MEDICAL POLICY

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Medical Policy Title	**Colorectal Cancer Screening and Surveillance**
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Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.
(Link to Product Disclaimer)

POLICY STATEMENT(S)

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

- A. Colonoscopy every 10 years;
- B. Flexible sigmoidoscopy every 5 years;
- C. Computed tomography colonography (CTC; virtual colonoscopy) every 5 years (CPT, 74263);
- D. High-sensitivity guaiac fecal occult blood test (gFOBT) every year;
- E. High-sensitivity fecal immunochemical test (FIT) every year;
- F. Multi-target stool DNA (mt-sDNA) (e.g., Cologuard and Cologuard Plus, CPT 81528 and 0464U) every 1 to 3 years;
- G. Multi-target stool RNA (mt-sRNA) (e.g., Colosense, CPT 0421U) every 3 years;
- H. Blood-based (e.g., Shield, CPT 0537U; SimpleScreen CRC) test every 3 years when documentation confirms **both** of the following:
  1. The individual declines or has not completed one of the American Cancer Society (ACS)-preferred CRC screening tests listed above; **and**
  2. The individual has been informed that blood-based CRC screening has lower sensitivity for detecting advanced precancerous lesions and early-stage colorectal cancer than the preferred screening tests.

II. A diagnostic CTC is considered **medically appropriate** for CRC screening or surveillance of individuals at increased/higher risk of CRC (see Policy Guidelines) when the following criteria are 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 biomarker testing and/or gene expression profiling not approved by the U.S. Food and Drug Administration (FDA);

B. Stool-based biomarker testing not approved by the FDA;

C. Urine-based testing, including metabolite biomarker testing (e.g., PolypDX) and microRNA;

D. Colon capsule endoscopy (Refer to Corporate Medical Policy #6.01.27).

IV. The following adjunctive endoscopic technologies for CRC 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

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

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

II. CRC screening tests must be approved by the U.S. Food and Drug Administration (FDA).

III. The U.S. Preventive Services Task Force (USPSTF) recommends that adults at average risk for CRC undergo routine CRC screening as follows:

A. Begin screening at age 45 years and continue through age 75 years (Grade A and B);

B. For ages 76 through 85 years, CRC screening should be individualized and include a

discussion of the risks and benefits of each modality (Grade C);

C. Recommended screening strategies and frequency intervals include:
   1. High-sensitivity gFOBT every year;
   2. FIT every year;
   3. sDNA-FIT every 1 to 3 years;
   4. CT colonography every 5 years;
   5. Flexible sigmoidoscopy every 5 years;
   6. Flexible sigmoidoscopy every 10 years + FIT every year;
   7. Colonoscopy screening every 10 years.

IV. The American Cancer Society (ACS) CRC screening guideline recommends that people at average risk of developing CRC undergo regular screening as follows:
   A. Beginning at age 45 years through the age of 75 years, with individualized screening decision for ages 76 through 85 years.
   B. Preferred screening options include:
      1. Stool-based tests:
         a. High-sensitivity fecal immunochemical test every year;
         b. High-sensitivity guaiac-based fecal occult blood test every year;
         c. Multitarget stool DNA test (original or next-generation) every 3 years;
         d. Multitarget stool RNA test every 3 years.
      2. Direct visual examinations:
         a. Colonoscopy every 10 years;
         b. Computed tomography colonography every 5 years;
         c. Flexible sigmoidoscopy every 5 years.
   C. Non-preferred screening options:
      1. Blood-based tests - only for individuals who decline or have not completed one of the preferred CRC screening tests.
      2. Per ACS, blood-based tests have lower sensitivity than high-sensitivity stool-based tests and direct visual examinations in detecting advanced precancerous lesions and stage I colorectal cancers, limiting their effectiveness for reducing colorectal cancer incidence and mortality relative to the preferred options

V. The National Comprehensive Cancer Network (NCCN) (v.2.2026) recommended screening modality and frequency intervals for individuals at average risk of colorectal cancer:
   A. Colonoscopy every 10 years;

B. Flexible sigmoidoscopy every 5 to 10 years;

C. CT colonography every 5 years;

D. High-sensitivity guaiac fecal occult blood test (gFOBT) every year;

E. Quantitative fecal immunochemical (FIT) (using OC-Sensor or OC-Light) every year;

F. Multi-targeted stool DNA test (mt-sDNA, sDNA-FIT) every 1 to 3 years;

G. Multi-targeted stool RNA test (mt-sRNA) every 3 years;

H. Blood-based circulating free DNA (bb-cfDNA) every 3 years.

1. Per NCCN, given bb-cfDNA modest performance, particularly among advanced precancerous lesions, this test is only recommended for individuals who would not be willing to undergo screening through another modality.

VI. The NCCN Colorectal Cancer Screening Clinical Practice Guidelines (v.2.2026) recommends that individuals at increased or higher risk of CRC undergo earlier or more frequent screenings, with colonoscopy as the preferred screening method.

VII. 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 inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease);

C. A personal history of childhood, adolescent, or young adult cancer treated with chemotherapy and/or radiation therapy;

D. A personal history of Cystic fibrosis;

E. A family history of first-degree relatives with colorectal cancer or polyps; 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]).

VIII. 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.

IX. 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-related illness and death among both men and women in the United States. Screening is one of the most effective strategies for identifying

precancerous lesions or early-stage cancer in people who have no symptoms. Because colorectal polyps can take 10 to 15 years to progress into cancer, routine screening allows for the detection and removal of polyps before malignant transformation, thereby preventing some cases of CRC. Screening also increases the likelihood of diagnosing colorectal cancer at an early stage, when it is smaller, has not spread, and is more responsive to treatment.

There are several testing options for CRC screening, divided into two three main groups: stool-based tests, structural exams/direct visualization, and blood-based tests. For individuals at increased risk, colonoscopy is the preferred method. Urine-based tests are being investigated as screening options and not yet supported by professional guidelines.

Direct Visualization:

Colonoscopy

Colonoscopy is the most comprehensive screening modality and is widely regarded as the gold standard for detecting colorectal polyps, cancer, and other mucosal abnormalities. The procedure requires a full bowel preparation to allow adequate visualization. During the exam, a flexible tube with a miniature camera (a colonoscope) is inserted through the anus to visualize the rectum and the entire colon. Polyps or suspicious tissue can be removed or biopsied during the procedure and submitted for pathological evaluation. While generally safe, potential adverse events include transient discomfort/bloating due to insufflation and, rarely, perforation, bleeding, or infection

Flexible Sigmoidoscopy

Flexible sigmoidoscopy examines the distal colon (rectum, sigmoid, and descending colon) using a shorter endoscope. Bowel preparation is required (often less extensive than for colonoscopy), sedation is typically not needed, and small polyps or tissue samples may be removed for evaluation. Because the instrument is approximately two feet long, the proximal colon is not visualized.

Computed Tomography Colonography (CTC; Virtual Colonoscopy)

CTC is a noninvasive imaging technique that produces two- and three-dimensional views of the colonic lumen from thin-section helical CT data. It requires full bowel preparation, does not require sedation, and uses gas insufflation to distend the colon for image acquisition. If polyps are detected, a follow-up optical colonoscopy is required for removal, which may necessitate a repeat bowel preparation

Stool-Based Tests:

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

Guaiac-based FOBT detects the heme component of hemoglobin through a peroxidase reaction. Its limitations include susceptibility to dietary and medication interferences and lower sensitivity for intermittent or minimal gastrointestinal bleeding. Historically, gFOBT required multiple stool specimens and adherence to specific dietary restrictions to improve accuracy. In contrast, the fecal immunochemical test (FIT) detects human globin using antibody-based methods, eliminating most dietary restrictions and typically requiring only a single sample. Any positive stool-based screening result should be followed by diagnostic colonoscopy.

Molecular Stool Testing (DNA- and RNA-Based Biomarkers)

Colorectal neoplasia is associated with characteristic cellular genetic alterations. Because colorectal epithelial cells are shed continuously into stool, tests have been developed to detect DNA or RNA from these exfoliated cells. While neoplastic bleeding may be intermittent, epithelial shedding is constant, potentially making stool-based molecular assays more sensitive than blood-based or occult blood tests for detecting early lesions.

Multi-Targeted Stool Deoxyribonucleic Acid (mt-sDNA)

Multi-targeted stool deoxyribonucleic acid (mt-sDNA) test combines FIT with DNA analysis of multiple stool biomarkers associated with colorectal neoplasia. The test is approved by the Food & Drug Administration (FDA) and guideline-recognized as a screening option for average-risk adults, at recommended intervals. Abnormal results require follow-up diagnostic colonoscopy.

Multi-targeted stool ribonucleic acid (mt-sRNA) tests combine FIT with measurement of RNA transcript in stools that reflect gene expression patterns associated with colorectal neoplasia. In the pivotal CRC-PREVENT Phase 3 study (JAMA 2023), a specific mt-sRNA assay (ColoSense) demonstrated 94% sensitivity for CRC, 46% sensitivity for advanced adenomas, and 88% specificity for absences of lesions on colonoscopy in adults ≥45 years. Sensitivity for both colorectal cancer and advanced adenomas was significantly higher than FIT in paired testing: however, the study did not include direct comparisons with existing mt-sDNA tests.

Blood-Based Biomarker Tests:

Blood-based biomarker tests for CRC screening analyze biomarkers in peripheral blood to detect signals associated with colorectal neoplasia. These tests vary in their analytic approach, from single-biomarker assays to multi-analyte platforms that use artificial intelligence to detect DNA methylation patterns, fragmentation patterns, and genomic alterations.

The methylated Septin 9 (SEPT9) assay (Epi proColon; Epigenomics) is a blood-based screening test that detects methylation of the SEPT9 gene promoter. The SEPT9 gene encodes a protein involved in cell division and cytoskeletal organization that functions as a tumor suppressor. Hypermethylation of the SEPT9 promoter silences gene expression and is associated with colorectal carcinogenesis. The Epi proColon test uses real-time PCR to detect methylated SEPT9 DNA in plasma.

Cell-free DNA (cfDNA) refers to fragmented DNA circulating in the blood, released through normal cellular processes such as apoptosis and necrosis. A small fraction of cfDNA may be tumor-derived, known as circulating tumor DNA (ctDNA), which carries genetic and epigenetic alterations of the originating tumor. Newer cfDNA-based CRC screening tests analyze ctDNA-associated signals including methylation patterns, DNA fragmentation, and genomic alterations to detect colorectal neoplasia. Examples include Shield (Guardant Health) and SimpleScreen (Freenome).

Urine-Based Testing:

Urinary biomarker screening aims to identify colorectal cancer or advanced adenomas at an earlier stage than would occur through clinical presentation alone. A noninvasive test capable of detecting precancerous polyps could improve referral for colonoscopy and facilitate earlier intervention.

PolypDx (Metabolomic Technologies) is a non-invasive urine-based test developed to detect colorectal cancer and adenomatous polyps. The test measures specific urine metabolites and applies an algorithmic analysis to estimate the likelihood of colonic adenomatous polyps, which are known precursors to colorectal cancer.

In-Vivo Adjunctive Procedures

Several real-time endoscopic imaging techniques are being investigated to enhance lesion detection and support in vivo assessment of colorectal polyps. These adjunctive technologies aim to improve the sensitivity of colonoscopy beyond standard white-light imaging.

Chromoendoscopy, also known as chromoscopy and chromocolonoscopy, involves applying topical stains or dyes during endoscopy to enhance mucosal visualization and improve detection of subtle lesions, such as flat or depressed polyps. Dye is sprayed through a catheter passed via the endoscope's working channel. Chromoendoscopy may be performed pancolonically or targeted to specific lesions. This technique differs from endoscopic tattooing, which involves permanent pigment marking for future localization rather than transient mucosal staining.

Virtual (electronic) chromoendoscopy uses built-in endoscopy system algorithms to digitally alter reflected light wavelengths, enhancing mucosal contrast without dye application. One example is Fujinon Intelligent Color Enhancement (FICE), which digitally processes white-light images to highlight surface structures and vascular patterns.

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy or optical endomicroscopy, provides real-time, microscopic visualization of cellular structure during endoscopy. This technology uses low-power laser illumination and a confocal detection system to capture high-resolution images from the same focal plane, while excluding scattered light.
CLE is being evaluated as a potential tool for real-time "optical biopsy," lesion characterization, and targeted sampling, including in patients with inflammatory bowel disease or Barrett esophagus.

SUPPORTIVE LITERATURE

Colonoscopy

In the 2021 Updated Evidence Report and Systematic Review for the United States Preventive Services Task Force (USPSTF), two large prospective observational studies evaluated the association between screening colonoscopy and colorectal cancer (CRC) incidence and mortality (Lin 2021). After 24 years of follow-up, a study of 88,902 health professionals found lower CRC-specific mortality among individuals who self-reported at least one screening colonoscopy compared with those who had never undergone screening (adjusted hazard ratio, 0.32; 95% CI, 0.24–0.45). This study reported lower CRC mortality for both distal and proximal cancers.

Flexible Sigmoidoscopy

Evidence from RCTs and meta-analyses demonstrates that flexible sigmoidoscopy reduces both the incidence of and mortality from CRC. Compared to colonoscopy, sigmoidoscopy typically does not require sedation, involves less intensive bowel preparation, and is limited to examination of the distal colon. In the 2021 USPSTF Updated Evidence Report and Systematic Review, the same four RCTs

from the 2016 review were re-evaluated. Although three of these trials have reported longer-term follow-up, the additional data did not change the conclusions regarding screening effectiveness. Across 22 studies (n=5.4 million), serious bleeding complications after screening colonoscopy were reported at a pooled rate of 14.6 per 10,000 procedures.

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

In the USPSTF Updated Evidence Report and Systematic Review (2021), six well-conducted trials (n= 780,458) of annual or biennial gFOBT screening demonstrated reductions in CRC incidence and mortality. Across five RCTs (n = 419,966) using intention-to-screen analyses, biennial Hemoccult II (Beckman Coulter) reduced CRC-specific mortality compared with no screening after 2 to 9 screening rounds at 11-30 years of follow-up.

Prospective diagnostic accuracy of FIT was evaluated by six qualitative and seven quantitative studies. In cohorts with colonoscopy follow-up for all participants, 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 for many individual tests limited comparisons.

Multi-Targeted Stool DNA

The 2021 USPSTF recommendations describe sDNA-FIT as a stool-based strategy that combines FIT with assays for abnormal stool DNA biomarkers shed from colorectal neoplasia. sDNA-FIT offers higher single-test sensitivity for CRC than FIT alone; however, its lower specificity yields more false positives and therefore more follow-up colonoscopies, increasing exposure to procedure-related harms. Evidence for optimal longitudinal management after an abnormal sDNA-FIT followed by a negative colonoscopy remains insufficient, raising concern for potentially intensive surveillance triggered by the test's genetic component.

Cologuard – (mt-sDNA)

Imperiale et al (2014) conducted a large-scale evaluation of FIT-DNA (Cologuard) with colonoscopy in 12,000 asymptomatic average-risk adults between the ages of 50 and 84 years (mean age, 64 years).

The results of this study supported the initial FDA approval of Cologuard. All participants provided stool within 90 days prior to screening colonoscopy (reference standard). In 9,989 evaluable subjects, sensitivity for CRC was 92.3% with sDNA-FIT vs 73.8% with FIT ($p<0.0001$). For advanced precancerous lesions, sensitivity was 42.4% with sDNA-FIT vs 23.8% with FIT. Sensitivity did not differ by cancer stage or location; among advanced precancerous lesions, sensitivity was higher for distal than proximal lesions and increased with lesion size. Specificity was lower for sDNA-FIT than FIT: 86.6% vs 94.9% when "no significant lesions" and negative colonoscopy defined true negatives; 89.8% vs 96.4% when restricted to negative colonoscopy only. The authors concluded that sDNA-FIT detects more cancers than FIT but yields more false positives.

Imperiale et al (2023) published a longitudinal cohort study evaluating a 3-year screening interval for the mt-sDNA. Of 2,044 participants with a valid baseline result, 1,760 were negative and invited to repeat mt-sDNA and colonoscopy at year 3; 591 completed both (intention-to-screen cohort), of whom 122 were mt-sDNA positive. The year-3 Predictive Summary Index (PSI) was 0% for CRC (p=1) and 9.3% for advanced precancerous lesions (p=0.01). Observed 3-year CRC yield was lower than expected (p=0.09), while yield for advanced precancerous lesions was higher than expected (p=0.009), indicating increased detection of advanced precancerous lesions with repeat 3-year testing.

Dolatkhah et al (2022) conducted a systematic review and meta-analysis that pooled 11 studies and reported combined sensitivity of 89% for CRC, 51% for advanced adenoma, and 76% for the composite of CRC/advanced adenoma, with specificity of 91%, 89%, and 90%, respectively. These values were lower than colonoscopy for detecting CRC and advanced adenoma.

Cologuard Plus (mt-sDNA)

Imperial et al (2024) reported the pivotal BLUE-C study of the next generation mt-sDNA test (Cologuard Plus) in asymptomatic adults 40 years of age or older undergoing screening colonoscopy (n=20,176). CRC prevalence was 0.5% (98 cases; 84% stage I–III). Most advanced findings were advanced precancerous lesions (10.6%); nonadvanced adenomas (34.6%); nonneoplastic findings (17.1%); and negative colonoscopy (37.2%). Among 2,144 participants with advanced precancerous lesions, the next-generation mt-sDNA test was positive in 931 (sensitivity 43.4%). Compared with a commercial FIT, the next-generation test had higher sensitivity for CRC and advanced precancerous lesions (both p<0.0001) but lower specificity for advanced neoplasia (p<0.0001). The study did not directly compare the next-generation and current mt-sDNA tests within the same participants/specimens; therefore, cross-study comparisons to the currently marketed test are not definitive.

Multi-Targeted Stool RNA Test (mt-sRNA)

Barnell et al (2023) reported the pivotal, blinded, prospective, cross-sectional CRC-PREVENT study of an mt-sRNA test (ColoSense). The assay combined a commercial FIT, eight RNA transcripts, and smoking status, with colonoscopy as the reference standard. A total of 8,920 eligible participants aged ≥45 years were enrolled (stool collected before colonoscopy) across >3,800 U.S. endoscopy centers. Primary outcomes were sensitivity for CRC and advanced adenomas and specificity for absence of lesions on colonoscopy. The mt-sRNA test demonstrated 94% sensitivity for CRC and 46% for advanced adenomas, with specificity of 88% for no colonoscopic lesions; sensitivity for colorectal neoplasia was significantly higher among adults <50 years (p=0.04). Limitations included decentralized recruitment, variability in colonoscopy quality and bowel preparation, and high attrition. The authors concluded that mt-sRNA is a noninvasive option with sensitivity for CRC and advanced adenomas comparable to existing molecular stool tests and a similar false-positive profile.

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 CRC, as well as for evaluating symptomatic individuals and other colorectal conditions. Based on current evidence,

CTC-based screening strategy is likely to produce outcomes similar to those of optical colonoscopy (e.g., Johnson 2008; Weinberg 2018; Sali 2022). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Overall, diagnostic accuracy of CTC is in the same range or slightly below optical colonoscopy, with a moderate-to-high sensitivity and high 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. 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.

Blood-Based Biomarker Tests

Early detection of CRC reduces disease-specific mortality, but many individuals do not participate in recommended screening with stool-based tests or colonoscopy. A simplified blood-based screening test could potentially improve participation; however, current evidence is insufficient to determine whether these technologies improve clinical outcomes.

Epi proColon was studied in the international prospective screening study, PRESEPT (Church 2014). Of 1516 patients selected for laboratory analysis, colonoscopy identified 53 invasive cancers (3%), 315 advanced adenomas (21%), and 210 nonadvanced adenomas (14%). Test sensitivity was 48% for any adenoma and 11% for advanced adenomas. The authors concluded that while the mSEPT9 assay can detect CRC signals in asymptomatic, average-risk individuals, its sensitivity for early cancers and advanced adenomas is insufficient for population-level screening.

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.

Shield (Guardant Health) is a multi-target, blood-based CRC screening assay that analyzes cell-free DNA (cfDNA). Its performance characteristics were evaluated in ECLIPSE, an industry-sponsored, prospective study of 7,861 average-risk adults undergoing screening colonoscopy (Chung 2024). Reported results were 83.1% sensitivity for CRC, 89.6% specificity for advanced neoplasia (CRC or advanced precancerous lesions), and 13.2% sensitivity for advanced precancerous lesions. Among participants without advanced colorectal neoplasia, 10.4% had a positive cfDNA result (false positive). Among participants with negative colonoscopy (no CRC, advanced, or non-advanced precancerous lesions), specificity was 89.9%. Stage-grouped sensitivity for stage I–III CRC combined was 87.5%. Study limitations include industry sponsorship with sponsor involvement in design, analysis, and manuscript drafting; a small number of CRC cases (n=65); and single-round screening in an average-risk cohort with exclusions that may limit generalizability. The authors concluded that additional real-world and longitudinal studies are warranted.

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 their use to screen asymptomatic individuals for precancerous colon polyps.

Deng et al (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 et al (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 et al (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.2.2026) 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 2026 ACS Colorectal Cancer Screening Guideline Update continues to recommend colonoscopy every 10 years for average-risk adults beginning at age 45 years.

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 (mt-sDNA) Testing

NCCN Colorectal Cancer Screening Guidelines (v.2.2026) recommend the inclusion of 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.

The 2026 ACS Colorectal Cancer Screening Guideline Update recommended mt-sDNA (original and next generation) every 3 years as one of the preferred stool-based screening options for average-risk adults beginning at age 45 years.

Multi-Targeted Stool RNA (mt-sRNA) Testing

To date, mt-sRNA testing for CRC screening has not been included in the USPSTF recommendations.

In 2025, NCCN updated the Colorectal Cancer Screening Guidelines to include mt-sRNA-based testing as a recommended screening modality for average risk individuals. The guideline specifies that individuals with a positive mt-sRNA result should undergo diagnostic colonoscopy as soon as possible. NCCN (v.2.2025) cites clinical performance data demonstrating 46% sensitivity and 86% specificity for detecting advanced adenomas.

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

NCCN Colorectal Cancer Screening Guidelines (v.2.2026) indicate that there is direct evidence from RCTs 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 by the USPSTF or any professional clinical guidelines (e.g., NCCN, American College of Gastroenterology).

Blood-Based Biomarker Tests

In 2025, NCCN updated the Colorectal Cancer Screening Guidelines (v.2.2025) to include blood-based circulating tumor DNA (bb-ctDNA) testing as a screening modality every 3 years for average risk individuals who would not be willing to undergo screening through another modality in 2025. The current guideline (v.2.2026) emphasizes, given its modest performance in CRC detection, particularly among advanced precancerous lesions (13% sensitivity; 90% specificity), this test is only recommended for individuals who would not be willing to undergo screening through another modality.

The 2026 ACS Colorectal Cancer Screening Guideline Update included blood-based testing as a not preferred screening option due to lower sensitivity for advanced precancerous lesions (APLs) and stage I CRC compared with established stool-based tests, as well as uncertainty regarding optimal screening intervals for long-term effectiveness. The guideline recommends blood-based screening tests only for individuals who decline or have not completed a preferred CRC screening test.

The American Gastroenterology Association (AGA) 2025 Clinical Practice Update (Shaukat 2025) concluded that blood tests are acceptable for patients who decline all other forms of CRC. Additionally, although novel blood tests may improve participation in CRC screening, use of these novel tests could result in net harm if they are substituted for more effective screening tests.

In 2024, the American Society for Gastrointestinal Endoscopy (ASGE) issued a position statement on blood-based colorectal cancer screening recognizing the potential for the blood-based test to improve screening participation, particularly among those who are unwilling to undergo other screening modalities; however, blood test is not recommended as a first line screening tool. ASGE has determined that blood-based tests are inferior to established screening options (i.e., colonoscopy and stool-based tests) and recommends that blood-based tests should only be recommended for patients who are otherwise unwilling to get screened for CRC with colonoscopy or stool-based tests.

The 2021 USPSTF Colorectal Cancer Screening recommendations specifically exclude serum-based tests from endorsed CRC screening strategies due to limited evidence regarding their accuracy, clinical utility, and impact on outcomes. The USPSTF notes that additional research is needed for

emerging blood-based screening technologies.

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

REGULATORY STATUS

In 2021, the United States Preventive Services Task Force (USPSTF) issued graded recommendations for CRC screening tests (see Policy Guidelines): 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.

New York State law requires health plans that provide physician office services to cover colorectal cancer screenings, examinations, and laboratory tests in accordance with the recommendations of the American Cancer Society for colorectal cancer screening within 6 months of any updated recommendations.

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 biomarkers and for the presence of occult hemoglobin in human stools. 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 stools 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

Several blood-based tests have been developed for CRC screening; however, FDA approval has not been granted for all commercially available assays.

The first FDA-approved blood-based test for CRC screening was Epi proColon, detected methylated Septin 9 (mSEPT9) DNA. In 2024, the FDA approved Shield (Guardant Health, Palo Alto, CA), which detects colorectal cancer-associated alterations in circulating cell-free DNA (cfDNA). SimpleScreen CRC (Freenome, Brisbane, CA) received FDA approval in July of 2026 CRC screening in adults aged 45 years and older who are at average risk for the disease.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA).

Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. More information is available at: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia [accessed 2026 Jul 24]

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. (e.g., 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. (e.g., FirstSightCRC CellMax Life)
0163U (E/I)	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent

Code	Description
	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 (e.g., BeScreened-CRC, Beacon Biomedical)
0421U	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 (e.g., 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) (e.g., ColonAiQ, Breakthrough Genomics, Singlera Genomics, Inc)
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 (e.g., Cologuard Plus, Exact Sciences Laboratories)
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 (e.g., ColoScape PLUS, DiaCarta)
0501U (E/I)	Oncology (colorectal), blood, quantitative measurement of cell- free DNA (cfDNA) (e.g., QuantiDNA Colorectal Cancer Triage Test, DiaCarta)
0537U	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. (e.g., Shield, Guardant Health)
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

Code	Description
	(e.g., IgoCheck)
44388 - 44391, 44392, 44394, 44401 - 44408, 45378 - 45382, 45384 - 45386, 45388 - 45390	Colonoscopy, flexible; (code range)
44799 (*E/I)	Unlisted procedure, intestine (*E/I when used to report chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, confocal fluorescent endomicroscopy.)
45330 - 45335, 45338, 45349	Sigmoidoscopy, flexible; (code range)
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	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 (e.g., Cologuard)
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

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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	Colorectal cancer screening; blood-based biomarker
G0328	Colorectal cancer screening; fecal occult blood test, immunoassay, one to three simultaneous determinations

ICD10 Codes

Code	Description
Multiple Codes	

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Computed tomographic colonography (CTC) is not addressed in National or Regional Medicare coverage determinations or policies.

Colorectal Cancer Screening Tests (NCD 210.3) [accessed 2026 Jul 22]

Screening for Colorectal Cancer-Non-Invasive Biomarker Tests (NCA, CAG-00440R) [accessed 2026

Jul 22]

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, 03/19/26, 09/17/26

Date	Summary of Changes
09/17/26	• Off-cycle review, policy statements revised for blood-based screening tests to change from investigational to medically necessary when criteria are met.
03/19/26	• Annual review, policy statement revised for mt-sRNA to change from investigational to medically necessary.
03/20/25	• Off-cycle policy update, policy statements revised for Cologuard Plus to change from investigational to medically necessary**.**
01/01/25	• Summary of changes tracking implemented.
08/17/17	• Original effective date