determine whether the specimen is cancerous. Although colonoscopy is considered the reference standard against which the sensitivity of other colorectal cancer screening tests is compared, complications from the procedure may occur. There may be some discomfort and bloating from the air that is used to inflate the colon during the procedure. There is also potential for the colonoscope to injure the intestinal wall, causing perforation, infection, or bleeding, although this is rare.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy is another screening modality that can detect colorectal polyps and cancer. A lighted endoscope with a tiny camera is passed through the rectum and lower part of the colon, allowing the operator to visualize the sigmoid and descending colon on a small monitor screen. The sigmoidoscope is approximately two feet long; consequently, only the lower colon can be visualized. Bowel preparation is necessary prior to the test, which usually takes about 10 to 20 minutes and can be performed without sedation. Small polyps or tissue samples may be removed and sent to the lab to determine whether the specimen is cancerous.

Computed Tomography Colonography (CTC)/ Virtual Colonoscopy

CTC is a non-invasive imaging technique for examination of the colonic lumen. The test involves the generation of both two-dimensional and three-dimensional views of the colon and rectum using data derived from helical computed tomography, involving thin-section helical CT to generate high-resolution two-dimensional axial images of the colon. Two- or three-dimensional images, which resemble the endoluminal images obtained with conventional endoscopic colonoscopy, are then reconstructed offline. Virtual colonoscopy has been investigated as an alternative to conventional endoscopic colonoscopy specifically as an alternative screening technique for colon cancer.

While CTC requires a full bowel preparation like conventional colonoscopy, no sedation is required, and the examination is less time-consuming. Gas insufflation of the intestine, which may be uncomfortable to the patient, is required, and interpretation of the images is a separate process. When polyps are detected with CTC, treatment requires that the patient undergoes a subsequent endoscopic colonoscopy, which may require another bowel preparation.

Multi-Targeted Stool Deoxyribonucleic Acid (DNA) or Ribonucleic Acid (RNA) Test

Several cellular genetic alterations have been associated with colorectal cancer. Since cancer cells are shed into stool, tests have been developed that detect these genetic alterations in the DNA or RNA from shed colorectal cancer cells isolated from stool samples. Gene mutations that characterize colorectal neoplasia are detectable in exfoliated epithelial cells in the stool. Whereas neoplastic bleeding is intermittent, epithelial shedding is continual, potentially making fecal DNA or RNA testing more sensitive than other methods for screening.

The currently available stool DNA test combines FIT and DNA analysis, also referred to as FIT-DNA, stool DNA (sDNA)-FIT and multitarget stool DNA (mt-sDNA). The currently available stool RNA test combines FIT and RNA analysis, also referred to as FIT-RNA, stool RNA (sDNA)-FIT and multitarget stool DNA (mt-sDNA).

Fecal Occult Blood Test (FOBT) Guaiac-Based (gFOBT) and Immunochemical (FIT)

Guaiac FOBT uses a chemical to detect heme, a component of the blood protein hemoglobin. One major disadvantage of gFOBT is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. Another limitation is the high false-positive rate resulting from reaction with non-human heme in food and blood from the upper GI tract. To compensate for these limitations, gFOBT should be performed on three successive stool specimens while the patient adheres to a prescribed diet.

Fecal immunochemical test (FIT) also direct detects human globin within hemoglobin. Unlike guaiac FOBT, FIT does not require dietary restrictions, and a single testing sample is sufficient.

Blood-Based Biomarker Tests

Blood-based biomarker tests designed to detect and measure specific gene mutations, methylation of genes, and antigens. Serum biomarkers that are shed from colorectal tumors have been identified and include Septin9 (SEPT9) hypermethylated DNA. The Septin 9 protein is involved in cell division, migration, and apoptosis and acts as a tumor suppressor; when hypermethylated, expression of SEPT9 is reduced.

Blood serum testing for colorectal cancer screening is currently available, including, but not limited to testing to detect methylated Septin9 DNA (e.g., ColoVantage and Epi proColon 2.0); multi-modal approaches to detect circulating tumor DNA (e.g., Shield, Guardant Health); the BeScreened-CRC which tests for three cancer-related blood-based proteins; and to assess the expression of genes to calculate relative risk of having colorectal cancer (e.g., seven-gene test ColonSentry). Galleri (GRAIL) is a multi-cancer early detection (MCED) test currently being investigated to analyze a blood sample to determine if a cancer signal is detected and, if so, to predict the origin of the cancer. The Galleri test does not detect all cancers and should be used in addition to routine cancer screening tests.

Urine-Based Testing

The purpose of screening tests for urinary markers in asymptomatic individuals is to detect disease at an earlier stage than it would present otherwise when treatment would permit improved outcomes. The availability of a noninvasive test for precancerous polyps could improve referral for colonoscopy and early detection of colon cancer.

PolypDx (Metabolomic Technologies) is a non-invasive urine-based test developed to detect colorectal cancer and adenomatous colon polyps, which are precursors to colorectal cancer. The test is a urine metabolite essay that uses an algorithm to compare urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps.

In-Vivo Adjunctive Procedures

Several real-time endoscopic procedures are being investigated as options for in vivo analysis of polyps to enhance the sensitivity of colonoscopy, including the analysis of lesions in the colon. These additional imaging methods include, but not limited to, chromoendoscopy, narrow band imaging, confocal microscopy, and fiberoptic analysis.

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

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

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows in vivo microscopic imaging of cells during endoscopy It is proposed for a variety of purposes, especially as a real-time alternative to biopsy/polypectomy and histopathologic analysis during colonoscopy and for targeting areas to undergo biopsy in patients with inflammatory bowel disease or Barrett esophagus. The process uses light from a low-power laser to illuminate tissue and, subsequently, the same lens detects light reflected from the tissue through a pinhole. The term confocal refers to having both illumination and collection systems in the same focal plane. Light reflected and scattered at other geometric angles that are not reflected through the pinhole is excluded from detection, which dramatically increases the resolution of CLE images.

SUPPORTIVE LITERATURE

Colonoscopy

In the 2021 USPSTF Updated Evidence Report and Systematic Review, two large prospective observational studies evaluated the association of obtaining a screening colonoscopy with CRC incidence or mortality. After 24 years of follow up, the one study amongst health professionals

(88,902) found that CRC specific mortality rate was lower when one self-reported colonoscopy was reported versus those who had never had a screening colonoscopy (adjusted hazard ratio 0.32 [95% CI, 0.24-0.45]). This study found that screening colonoscopies were associated with lower CRC mortality from both distal and proximal cancers. The other study, which was completed with Medicare beneficiaries (348,025), with shorter follow up found that people aged 70-74 years who underwent a screening colonoscopy had a lower 8-year standardized risk of CRC versus those who did not test. There is also more data on colonoscopy harms demonstrating higher estimates of major bleeding than previously described in 2016.

Flexible Sigmoidoscopy

Evidence from RCTs and meta-analyses have demonstrated that flexible sigmoidoscopy reduces the incidence of and mortality from CRC (NCCN 2024). Compared to colonoscopy, sigmoidoscopy requires no sedation and less bowel preparation but is limited to examination of the distal colon.

In the USPSTF's Updated Evidence Report and Systematic Review (2021), the same four randomized control trials from the 2016 review were used. While three of the four trials have published longer term follow up, the conclusion drawn from the new data did not change the conclusions related to screening effectiveness. There were 22 studies (n=5.4 million people) that reported serious bleeding complications in people receiving screening colonoscopies, the pooled estimate was 14.6 bleeds per 10,000 procedures.

CT Colonography (CTC)/Virtual Colonoscopy

CT colonography (CTC) has been investigated as an alternative to conventional endoscopic colonoscopy. It has been most widely studied as an alternative screening technique for colon cancer, and for the diagnosis of CRC in people with related symptoms and for other colorectal conditions. Based on current evidence, a colon cancer screening strategy using CTC is likely to produce outcomes like those with optical colonoscopy.

For individuals who are asymptomatic and undergoing CRC screening with CTC, the evidence includes systematic reviews with meta-analysis, randomized and nonrandomized controlled trials, and modeling studies. The available evidence supports the conclusion that the diagnostic accuracy of CTC is in the same range or slightly below optical colonoscopy, with a moderate-to-high sensitivity and ahigh specificity for the detection of larger polyps and CRC. As a result, screening with CTC may provide similar diagnostic results to screening using conventional optical colonoscopy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Results of available studies indicate CTC can have relatively high sensitivity and specificity for detection of cancerous colorectal lesions that are at least 6-10 mm in diameter, with lower sensitivity for precancerous, smaller, and flat lesions. The sensitivity of CTC in published studies is heterogeneous, varying widely, but improving as polyp size increases. CTC specificity in published studies is homogeneous, also improving as polyp size increases. CTC does not allow for removal of lesions during the procedure, as can be done during conventional colonoscopy.

Johnson and colleagues (2008) published results from an interventional, screening, open-label trial of 2,600 participants who had a CTC followed by their scheduled colonoscopy, showed that, for large

adenomas and cancers, the mean (±SE) per-patient estimated sensitivity, specificity, positive and negative predictive values, and area under the receiver-operating-characteristic curve for CT colonography were 0.90±0.03, 0.86±0.02, 0.23±0.02, 0.99±<0.01, and 0.89±0.02, respectively. The sensitivity of 0.90 (i.e., 90%) indicated that CT colonography failed to detect a lesion measuring 10 mm or more in diameter in 10% of patients. The per-polyp sensitivity for large adenomas or cancers was 0.84±0.04. The per-patient sensitivity for detecting adenomas that were 6 mm or more in diameter was 0.78. These findings support and extend previously published data regarding the role of CT colonography in screening patients with an average risk of colorectal cancer.

Weinberg and colleagues (2018) compared CTC versus optical colonoscopy in 231 patients undergoing screening at 1 year post curative surgery for CRC. All patients underwent CTC followed by optical colonoscopy. Compared with optical colonoscopy, CTC had a sensitivity of 44% and specificity of 85.8% for detecting lesions (all types) 6 mm or larger and a sensitivity of 76.9% and specificity of 89% for detection lesions (all types) 10 mm or larger. For serrated adenomas, CTC had a sensitivity of 60% and specificity of 76% for sizes 6 mm or larger and a sensitivity of 75% and specificity of 75.3% for sizes 10 mm or larger. The results with CTC were significantly different from the null hypothesis of 90% for sensitivities to detect all lesions or serrated adenomas 6 mm or larger and for specificities for serrated adenomas of all sizes (p<.05 for all comparisons).

Sali and colleagues (2022) compared CTC (n=5242) and 3 rounds of fecal immunochemical testing (n=9739) in patients aged 54 to 65 years who had never been previously screened for CRC. Each fecal immunochemical test was separated by 2 years. Rates of participation in the screening intervention were similar between CTC (26.7%) and patients who had all 3 rounds of fecal immunochemical testing (33.4%). The primary outcome was the detection rate for advanced neoplasia. Advanced CRC was detected more commonly with fecal immunochemical testing than CTC (2.0% vs. 1.4%; p=.0094) in the modified intent to treat population. The detection rate was higher in the CTC group than the fecal immunochemical testing group (5.2% vs. 3.1%; p=.0002) in the per protocol population. Referral for workup colonoscopy was less common among patients who underwent CTC than fecal immunochemical testing in the intention to treat population (2.7% vs. 7.5%; p<.0001).

Fecal Occult Blood Test (FOBT): Guaiac-Based (gFOBT) and Immunochemical (FIT)

In the USPSTF's Updated Evidence Report and Systematic Review (2021), there were six well-conducted trials (n = 780 458) of biennial or annual gFOBT screening that demonstrated a reduction in CRC incidence and mortality. Based on 5 RCTs (n = 419,966) that used intention-to-screen analyses, biennial screening with Hemoccult II (Beckman Coulter) was associated with a reduction of CRC-specific mortality compared with no screening after 2 to 9 rounds of screening at 11 to 30 years of follow-up (relative risk [RR], 0.91 [95% CI, 0.84-0.98] at 19.5 years; RR, 0.78 [95% CI, 0.65-0.93] at 30 years). One additional trial of screening with Hemoccult II in Finland (n = 360 492) reported only interim findings, with a follow-up of 4.5 years.

The prospective diagnostic accuracy of FIT was evaluated by six qualitative and seven quantitative studies. In studies with colonoscopy follow-up for all, FIT sensitivity varied considerably across assays for each outcome. OC-Light had the highest sensitivity and specificity for CRC, from 88% and 91%, respectively, to 79% and 93%, respectively. OC FIT-CHEK had the best sensitivity and specificity for

CRC, from 73% and 96%, respectively, to 92% and 87%, respectively. Variation in test performance resulted from the use of 18 different FITs (FIT families), different numbers of stool samples, and, to some extent, different assay cut-off values. Sparse data on most individual tests limited comparisons.

Multi-Targeted Stool DNA Test

The 2021 USPSTF recommendations for colorectal cancer screening state that multi-targeted stool DNA testing (sDNA-FIT) is an emerging screening strategy that combines a FIT with testing for altered DNA biomarkers in cells shed into the stool. Multi-targeted stool DNA testing has increased single-test sensitivity for detecting colorectal cancer, compared with FIT alone. The harm of stool-based testing primarily results from adverse events associated with follow-up colonoscopy of positive findings. The specificity of FIT-DNA is lower than that of FIT alone, which means that it has a higher number of false-positive results and higher likelihood of follow-up colonoscopy, thereby increasing the likelihood of experiencing an associated adverse event per screening test. There is insufficient evidence about the appropriate longitudinal follow-up for an abnormal FIT-DNA test result followed by a negative colonoscopy; however, there is potential for overly intensive surveillance due to clinician and patient concerns about the implications of the genetic component of the test.

Cologuard

A large-scale evaluation of FIT-DNA (Cologuard) in a screening population was published by Imperiale and colleagues (2014), who compared FIT-DNA with colonoscopy in 12,000 asymptomatic adults between the ages of 50 and 84 years (mean age, 64 years) at average risk for CRC. The results of this study supported the initial FDA approval of this FIT-DNA test (Cologuard. All enrolled subjects were scheduled to undergo a screening colonoscopy. Stool specimens were collected and tested no more than 90 days before the screening colonoscopy. Screening colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of FIT-DNA for detecting CRC and cancer precursors. In 9,989 subjects, sensitivity for detecting CRC was 92.3% with FIT-DNA and 73.8% with FIT ($p<0.0001$). For detection of advanced precancerous lesion, FIT-DNA test sensitivity was 42.4% and FIT sensitivity was 23.8%. In analyses of specific types of lesions, the sensitivity of FIT-DNA did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of FIT-DNA testing was higher for distal lesions than for proximal lesions. FIT-DNA sensitivity increased as lesion size increased. The specificity of FIT-DNA was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, the specificity of FIT-DNA was 86.6% and 94.9% for FIT. For identification of patients only with negative colonoscopy, specificity of FIT-DNA was 89.8% and 96.4% for FIT. The authors concluded that in asymptomatic persons at average risk for CRC, multi-target stool DNA testing detected significantly more cancers than did FIT but had more false-positive results.

Imperiale and colleagues (2023) published a longitudinal cohort study evaluating a 3-year interval for the multitarget stool DNA test (mt-sDNA) for CRC screening. Participants enrolled in the study had a valid baseline mt-sDNA result (N=2044); those with a negative baseline test (n=1760) were followed up to 3 years and asked to undergo repeat mt-sDNA testing and colonoscopy. Patients contributed to the baseline intention to screen (ITS) analysis population if they were mt-sDNA positive at baseline and had an evaluable colonoscopy result or if they were mt-sDNA negative at baseline, had a valid mt-sDNA test result at year 3, and evaluable colonoscopy result. Following attrition, the ITS cohort at

year 3 included 591 of 1,760 patients with valid mt-sDNA and colonoscopy results; 122 of these patients were mt-sDNA positive. The Predictive Summary Index (PSI) year 3 value for CRC was 0% (p=1); the PSI for advanced precancerous lesions was 9.3% (two-sided p=.01). The observed 3-year colorectal cancer yield was lower than expected (one-sided p=.09), while the yield for advanced precancerous lesions was higher than expected (two-sided p=.009). The detection of advanced precancerous lesions increased and was statistically significant after repeat mt-sDNA screening at a 3-year interval.

A systematic review and meta-analysis conducted by Dolatkhah and colleagues (2022) assessed the sensitivity and specificity of FIT-DNA compared to colonoscopy. Data were pooled from 11 studies and outcomes evaluated were detection of CRC and any precancerous lesions. The meta-analyses of FIT-DNA found a combined sensitivity of 89%, 51%, and 76% for the detection of CRC, advanced adenoma, and combined CRC and advanced adenoma, respectively. The overall specificity was 91%, 89%, and 90% for the detection of CRC, advanced adenoma, and combined CRC and advanced adenoma, respectively. The sensitivity and specificity of FIT-DNA, while indicating its diagnostic accuracy, were lower than colonoscopy for CRC and diagnosis of advanced adenoma.

Cologuard Plus

Imperial and colleagues (2024) reported results of the pivotal study (BLUE-C) on the next generation multi-target stool DNA (mt-sDNA) test, Cologuard Plus. This prospective industry-sponsored study evaluated the next generation mt-sDNA test in asymptomatic adults 40 years of age or older who were undergoing screening colonoscopy. Of the 20,176 participants, CRC was detected in 98 participants (0.5%), of whom 82 (84%) had stage I, II, or III disease. The most advanced findings were advanced precancerous lesions in 2144 participants (10.6%), nonadvanced adenomas in 6973 (34.6%), nonneoplastic findings in 3451 (17.1%), and negative results on colonoscopy in 7510 (37.2%). Among 2144 participants with advanced precancerous lesions, the next-generation mt-sDNA test was positive in 931, for a sensitivity of 43.4%. Comparing the next-generation mt-sDNA test with the FIT, the next-generation test had higher sensitivity detecting CRC and advanced precancerous lesions ($p<0.0001$) but had lower specificity for advanced neoplasia ($p<0.0001$). The authors concluded that this new version of the test was more sensitive than a commercial FIT for all screening-relevant lesions, but FIT had higher specificity. The authors noted that this study did not directly compare the performance of the next-generation mt-sDNA test with the current version of the mt-sDNA test; therefore, results from this study cannot be reliably compared with published findings for the mt-sDNA test that is currently available for screening purposes, and valid comparisons would require the assessment of both tests in the same persons and specimens concurrently in the context of screening.

Multi-Targeted Stool RNA Test

Barnell and colleagues (2023) reported results of the pivotal, blinded, prospective, cross-sectional study (CRC-PREVENT) of the multi-target stool RNA (mt-sRNA) test, Colosense. The study compared the sensitivity and specificity of mt-sRNA test results, which incorporated a commercially availability FIT, with colonoscopy results from 8,920 study participants who were identified through an online social media platform from 2021 to 2022. Stool samples were collected prior to participants completing a colonoscopy at 3,800 different endoscopy centers. The mt-sRNA test showed

comparable levels of sensitivity for colorectal cancer (94%) and advanced adenomas (46%) relative to the mt-sDNA test (92% for colorectal cancer and 42% for advanced adenomas) for individuals 50 years or older, and a significant increase in sensitivity for colorectal neoplasia for individuals younger than 50 years (p = .04). Study limitations include the use of a decentralized clinical trial for participant recruitment, center-to-center variations in colonoscopy quality metrics, difference in participant treatment (e.g., bowel preparation), and high dropout rate of participants. The authors concluded that the mt-sRNA test can be an effective noninvasive test that is sensitive for colorectal cancer and advanced adenomas, with a comparable level of false-positive results compared with existing molecular screening tests.

Blood-Based Biomarker Tests

Early detection of CRC reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy. A simpler screening blood test may have the potential to encourage screening and decrease mortality if associated with increased screening compliance. However, there is insufficient clinical evidence to determine the effects of these technologies on health outcomes.

The 2021 USPSTF recommendations for colorectal cancer screening specifically indicates that the recommendation does not include serum-based tests for colorectal cancer screening due to limited available evidence on these tests, that other effective tests are available, and additional more research is needed on the accuracy and effectiveness of emerging screening technologies such as serum-based tests.

Epi proColon was studied in an international prospective screening study, PRESEPT (Church 2014). Of 1516 patients selected for laboratory analysis, colonoscopy identified 53 (3%) patients with invasive adenocarcinoma, 315 (21%) with advanced adenoma, and 210 (14%) with nonadvanced adenoma. Sensitivity for any adenoma was 48% and advanced adenoma was 11%. Authors concluded that the mSEPT9 test showed that CRC signal in blood can be detected in asymptomatic average risk individuals undergoing screening. However, the authors noted that the utility of the test for population screening for CRC will require improved sensitivity for detection of early cancers and advanced adenomas.

Methylated SEPT9 biomarker testing underwent a systematic review and meta-analysis (Hariharan and Jenkins 2020). Pooled data from 19 studies found that the mSEPT9 test has high specificity (92%) and moderate sensitivity (69%) for CRC; however, the mSEPT9 test is limited by its poor diagnostic performance for precancerous lesions (advanced adenomas and polyps) and is more expensive.

Chung and colleagues (2024) conducted an industry-sponsored study to assess the performance characteristics of the Shield (Guardant Health), a cell-free DNA (cfDNA) blood-based test for colorectal cancer screening. Of the 7,861 average-risk screening participants who met eligibility criteria and were evaluable, the authors reported that the Shield (Guardant Health) cfDNA blood-based test had 83% sensitivity for the detection of CRC, 90% specificity for advanced neoplasia, and 13 % sensitivity for advanced pre-cancerous lesions. The false positive rate of the Shield blood-based test was 10.1%. The authors noted evaluating these percentages in the real-world setting will be

important to understand population effect, and that future studies to understand the effect of longitudinal testing on sensitivity for advanced neoplasia warrant consideration.

Urine-Based Testing

The clinical data supporting a urine metabolite assay for adenomatous polyps involves a report of a training and validation set. There is insufficient evidence on the diagnostic accuracy of urinary tumor markers to draw conclusions about its use to screen asymptomatic individuals for precancerous colon polyps.

Deng and colleagues (2017) reported on the development and validation of PolypDx. PolypDx (Metabolomic Technologies) is a urine metabolite assay that uses an algorithm to compare urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps. Urine and stool samples were prospectively collected from 695 individuals participating in a colorectal cancer screening program to undergo colonoscopy. Metabolites in urine that were associated with adenomatous polyps were determined from 67% of the samples using nuclear magnetic resonance spectroscopy. Blinded testing on the validation set was performed in 33% of the samples using mass spectrometry, with a resulting area under the curve of 0.692. No direct evidence on clinical utility was identified.

The 2021 USPSTF recommendations for colorectal rectal screening tests specifically indicate that the recommendation does not include urine-based tests for colorectal cancer screening due to limited available evidence on these tests, that other effective tests are available, and additional more research is needed on the accuracy and effectiveness of emerging screening technologies such as urine-based tests.

In-Vivo Adjunctive Procedures:

Chromoendoscopy

For individuals who have an average risk of CRC who receive chromoendoscopy, the evidence includes randomized controlled trials (RCTs) and a meta-analysis of these RCTs. The meta-analysis conducted by Antonelli and colleagues (2022) evaluated the efficacy of dye-based chromoendoscopy in detecting colorectal neoplasia. The analysis included 10 RCTs of individuals at average or increased risk of colon cancer undergoing conventional (standard or high-definition white light) colonoscopy, or colonoscopy with dye-based chromoendoscopy. Patients with IBD or genetic/familial syndromes were excluded. In patients at average or increased risk of colon cancer, the meta-analysis showed that dye-based chromoendoscopy increased adenoma detection rate by 20%, and adenomas per colonoscopy by 50%. Several RCTs included in the meta-analysis showed that the use of dye-based chromoendoscopy improved detection of colorectal neoplasia compared to conventional colonoscopy, but clinical outcomes were lacking. Limitations of the meta-analysis included unclear indication for use of colonoscopy in the studies and some heterogeneity in mean adenomas per patient. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome for colorectal cancer screening patients at average risk.

Virtual Chromoendoscopy

Desai and colleagues (2019) published a systematic review and meta-analysis that assessed the

adenoma miss rate of white-light colonoscopy compared with virtual chromoendoscopy (e.g., narrow-band imaging (NBI) Fujinon intelligent chromoendoscopy, blue-light imaging, linked-color imaging, and i-SCAN) in a total of 3507 patients from 7 eligible RCTs. Of these patients, 1423 underwent a white-light colonoscopy as the first of tandem examinations; the remaining patients underwent virtual chromoendoscopy first. Results revealed a pooled adenoma miss rate for virtual chromoendoscopy compared to white-light colonoscopy of 17.9% versus 21% (p=.13). Additionally, the pooled adenoma detection rate was not significantly different with virtual chromoendoscopy as compared to white-light colonoscopy (p=.78).

The available RCTs have not found that virtual chromoendoscopy improves the detection of clinically important polyps compared with standard white-light colonoscopy. Moreover, there is a lack of studies assessing the impact of virtual chromoendoscopy on CRC incidence and mortality rates compared with standard colonoscopy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PROFESSIONAL GUIDELINE(S)

Colonoscopy

NCCN Colorectal Cancer Screening Guidelines (v.1.2024) indicate that colonoscopy is the most commonly employed CRC screening procedure and is considered the gold standard for assessing the sensitivity of detecting neoplasia for other screening modalities. There are numerous case controls and cohort studies that support that a colonoscopy has the potential ability to prevent CRC associated morbidity and cancer deaths. Per NCCN, the general consensus is that a 10-year interval is appropriate for most average-risk individuals who had a high-quality normal colonoscopy, defined as an exam complete to the cecum with bowel preparation adequate to detect polyps greater than 5 mm in size. And, if a colonoscopy is incomplete or preparation is suboptimal, consider either repeating colonoscopy within a year or screening with another modality.

The American College of Gastroenterology (ACG) Clinical Guidelines for Colorectal Cancer Screening 2021 (Shaukat 2021) recommends colonoscopy and fecal immunochemical testing (FIT) as the primary screening modalities for CRC screening [strong recommendation; low quality] and suggests consideration of flexible sigmoidoscopy, multitarget stool DNA test, CT colonography, or colon capsule [conditional recommendation; very low quality].

Multi-Targeted Stool DNA Test

The NCCN Colorectal Cancer Screening Guidelines (v.1.2024) recommend the inclusion of multi-target stool DNA test (mt-sDNA or sDNA-FIT) as a potential screening modality in patients with an average risk for colon cancer. Following a negative test, the recommendation is to rescreen with any modality in 3 years. Use of sDNA-FIT is not described for the screening of high-risk individuals.

Multi-Targeted Stool RNA Test

To date, the use of multi-targeted stool RNA testing for colorectal cancer screening is not recommended within any professional clinical guidelines (e.g., NCCN, American College of Gastroenterology) or the USPSTF.

Fecal Occult Blood Test (FOBT): Guaiac-Based (gFOBT) and Immunochemical (FIT)

The NCCN Colorectal Cancer Screening Guidelines (v.1.2024) indicate that there is direct evidence from randomized control that FOBT reduces CRC incidence and mortality by detecting precancerous polyps at an early, curable stage.

Urine-Based Testing

To date, the use of urine metabolite assay for colorectal cancer screening is not recommended within any professional clinical guidelines (e.g., NCCN, American College of Gastroenterology).

Blood-Based Biomarker Tests

The NCCN Colorectal Cancer Screening Guidelines V.1.2024 acknowledges that blood-based tests have been evaluated under the emerging options of the screening modalities section. NCCN maintains the earlier position that, based on current data, the panel concludes that the interval for repeat testing is unclear and NCCN will continue to review this strategy and monitor any new, emerging data.

The 2021 American College of Gastroenterology recommendations suggest against the use of Septin 9 for CRC screening; Conditional recommendation, very low-quality of evidence (Shaukat 2021).

The U.S. Multi-Society Task Force (MSTF) issued colorectal cancer screening recommendations suggesting that Sept9 not be used for colorectal cancer screening (Rex 2017). Stating that although the test appears to have higher sensitivity for late-stage compared with early-stage cancer, there are disadvantages including markedly inferior performance characteristics compared with FIT, including lower sensitivity for cancer, inability to detect advanced adenomas, and low cost-effectiveness relative to other screening tests.

REGULATORY STATUS

In 2021, the United States Preventive Services Task Force (USPSTF) issued recommendations for CRC screening: Grade A recommendation for all adults aged 50 to 75 years; Grade B recommendation for adults aged 45 to 49 years; Grade C recommendation for adults aged 76 to 85 years.

Based on the recommendation from the USPSTF, New York State signed into law as Chapter 739 of the Laws of 2022, a law requiring Health Plans issuing policies that cover physician office visits to cover colon cancer screenings, examinations, and laboratory tests in accordance with the recommendations of the American Cancer Society for colorectal cancer screening of average risk individuals ages 45 or older, at average risk for CRC.

Multi-Targeted Stool DNA Test

Cologuard (Exact Sciences, Madison, WI) was approved by the FDA on August 11, 2014. The test includes molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, β-actin, and an immunochemical assay for human hemoglobin.

Cologuard Plus (Exact Science, Madison, WI), the next generation multi-target stool DNA test, received FDA premarket approval on October 03, 2024. Cologuard Plus is a qualitative in vitro diagnostic test intended for the detection of colorectal neoplasia-associated DNA biomarker and for

the presence of occult hemoglobin in human stool. Results from the molecular and hemoglobin assays are integrated by the Exact Sciences Analysis Software to determine a positive, negative, or invalid result. The test is indicated to screen adults 45 years or older, who are at average risk for CRC, and is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Multi-Targeted Stool RNA Test

ColoSense (Geneoscopy, ST. Louis, MO) received FDA approval to market ColoSense in May 2024. ColoSense is a multi-target stool test that measures RNA and hemoglobin in human stool and is FDA indicated as a screening test for adults, 45 years of age or older, who are at average-risk for developing CRC. ColoSense is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Fecal Occult Blood Test (FOBT) Guaiac-Based (gFOBT) and Immunochemical (FIT)

Two types of FOBT are approved by the Food and Drug Administration (FDA) to screen for colorectal cancer: guaiac FOBT (gFOBT) and the fecal immunochemical (or immunohistochemical) test (FIT). With both types of FOBT, stool samples are collected by the patient using a kit, and the samples are returned to the doctor.

CT Colonography (CTC)/Virtual Colonoscopy

Reformatted software systems for interpretation of virtual colonoscopy have been approved by the FDA. One example is the Viatronix V3D-colon virtual colonoscopy system (Viatronix, Inc., Stonybrook, NY), which was cleared for marketing by the FDA via the Section 510(k) process on April 19, 2004, for use as a screening tool in detecting colon cancer.

Blood-Based Biomarker Tests

The first FDA-approved blood serum test for CRC screening was for the detection of methylated septin 9 (mSEPT9) DNA, Epi proColon (Epigenomics, Seattle, Wash). In 2024, the FDA approved a test to detect colorectal cancer derived alterations in cell-free DNA (cfDNA), Shield (Guardant Health, Palo Alto, CA). ColonSentry (Stage Zero Life Science) is a proprietary liquid biopsy (blood sample) test that uses advance gene expression (mRNA) technology to detect the expression of 7 genes found to be differentially expressed in individuals with CRC compared with controls. BeScreened-CRC (Beacon Biomedical) is a PCR assay blood-based test to detect 3 protein biomarkers for colorectal cancer screening. BeScreened-CRC is available for clinical use, and it does not require FDA clearance or approval. In late 2023, the FDA approved an Investigational Device Exemption clinical trial (NCT05155605) to evaluate the Galleri multi-cancer early detection test (GRAIL, Menlo Park, CA).

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
0002U (E/I)	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. (Includes PolypDx, Atlantic Diagnostic Laboratories, LLC, Metabolomic Technologies, Inc)
0091U (E/I)	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result. (Includes FirstSightCRC CellMax Life)
0163U (E/I)	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of three plasma or serum proteins (teratocarcinoma-derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas (BeScreened-CRC, Beacon Biomedical)
0421U (E/I)	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 8 RNA markers (GAPDH, SMAD4, ACY1, AREG, CDH1, KRAS, TNFRSF10B, and EGLN2) and fecal hemoglobin, algorithm reported as a positive or negative for colorectal cancer risk (Colosense, Geneoscopy)
0453U (E/I)	Oncology (colorectal cancer), cell-free DNA (cfDNA), methylation-based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA) (ColonAiQ, Breakthrough Genomics, Singlera Genomics, Inc) (Effective 07/01/24)
0464U	Oncology (colorectal) screening, quantitative real-time target and signal amplification, methylated DNA markers, including LASS4, LRRC4 and PPP2R5C, a reference marker ZDHHC1, and a protein marker (fecal hemoglobin), utilizing stool, algorithm reported as a positive or negative result (Cologuard Plus, Exact Sciences Laboratories, LLC, Exact Sciences Corporation) (Effective 07/01/24)
0496U (E/I)	Oncology (colorectal), cell free DNA, 8 genes for mutations, 7 genes for methylation by real time RT PCR, and 4 proteins by enzyme linked immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk (ColoScape PLUS, DiaCarta) (Effective 10/01/24)
0501U (E/I)	Oncology (colorectal), blood, quantitative measurement of cell- free DNA (cfDNA) (QuantiDNA Colorectal Cancer Triage Test, DiaCarta) (Effective 10/01/24)

Code	Description
0537U (E/I)	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, >2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative. (Shield, Guardant Health) (Effective 04/01/25)
0558U (E/I)	Oncology (colorectal), quantitative enzyme-linked immunoassay (ELISA) for secreted colorectal cancer protein marker (BF7 antigen), using serum, result reported as indicative of response/no response to therapy or disease progression/regression (e.g., IgoCheck) (effective 07/01/25)
44799 (*E/I)	Unlisted procedure, intestine *E/I when used to report chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, confocal fluorescent endomicroscopy.
45378	Colonoscopy, flexible; diagnostic, including collection of specimens(s) by brushing or washing, when performed (separate procedure)
45399 (*E/I)	Unlisted procedure, colon *E/I when used to report chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, confocal fluorescent endomicroscopy.
45999 (*E/I)	Unlisted procedure, rectum *E/I when used to report chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, confocal fluorescent endomicroscopy.
74261	Computed tomographic (CT) colonography, diagnostic, including image postprocessing; without contrast material
74262	Computed tomographic (CT) colonography, diagnostic, including image postprocessing; with contrast material(s) including non-contrast images, if performed
74263	Computed tomographic (CT) colonography, screening, including image postprocessing
81327 (E/I)	SEPT9 (Septin9) (e.g., colorectal cancer) promoter methylation analysis
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 (e.g., guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening

Code	Description
	(i.e., 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

Code	Description
G0104	Colorectal cancer screening; flexible sigmoidoscopy
G0105	Colorectal cancer screening; colonoscopy on individual at high risk
G0121	Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
G0327 (E/I)	Colorectal cancer screening; blood-based biomarker
G0328	Colorectal cancer screening; fecal occult blood test, immunoassay, one to three simultaneous determinations
G9936	Surveillance colonoscopy - personal history of colonic polyps, colon cancer, or other malignant neoplasm of rectum, rectosigmoid junction, and anus
G9937	Diagnostic colonoscopy

ICD10 Codes

Code	Description
C26.0-C26.9	Malignant neoplasm of other and ill-defined digestive organs (code range)
Z12.11	Encounter for screening for malignant neoplasm of colon

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SEARCH TERMS

Not applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Based on our review, computed tomographic (CT) colonography is not addressed in National or Regional Medicare coverage determinations or policies.

Colorectal Cancer Screening Tests (NCD 210.3) [accessed 2025 Feb 13]

Screening for Colorectal Cancer - Blood-Based Biomarker Tests (NCA, CAG-00454N) [accessed 2025 Feb 13]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

08/17/17, 05/17/18, 06/20/19, 08/20/20, 05/20/21, 08/19/21, 08/18/22, 10/19/23, 10/17/24,

03/20/25	
Date	**Summary of Changes**
03/20/25	• Off-cycle policy update, policy statements revised for Cologuard Plus to change from E/I to MN.
01/01/25	• Summary of changes tracking implemented.
08/17/17	• Original effective date