MEDICAL POLICY

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MEDICAL POLICY DETAILS	
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Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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) 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 STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, including the recommendations of the National Comprehensive Cancer Network (NCCN), the United States Preventive Services Task Force (USPSTF), and the American Cancer Society (ACS), the following colorectal cancer (CRC) screening modalities are considered **medically necessary** for individuals aged 45 years or older, who are average risk for colon cancer:

Direct Visualization Screening Tests:
A. Colonoscopy every ten (10) years; or
B. *Flexible sigmoidoscopy every five (5) years; or
C. *Computed tomography colonography (CTC)/virtual colonoscopy every five (5) years (CPT 74263, *see Policy Statement III.);* or

Stool-based Screening Tests:
D. *Highly sensitive guaiac fecal occult blood test (gFOBT) annually; or
E. *Fecal immunochemical test (FIT) annually; or
F. *Multitarget stool DNA test (sDNA-FIT) (i.e., Cologuard) every one (1) to three (3) years.

* If the screening test result is abnormal (positive), then a colonoscopy should be performed to complete CRC screening**.**

II. Based upon our criteria and assessment of the peer-reviewed literature, a diagnostic CT colonography (CTC)/virtual colonoscopy has been medically proven to be effective and, therefore, is considered **medically appropriate** for CRC screening or surveillance of individuals at increased/higher risk of CRC (e.g., history of colon polyps, evaluation of a change in bowel habits, abdominal pain, bleeding, etc.) when **ANY** of the following criteria is met:

CTC without contrast (CPT 74261):
A. Failed conventional colonoscopy (e.g., due to known colonic lesion, structural abnormality, or technical difficulty); and/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]).

CTC with contrast (CPT 74262):

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

III. Based upon our criteria and assessment of the peer-reviewed literature, the following testing modalities have not been medically proven to be effective for CRC screening and/or surveillance; therefore, they are considered **investigational**:
A. Blood-based marker testing (e.g., SEPT9 methylated DNA testing [e.g., ColoVantage, Epi proColon, FirstSightCRC] and/or gene expression profiling [e.g., ColonSentry, BeScreened-CRC]);
B. Urine-based testing (e.g., PolypDX);
C. Any testing modality not addressed in this policy.

IV. Based upon our criteria and assessment of the peer-reviewed literature, the following real-time adjunct endoscopic techniques have not been medically proven to be effective for CRC screening and/or surveillance; therefore, they are considered **investigational**:
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.

Refer to Corporate Medical Policy #2.02.11 Genetic Testing for Inherited Susceptibility to Colorectal Cancer

Refer to Corporate Medical Policy #6.01.27 Wireless Capsule Endoscopy for Gastrointestinal Disorders

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES

I. The USPSTF (2021) and NCCN (2023) all 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 be based on overall health, prior screening history, and preferences.

II. Individuals at increased or higher risk of colorectal cancer (CRC) include those with **any** of the following:
A. A personal history of colorectal cancer or adenomatous polyps;
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]).

III. Recommended screening intervals for individuals at average risk:

Screening Modality	**Time Interval**

Guaiac fecal occult blood test (gFOBT) or Fecal immunochemical (FIT)	Annually
DNA analysis of stool samples using the Cologuard multi-targeted stool DNA test (sDNA-FIT)	Every 1- 3 years
Virtual colonoscopy (CT colonography)	Every 5 years
Flexible sigmoidoscopy	Every 5 years; or every 10 years plus FIT annually
Colonoscopy	Every 10 years

IV. The NCCN Colorectal Cancer Screening Clinical Practice Guidelines (v1.2023 – May 17, 2023), recommends that individuals at an increased or higher risk of CRC begin screening at a younger age and at more frequent time intervals.

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.

Several 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 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 testing more sensitive than other methods for screening.

In the proposed multistep model of carcinogenesis, the tumor suppressor gene p53 and the proto-oncogene KRAS are most frequently altered. Mutations in APC (Adenomatous polyposis coli) genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. Colorectal cancer is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability or MSI) in patients with hereditary nonpolyposis colorectal cancer (HNPCC) and in a subgroup of patients with sporadic colon carcinoma.

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. Guaiac FOBT uses a chemical to detect heme, a component of the blood protein hemoglobin. Because the gFOBT can also detect heme in some foods (e.g., red meat), people have to avoid certain foods before having this test. FIT uses antibodies to detect human hemoglobin protein specifically. Dietary restrictions are typically not required for FIT.

Blood-based Biomarker Tests

Blood tests designed to measure methylated DNA in circulating tumor tissue have been proposed as a method to screen for colorectal cancer or to detect disease recurrence. Gene expression testing in blood has also been investigated for colorectal cancer screening. 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: (1) the Methylated Septin9 DNA plasma assay test (ColoVantage and Epi proColon 2.0); (2) the BeScreened-CRC, which tests for three cancer-related, blood-based proteins; and seven-gene test (ColonSentry).

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.

RATIONALE

Colonoscopy

In the 2021 USPSTF's 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.

The National Comprehensive Cancer Network (NCCN) notes that colonoscopy is the most commonly employed CRC screening test and the gold standard for average and high-risk individuals. 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.

The American College of Gastroenterology Clinical Guidelines for Colorectal Cancer Screening 2021 (Shaukat et al., 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].

Flexible Sigmoidoscopy

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) 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. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. 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. Results from the National CT Colonography Trial, ACRIN-6664 (NCT00084929), which is 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.

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.

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. Guaiac

The USPSTF Final Recommendation Statement: Colorectal Cancer Screening (2021) stated that multi-targeted stool DNA testing (FIT-DNA) 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 are no empirical data on 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.

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.

The NCCN V.1.2023 guidelines note that there is direct evidence from randomized control that FOBT reduces CRC incidence and mortality by detecting precancerous polyps at an early, curable stage.

Blood-Based Biomarker Tests

The first FDA-approved blood serum test for CRC screening is the SEPT9 assay (Epigenomics, Seattle, Wash). Methylated Septin9 (mSEPT9) DNA plasma assay is a blood-based biomarker for CRC screening. In a large screening colonoscopy study, this test had a sensitivity of 48% for detection of CRC and 0% sensitivity for detection of precancerous polyps. The Sept9 assay has 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. The test appears to have higher sensitivity for late-stage cancer, compared with early-stage cancer. Therefore, the U.S. Multi-Society Task Force of Colorectal Cancer (MSTF) suggests that Sept9 not be used for colorectal cancer screening.

The USPSTF's (2021) colorectal cancer screening recommendations included a search for studies to include methylated SEPT9 DNA blood tests, but the task force concluded that there is limited evidence evaluating use of the test.

The NCCN Guidelines V.1.2023 maintains the earlier position that, based on current data, the interval for repeat testing is unclear. The NCCN will continue to review this strategy and monitor any new emerging data.

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

The Septin9 assay test has received FDA approval; however, as a laboratory developed test (LDT), under the Centers for Medicare and Medicaid Services' Clinical Laboratory Improvement Amendments (CLIA), BeScreened-CRC is available for clinical use, and it does not require FDA clearance or approval. BeScreened-CRC is a simple, blood-based, test for colorectal cancer screening. It is intended only for people 50-years of age or older who are at average risk for colorectal cancer or who are unable or unwilling to be screened by colonoscopy or fecal-based tests (with or without DNA). The panel tests three cancer-related, blood-based proteins that are combined into a single positive or negative result that indicates the potential presence of colorectal cancer or precancerous polyps.

The Epi proColon (mSEPT9 -DNA testing) test has emerged as another potential non-invasive option for the early detection of colorectal cancer. While the Epi proColon test is the only FDA-approved blood-based biomarker test for colorectal cancer screening, there are other blood-based tests in development using different biomarkers.

Overall, there is insufficient clinical evidence to determine the effects of these technologies on health outcomes, and, therefore, the USPSTF and the NCCN do not currently identify blood serum testing as a means for CRC screening. The 2021 American College of Gastroenterology recommendation suggests against the use of Septin9 for CRC screening; Conditional recommendation, very low-quality of evidence (Shaukat et al, 2021).

Urine-Based Testing

Deng et al (2017) reported on the development and validation of PolypDx. 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 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.

The USPSTF recommendation for screening for colorectal cancer does not include urine biomarker testing for colorectal cancer screening due to the limited available evidence on these tests and that other effective tests are available (USPSTF, 2021). The NCCN Guidelines V1.2023 for Colorectal Cancer Screening (2023) and the American College of Gastroenterology Colorectal Screening Clinical Guidelines (Shaukat et al, 2021) do not mention urine-best testing as a screening option for CRC.

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.

In-Vivo Adjunctive Procedures:

Chromoendoscopy

For individuals who have an average risk of CRC who receive chromoendoscopy, the evidence includes randomly controlled trials (RCTs) and a meta-analysis of these RCTs. The meta-analysis demonstrated that dye-based chromoendoscopy increased the adenoma detection rate and adenomas per colonoscopy in patients at average or increased risk of CRC, compared to standard or high-definition white light colonoscopy. However, limitations included unclear indication of colonoscopy in the studies (which included patients with screening and surveillance), 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.

Virtual Chromoendoscopy

For individuals who have an average and/or risk of CC who receive virtual chromoendoscopy, the evidence includes several RCTs and systematic reviews. 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.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

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 (Includes Colosense by Geneoscopy) (*Effective 01/01/24*) ***Refer to Policy Statement III.C**.*
45378	Colonoscopy, flexible; diagnostic, including collection of specimens(s) by brushing or washing, when performed (separate procedure)
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 (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
44799 **(*E/I)**	Unlisted procedure, intestine ***E/I when used to report chromoendoscopy, fiberoptic polyp analysis, narrow band imaging, confocal fluorescent endomicroscopy.***
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.***

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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*Key Article

KEY WORDS

Cologuard, CT Colonography, virtual colonoscopy, FIT, gFOBT, fecal DNA, fecal occult blood test, Septin9, ColoVantage, BeScreened-CRC**,** PolypDX, Chromoendoscopy

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3). Please refer to the following NCD website for Medicare Members: [https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=281&ncdver=5&bc=AgAAgAAAAQAAAA%3d%3d&] accessed 06/28/23.

There is currently a Local Coverage Determination (LCD) for Computed Tomographic (CT) Colonography for Diagnostic Uses (L33562). Please refer to the following LCD website for Medicare Members: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33562&ver=26&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAIAgAAA&] accessed 06/28/23.

There is currently a Proposed Decision Memo for Screening for Colorectal Cancer - Blood-Based Biomarker Tests. Please refer to the following website for Medicare members: [https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=299] accessed 06/28/23.