Colorectal Cancer Screening

Policy Number: AHS – G2181 – Colorectal Cancer Screening	Prior Policy Name and Number, as applicable:
Effective Date: 12/01/2023	

I. Policy Description

Colorectal cancer (CRC) is the term used to describe the development of cancer in the colon or the rectum. Colon cancer and rectal cancer are often grouped together because the two diseases share similar characteristics and features.

Screening is key in detecting colorectal cancer early and has a major impact on colorectal cancer incidence and mortality rates. Screening for colorectal cancer occurs through a preventive visit with a healthcare provider who provides an individual risk assessment.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1) For asymptomatic individuals 45 to 75 years of age, screening for colorectal cancer **MEETS COVERAGE CRITERIA** using **any** of the following screening strategies:
   a) A stool-based test (every year):
      i) Guaiac fecal occult blood test (gFOBT) every year.
      ii) Fecal immunochemical test (FIT) every year.
   b) Direct visualization tests:
      i) Colonoscopy every 10 years.
      ii) Computerized tomography (CT) every 5 years.
      iii) Flexible sigmoidoscopy every 5 years.
      iv) Flexible sigmoidoscopy every 10 years with FIT every year.
2) The use of methylated Septin 9 (ColoVantage) or FIT-DNA (Cologuard) for colorectal cancer screening **MEETS COVERAGE CRITERIA**.

3) For average risk, asymptomatic individuals over 75 years of age, colorectal cancer screening **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

4) Colorectal cancer screening using **any** of the following techniques **DOES NOT MEET COVERAGE CRITERIA**:

   a) Screening for anal cytological abnormalities (anal pap smear).

   b) Screening for anal HPV infection**.**

   c) Colon capsule endoscopy.

III. Table of Terminology

Term	Definition
AA	Advanced adenoma
ACA	The Patient Protection and Affordable Care Act
ACPM	American College of Preventive Medicine
ACS	American Cancer Society
CDC	Centers for Disease Control and Prevention
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CRC	Colorectal Cancer
CT	Computerized tomography
CUC	Chronic ulcerative colitis
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FIT	Fecal immunochemical test
FIT-DNA	Fecal immunochemical test plus DNA test (multi-target)
gFOBT	Guaiac fecal occult blood test
HNPCCC	Hereditary non-polyposis colorectal cancer syndrome
IBD	Inflammatory bowel disease
IOM	Institute of Medicine
MAP	MYH-associated polyposis
PCR	Polymerase chain reaction
USPSTF	U.S. Preventive Services Task Force

IV. Scientific Background

Colorectal cancer (CRC) describes cancer that develops in the colon or rectum. The etiology of colorectal cancer involves a combination of genetic and environmental risk factors.

Approximately 75% of patients diagnosed with CRC have a negative family history for colorectal cancer. However, the lifetime risk of developing colorectal cancer increases when an individual has a first-degree relative who was diagnosed under 50 years of age, as well as with other positive family history factors such as two or more affected family members (Kuipers et al., 2015).

Colorectal cancer is a predominant cancer that accounts for 10% of cancer-related mortality in western countries (Kuipers et al., 2015) and is the third leading cause of cancer-related deaths in the United States (Shaukat et al., 2021). For the year 2022, the American Cancer Society (ACS) estimated 106,180 new cases of colon cancer and 44,850 new cases of rectal cancer. Overall, the lifetime risk of developing colorectal cancer is about 1 in 23 (4.3%) for men and 1 in 25 (4.0%) for women (ACS, 2022).

A colorectal cancer screen is typically performed after a risk factor assessment and during an annual wellness visit. Screening efforts focus on finding and removing adenomas and detecting early-stage colorectal cancer. Available screening modalities include CT colonography and stool-based testing (Shaukat et al., 2021). During an annual checkup, providers review an individual's personal history and family history, perform a physical examination, and run a battery of tests.

The types and number of tests performed can vary widely. Several tests for CRC screening are available. These screening tests are designed to detect colorectal cancer and to look for any signs of adenomatous polyps. Stool-based tests detect hemoglobin in blood that comes from a lesion (Doubeni, 2022).

A fecal immunochemical test (FIT) directly measures hemoglobin in the stool; a patient provides a sample and places it in a specimen collection kit, after which the sample is returned to the lab for processing within 24 hours of collection. FIT tests generate a quantitative result or a qualitative test result and require only one sample, rather than the three days of consecutive sample collection for guaiac-based fecal occult blood tests (gFOBT) (Doubeni, 2022). Quantitative FIT tests– as compared to qualitative FIT tests– are more standardized, produce more consistent results, and have a higher PPV (Doubeni, 2022).

According to the USPSTF, the FIT test has several advantages (one of which is patient convenience) that lead it to be preferred in usage as compared to gFOBT tests. The USPSTF notes that "the fecal immunochemical test (FIT), as a direct measure of human hemoglobin in stool has a number of advantages relative to conventional FOBT and is increasingly used relative to that test" (Robertson et al., 2017). In addition to convenience of use, when compared with gFOBT screening, screening using FIT shows higher detection rates for CRC and advanced adenomas. FIT is also more sensitive than gFOBT for colon lesions (Robertson et al., 2017). Higher sensitivity and higher screening participation rates for FIT contribute to its rate of clinical usage.

A guaiac-based fecal occult blood test is another stool-based test. gFOBT testing detects hemoglobin by turning guaiac reagent-impregnated paper blue through a peroxidase reaction. Hemoglobin identification is necessary to detect any bleeding that may come from a colon lesion. Testing involves a test "card" that is received from a physician's office or through the mail. These test cards are used for three consecutive bowel movements to collect a sample on the card; the cards are mailed into the laboratory for analysis. Several randomized trials have shown that gFOBT screening is effective at reducing CRC mortality. Guidelines recommend providers and

laboratories who provide gFOBT screening use only highly sensitive guaiac reagents. One highly sensitive agent is the Hemoccult SENSA, with a reported sensitivity for CRC of 64 to 80 percent, whereas sensitivity for nonrehydrated Hemoccult II tested markedly lower at 25 to 38 percent. Two disadvantages of gFOBT screening should be noted: (1) the sensitivity of gFOBT for advanced adenomas is "substantially less than for CRC" (Doubeni, 2022) and (2) the detection rate for colon lesions on the right side is lower than the detection rate for left-sided lesions.

A multi-target stool DNA test (FIT-DNA) is a composite test made up of a fecal immunochemical test (FIT) and a DNA test that analyzes DNA alterations. Multi-target stool DNA tests are known by a variety of acronyms: sDNA-FIT, MT-sDNA, or FIT-DNA. In the United States, the test is also sometimes listed by its proprietary name: Cologuard. FIT-DNA tests are comprised of molecular assays to test for DNA (*KRAS* mutations); a gene amplification technique to test for methylation markers that arise from colorectal neoplasia; and an immunochemical assay (FIT) to test for hemoglobin, which may be found in blood due to colorectal lesions. The FIT-DNA test procedure involves the patient collecting a stool sample in a specimen collection kit. The collection kit is mailed into the company for testing and should arrive within a 72-hour period after the stool was collected. As of 2022, there are currently no randomized trial results of multi-target sDNA screening for colorectal cancer but there are comparison studies of other screening strategies against multi-target sDNA (Doubeni, 2022).

Proprietary Tests

Cologuard™

Cologuard™ by Exact Sciences Corporation is a test intended to screen adults 45 years of age and older who are at average risk for colorectal cancer (Sciences, 2022). It is intended for the "qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool." It is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals, but is intended to screen those at average risk (Sciences, 2022).

Imperiale et al. (2014) investigated the screening performance of Cologuard (a noninvasive multi-target DNA test) as compared with a fecal immunochemical test (FIT). Of the 9,989 individuals enrolled in the study, colonoscopy results (as the reference standard) confirmed that 65 individuals (0.7%) had colorectal cancer and 757 (7.6%) had "advanced precancerous lesions." The DNA multi-target stool test used in the study was comprised of a quantitative molecular assay (the assay analyzed *KRAS* mutation, aberrant *NDRG4* and *BMP3* methylation, and β-actin) and a hemoglobin immunoassay. Multi-target stool DNA testing evidenced specificity of 86.6% for individuals with nonadvanced or negative findings. The sensitivity for detecting advanced precancerous lesions with FIT was 42.4%. Specificity was 94.9% for FIT among participants with nonadvanced or negative findings ($P < 100$). According to the authors, "The sensitivity of the DNA test for the detection of both colorectal cancer (92.3%) and advanced precancerous lesions (42.4%) exceeded that of FIT by an absolute difference of nearly 20 percentage points. This difference may be attributed to the DNA marker and algorithm components of the test since the test performance of the hemoglobin immunoassay component of the DNA test was nearly identical to that of FIT." In conclusion, the authors noted "the numbers of persons who would need to be screened to detect one cancer were 154 with

colonoscopy, 166 with DNA testing, and 208 with FIT" and that "in asymptomatic persons at average risk for colorectal cancer, multi-target stool DNA testing detected significantly more cancers than did FIT but had more false positive results" (Imperiale et al., 2014).

Colovantage®

Colovantage® by Clinical Genomics is a plasma-based test that is used to screen for colorectal cancer and to detect colorectal disease. The test detects circulating methylated DNA from the *SEPT9* gene which is a part of cytokinesis and cell control. The ColoVantage test has yet to be clinically validated as a screening test, but a few small studies are available on this type of test. Grützmann et al. (2008) performed two case-control studies as a part of validation study on *Septin 9* DNA methylation in plasma for screening purposes. The authors used a PCR assay for analysis of *SEPT9*; The samples included 354 samples (252 CRC, 102 controls). A separate study validated the initial one with a blinded, independent study of 309 samples (126 CRC, 183 controls). The use of a *SEPT9* to classify the samples resulted in detection in 120/252 CRCs (48%) and 7/102 (7%) controls; the second case-study resulted in 73/126 CRCs detected (58%) and 18/183 control samples (10%) testing positive for *SEPT9*, validating the initial results. The rate of polyp detection (>1cm) was approximately 20%. According to the authors, "inclusion of an additional measurement replicate increased the sensitivity of the assay in the testing set to 72% while maintaining 90% specificity"(Grützmann et al., 2008).

Analytical Validity

Burch et al. (2007) reported on the accuracy of guaiac testing as compared to immunochemical fecal occult blood tests (FOBTs) for the detection of colorectal cancer in an average-risk screening population. Of the 59 studies evaluated for analytical validity, 33 evaluated guaiac FOBTs and 35 analyzed immunochemical FOBTs. The results showed sensitivities for the detection of all neoplasms ranged from 6.2% to 83.3% for guaiac tests. Specificity ranged from 98.0% to 98.4% for guaiac tests. Sensitivity ranged from 5.4% to 62.6% for immunochemical FOBTs while specificity ranged from 94.3%-98.5% for immunochemical FOBTs (Burch et al., 2007). Sensitivities were also higher for the detection of CRC and lower for adenomas in both the diagnostic cohort and diagnostic case-control studies for both guaiac and immunochemical FOBTs. Of the immunochemical FOBTs, the Immudia HemSp test was the most accurate, but there was "no clear evidence" to prefer either guaiac or immunochemical FOBTs (one over the other) (Burch et al., 2007).

Shapiro et al. (2017) enrolled 1,006 asymptomatic individuals in a study. Participants were 50-75 years of age and had been recommended for a screening colonoscopy (based on colonoscopy screening recommendations). The performance of each test was analyzed, with colonoscopy results used as the reference standard. The InSure FIT test had the highest sensitivity for detecting advanced colorectal neoplasia at 26.3%. The OC FIT-CHEK had a 15.1% sensitivity value. The Hemoccult II SENSA had a test sensitivity value of 7.4%. Statistically, the InSure FIT was more sensitive than the other two tests. Specificity ranged in value from 96.8% to 98.6%. The authors concluded that some FITs were more sensitive than others, but that the results should be confirmed in larger populations (Shapiro et al., 2017).

Kisiel et al. (2022) analyzed the performance of a multi-target stool DNA (mt-sDNA) test that combines the detection of methylation DNA markers (MDMs), *KRAS* mutations and fecal

hemoglobin. This verification study included 777 samples – 210 cases and 567 controls. The average age of participants in the study was 65.5 years. The results of the study showed a sensitivity of 95.2% for colorectal cancer (CRC) and a sensitivity of 57.2% for advanced precancerous lesions (APL). Specificity for CRC and advanced precancerous lesions was 89.8% (that is, no CRC or advanced precancerous lesions). A specificity of 92.4% for neoplasia was calculated. Through sub-group analyses, a sensitivity for early-stage CRC of 93.4% at stage I and 94.2% at stage II were determined (Kisiel et al., 2022).

Clinical Utility and Validity

High-sensitivity gFOBTs and FIT tests have been involved in repeated randomized controlled trials for validity and have been shown to reduce colorectal cancer mortality (USPSTF, 2021b).

Faivre et al. (2004) investigated whether a benefit to FOBTs could be ascertained within countries that already had a high performance in the diagnosis and management of colorectal cancer. There were 91,199 individuals ages 45-74 years old who participated in the study. Individuals were allocated to either FOBT screening or no screening. Participants were followed up on for over eleven years. The results of the study showed positivity rates of 2.1% initially and 1.4% on average in subsequent rounds of screening (six screenings were performed over eleven years). Overall CRC mortality was "significantly lower in the screening population compared with the control population (mortality ratio, 0.84; 95% confidence interval)." The authors concluded that "biannual screening by FOBTs could reduce CRC mortality" (Faivre et al., 2004).

Kim et al. (2021) studied the usage of colonoscopy and FIT testing for CRC detection using FIT claims data along with colonoscopy data from the Korean National Health Insurance system over a period of eleven years. Over 61,221 patient records (of individuals newly diagnosed with colorectal cancer) comprised the data used for the study. Another 306,099 individuals who did not have colorectal cancer were used as a control group. Through multivariable logistic regression models, the authors found an association between colonoscopy and reduced subsequent colorectal cancer risk (adjusted odds ratio of 0.29). Between colonoscopy and distal CRC, there was an even stronger association than with proximal CRC (0.24 vs 0.47). FIT tests were associated with a colorectal cancer risk odds ratio of 0.74. The authors concluded that FIT testing showed less risk reduction than colonoscopy. However, "as the frequency of cumulative FIT assessments increased, the association with CRC prevention became stronger" (Kim et al., 2021).

V. Guidelines and Recommendations

U.S. Preventive Services Task Force (USPSTF)

The USPSTF provides recommendations regarding clinical preventive services such as screening and counseling. The task force is comprised of an independent panel of experts in primary care and prevention that further specialize in numerous fields. Recommendations are segmented primarily based on factors such as age, gender, and pregnancy status. The USPSTF assigns one of five letter grades to a recommendation (A, B, C, D, or I). Costs are not considered when grading a practice. Furthermore, the recommendations only apply to people who are asymptomatic for a given condition (USPSTF, 2017).

The below chart represents screening recommendations from the USPSTF for adults.

Topic	Date	Grade	Recommendation
Colorectal cancer screening: Adults 45-49 years old (USPSTF, 2021a)	May 2021	B	Recommends screening for colorectal cancer in adults aged 45 to 49 years.
Colorectal cancer screening: Adults 50-75 years old (USPSTF, 2021a)	May 2021	**A**	Recommends screening for colorectal cancer in all adults aged 50 to 75 years.
Colorectal cancer screening: Adults 76-85 years old (USPSTF, 2021a)	May 2021	**C**	Recommends offering screening selectively for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the benefit of such screening in this age group is small. Clinicians should consider the patient's overall health, prior screening history, and preferences.

The USPSTF provides frequency and efficacy information on available screening methods (USPSTF, 2021b):

Screening method[a]	Frequency[b]	Evidence of efficacy	Other considerations
Stool-based tests			
High-sensitivity gFOBT	Every year	• Evidence from RCTs that gFOBT reduces colorectal cancer mortality • High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II), although there is still uncertainty about the precision of test sensitivity estimates. Given this uncertainty, it is unclear whether high-sensitivity gFOBT can detect as many cases of advanced adenomas and colorectal cancer as other stool-based tests	• Harms from screening with gFOBT arise from colonoscopy to follow up abnormal gFOBT results • Requires dietary restrictions and three stool samples • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT	Every year	• Evidence from 1 large cohort study that screening with FIT reduces colorectal cancer mortality	• Harms from screening with FIT arise from colonoscopy to follow up abnormal FIT results

		• Certain types of FIT have improved accuracy compared with gFOBT and HSgFOBT (20 µg hemoglobin per gram of feces threshold was used in the CISNET modeling)	• Can be done with a single stool sample • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
sDNA-FIT	Every 1 to 3[c] y	• Improved sensitivity compared with FIT per 1-time application of screening test • Specificity is lower than that of FIT, resulting in more false-positive results, more follow-up colonoscopies, and more associated adverse events per sDNA-FIT screening test compared with per FIT test • Modeling suggests that screening every 3 y does not provide a favorable (ie, efficient) balance of benefits and harms compared with other stool-based screening options (ie, annual FIT or sDNA-FIT every 1 or 2 y) • Insufficient evidence about appropriate longitudinal follow up of abnormal findings after a negative follow-up colonoscopy • No direct evidence evaluating the effect of sDNA-FIT on colorectal cancer mortality	• Harms from screening with sDNA-FIT arise from colonoscopy to follow up abnormal sDNA-FIT results • Can be done with a single stool sample but involves collecting an entire bowel movement • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
Direct visualization tests			
Colonoscopy	Every 10 y	• Evidence from cohort studies that colonoscopy reduces colorectal cancer mortality • Harms from colonoscopy include bleeding and	• Screening and diagnostic follow-up of positive results can be performed during the same examination

		perforation, which both increase with age	• Requires less frequent screening • Requires bowel preparation, anesthesia or sedation, and transportation to and from the screening examination
CT colonography	Every 5 y	• Evidence available that CT colonography has reasonable accuracy to detect colorectal cancer and adenomas • No direct evidence evaluating effect of CT colonography on colorectal cancer mortality • Limited evidence about the potential benefits or harms of possible evaluation and treatment of incidental extracolonic findings, which are common. Extracolonic findings detected in 1.3% to 11.4% of exams; <3% required medical or surgical treatment	• Additional harms from screening with CT colonography arise from colonoscopy to follow up abnormal CT colonography results • Requires bowel preparation • Does not require anesthesia or transportation to and from the screening examination
Flexible sigmoidoscopy	Every 5 y	• Evidence from RCTs that flexible sigmoidoscopy reduces colorectal cancer mortality • Risk of bleeding and perforation but less than risk with colonoscopy • Modeling suggests that it provides fewer life-years gained alone than when combined with FIT or in comparison to other strategies	• Additional harms may arise from colonoscopy to follow up abnormal flexible sigmoidoscopy results • Test availability has declined in the US but may be available in some communities where colonoscopy is less available
Flexible sigmoidoscopy with FIT	Flexible sigmoidoscopy every 10 y plus FIT every year	• Evidence from RCTs that flexible sigmoidoscopy + FIT reduces colorectal cancer mortality • Modeling suggests combination testing provides similar benefits to those of	• Additional potential harms from colonoscopy to follow up abnormal flexible sigmoidoscopy or FIT results • Flexible sigmoidoscopy availability has declined in the US but may be

		colonoscopy, with fewer complications • Risk of bleeding and perforation from flexible sigmoidoscopy but less than risk with colonoscopy	available in some communities where colonoscopy is less available • Screening with FIT requires good adherence over multiple rounds of testing

"[a] To achieve the benefits of screening, abnormal results from stool-based tests, CT colonography, and flexible sigmoidoscopy should be followed up with colonoscopy.
[b] Applies to persons with negative findings (including hyperplastic polyps) and is not intended for persons in surveillance programs. Evidence of efficacy is not informative of screening frequency, with the exception of gFOBT and flexible sigmoidoscopy alone.
[c] As stated by the manufacturer"

American Cancer Society (ACS)

For colorectal cancer (CRC), the ACS recommends screening people at average risk starting at age 45. The ACS notes that a stool test an option for screening. The ACS states that regular screening should continue at least through age 75. From ages 76-85, the ACS writes that the decision to continue screening should be discussed between patient and provider. From age 85 onward, a patient should no longer receive colorectal cancer screening (ACS, 2022).

The ACS notes the following options for CRC screening using stool: "Fecal immunochemical test every y[ear], High-sensitivity, guaiac-based fecal occult blood test every y[ear] or a multitarget stool DNA test every 3 y[ears]" For structural examination, the ACS notes the following options: "colonoscopy every 10 y[ears], CT colonography every 5 y[ears], or flexible sigmoidoscopy every 5 y[ears] (Wolf et al., 2018).

The American College of Gastroenterology (ACG)

The ACG developed both guidance and a modified Grading of Recommendations, Assessment, Development and Evaluation methodology to evaluate the quality of evidence and strength of recommendations. They used "we recommend" for strong recommendations and "we suggest" for conditional recommendations. The following are CRC screening recommendations:

1. "We recommend CRC screening in average-risk individuals between ages 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. Strong recommendation; moderate-quality evidence
2. We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. Conditional recommendation; very low-quality evidence
3. We suggest that a decision to continue screening beyond age 75 years be individualized. Conditional recommendation; very low-quality evidence
4. We recommend colonoscopy and FIT as the primary screening modalities for CRC screening. Strong recommendation; low-quality evidence
5. We suggest consideration of the following screening tests for individuals unable or unwilling to undergo colonoscopy or FIT: flexible sigmoidoscopy, multitarget stool DNA

test, CT colonography or colon capsule. Conditional recommendation; very low-quality evidence

6. We suggest against Septin 9 for CRC screening. Conditional recommendation, very low-quality of evidence
7. We recommend that the following intervals should be followed for screening modalities: FIT every 1 year, Colonoscopy every 10 years. Strong recommendation; low-quality evidence
8. We suggest that the following intervals should be followed for screening modalities: Multitarget stool DNA test every 3 years, Flexible sigmoidoscopy every 5–10 years, CTC every 5 years, CC every 5 years. Conditional recommendation; very low-quality evidence
9. We suggest initiating CRC screening with a colonoscopy at age 40 or 10 years before the youngest affected relative, whichever is earlier, for individuals with CRC or advanced polyp in 1 first degree relative (FDR) at age <60 years or CRC or advanced polyp in ≥2 FDR at any age. We suggest interval colonoscopy every 5 years. Conditional recommendation; very low-quality evidence
10. We suggest consideration of genetic evaluation with higher familial CRC burden (higher number and/or younger age of affected relatives). Conditional recommendation; very low-quality evidence
11. We suggest initiating CRC screening at age 40 or 10 years before the youngest affected relative and then resuming average-risk screening recommendations for individuals with CRC or advanced polyp in 1 FDR at age ≥60 years. Conditional recommendation; very low-quality evidence
12. In individuals with 1 second-degree relative (SDR) with CRC or advanced polyp, we suggest following average-risk CRC screening recommendations. Conditional recommendation; low-quality evidence" (Shaukat et al., 2021).

U.S. Multi-Society Task Force on Colorectal Cancer -- American College of Gastroenterology, American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy

The U.S. Multi-Society Task Force on Colorectal Cancer published a 2022 update. The update focused on addressing the age of beginning CRC screening in average-risk individuals as well as the age of stopping CRC screening. The guideline recommends that screening begin at age 45 because there is "increasing disease burden among individuals under age 50, emerging data that the prevalence of advanced colorectal neoplasia in individuals ages 45 to 49 approaches rates in individuals 50 to 59, and modeling studies demonstrate the benefits of screening outweigh the potential harms and costs. For individuals ages 76 to 85, the decision to start or continue screening should be individualized and based on prior screening history, life expectancy, CRC risk, and personal preference. Screening is not recommended after age 85" (Patel et al., 2022).

VI. Applicable State and Federal Regulations

Food and Drug Administration (FDA)

The FDA approved the Epi proColon by Epigenomics AG on April 12, 2016.

"The Epi proColon test is a qualitative in vitro diagnostic test for the detection of methylated Septin 9 DNA in EDTA plasma derived from patient whole blood specimens. Methylation of the

target DNA sequence in the promoter region of the SEPT9_v2 transcript has been associated with the occurrence of colorectal cancer (CRC). The test uses a real-time polymerase chain reaction (PCR) with a fluorescent hydrolysis probe for the methylation specific detection of the Septin 9 DNA target. The Epi proColon test is indicated to screen adults of either sex, 50 years or older, defined as average risk for CRC, who have been offered and have a history of not completing CRC screening. Tests that are available and recommended in the USPSTF 2008 CRC screening guidelines should be offered and declined prior to offering the Epi proColon test. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. The Epi proColon test results should be used in combination with physician's assessment and individual risk factors in guiding patient management" (FDA, 2016).

The FDA approved Cologuard™ by Exact Sciences Corporation on August 11, 2014.

"Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals" (FDA, 2014).

The FDA also lists contraindications for Cologuard, noting that certain populations were not clinically evaluated for Cologuard use. These populations include:

- "Patients with a history of colorectal cancer, adenomas, or other related cancers.
- Patients who have had a positive result from another colorectal cancer screening method within the last 6 months.
- Patients who have been diagnosed with a condition that is associated with high risk for colorectal cancer. These include but are not limited to:
  - Inflammatory Bowel Disease (IBD)
  - Chronic ulcerative colitis (CUC)
  - Crohn's disease
  - Familial adenomatous polyposis (FAP)
  - Family history of colorectal cancer
- Patients who have been diagnosed with a relevant familial (hereditary) cancer syndrome, such as Hereditary non-polyposis colorectal cancer syndrome (HNPCCC or Lynch Syndrome), Peutz-Jeghers Syndrome, MYH-Associated Polyposis (MAP), Gardner's syndrome, Turcot's (or Crail's) syndrome, Cowden's syndrome, Juvenile Polyposis, Cronkhite-Canada syndrome, Neurofibromatosis, or Familial Hyperplastic Polyposis." (FDA, 2014)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
81327	SEPT9 (Septin9) (eg, 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 (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided 3 cards or single triple card for consecutive collection)
82274	Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations
87624	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
87625	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
88112	Cytopathology, selective cellular enhancement technique with interpretation (eg, liquid based slide preparation method), except cervical or vaginal
0500T	Infectious agent detection by nucleic acid (DNA or RNA), Human Papillomavirus (HPV) for five or more separately reported high-risk HPV types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) (ie, genotyping)

VIII. Evidence-based Scientific References

ACS. (2022, March 14, 2022). *American Cancer Society Guidelines for the Early Detection of Cancer*. https://www.cancer.org/healthy/find-cancer-early/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html#references

Burch, J. A., Soares-Weiser, K., St John, D. J. B., Duffy, S., Smith, S., Kleijnen, J., & Westwood, M. (2007). Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. *Journal of Medical Screening*, *14*(3), 132-137. https://doi.org/10.1258/096914107782066220

Doubeni, C. (2022, Nov 2022). *Screening for colorectal cancer*. https://www.uptodate.com/contents/tests-for-screening-for-colorectal-cancer?source=history

Faivre, J., Dancourt, V., Lejeune, C., Tazi, M. A., Lamour, J., Gerard, D., Dassonville, F., & Bonithon-Kopp, C. (2004). Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study¹. *Gastroenterology*, *126*(7), 1674-1680. https://doi.org/10.1053/j.gastro.2004.02.018

FDA. (2014). *SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)*. Food & Drug Administration. Retrieved 11/14/2018 from https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017B.pdf

FDA. (2016). *Epi ProColon*. Retrieved 11/14/2018 from https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p130001

Grützmann, R., Molnar, B., Pilarsky, C., Habermann, J. K., Schlag, P. M., Saeger, H. D., Miehlke, S., Stolz, T., Model, F., Roblick, U. J., Bruch, H.-P., Koch, R., Liebenberg, V., deVos, T., Song, X., Day, R. H., Sledziewski, A. Z., & Lofton-Day, C. (2008). Sensitive Detection of Colorectal Cancer in Peripheral Blood by Septin 9 DNA Methylation Assay. *PLOS ONE*, *3*(11), e3759. https://doi.org/10.1371/journal.pone.0003759

Imperiale, T. F., Ransohoff, D. F., Itzkowitz, S. H., Levin, T. R., Lavin, P., Lidgard, G. P., Ahlquist, D. A., & Berger, B. M. (2014). Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*, *370*(14), 1287-1297. https://doi.org/10.1056/NEJMoa1311194

Kim, S. Y., Kim, H. S., Kim, Y. T., Lee, J. K., Park, H. J., Kim, H. M., & Kang, D. R. (2021). Colonoscopy Versus Fecal Immunochemical Test for Reducing Colorectal Cancer Risk: A Population-Based Case-Control Study. *Clin Transl Gastroenterol*, *12*(5), e00350. https://doi.org/10.14309/ctg.0000000000000350

Kisiel, J. B., Gagrat, Z. D., Krockenberger, M., Bhattacharya, A., Bourne, B. L., Leduc, C. M., Matter, M. B., Fourrier, K. D., Edwards, D., Limburg, P. J., & Domanico, M. J. (2022). Can second-generation multitarget stool DNA panels reliably detect colorectal cancer and advanced precancerous lesions? *Journal of Clinical Oncology*, *40*(4_suppl), 63-63. https://doi.org/10.1200/JCO.2022.40.4_suppl.063

Kuipers, E. J., Grady, W. M., Lieberman, D., Seufferlein, T., Sung, J. J., Boelens, P. G., van de Velde, C. J., & Watanabe, T. (2015). Colorectal cancer. *Nat Rev Dis Primers*, *1*, 15065. https://doi.org/10.1038/nrdp.2015.65

Patel, S. G., May, F. P., Anderson, J. C., Burke, C. A., Dominitz, J. A., Gross, S. A., Jacobson, B. C., Shaukat, A., & Robertson, D. J. (2022). Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*, *162*(1), 285-299. https://doi.org/https://doi.org/10.1053/j.gastro.2021.10.007

Robertson, D. J., Lee, J. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., Kaltenbach, T., Lieberman, D., Levin, T. R., & Rex, D. K. (2017). Recommendations on Fecal Immunochemical Testing to Screen for Colorectal Neoplasia: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*, *152*(5), 1217-1237.e1213. https://doi.org/10.1053/j.gastro.2016.08.053

Sciences, E. (2022). *Cologuard*. https://www.cologuardhcp.com/about/clinical-offer

Shapiro, J. A., Bobo, J. K., Church, T. R., Rex, D. K., Chovnick, G., Thompson, T. D., Zauber, A. G., Lieberman, D., Levin, T. R., Joseph, D. A., & Nadel, M. R. (2017). A Comparison of Fecal Immunochemical and High-Sensitivity Guaiac Tests for Colorectal Cancer Screening. *Am J Gastroenterol*, *112*(11), 1728-1735. https://doi.org/10.1038/ajg.2017.285

Shaukat, A., Kahi, C. J., Burke, C. A., Rabeneck, L., Sauer, B. G., & Rex, D. K. (2021). ACG Clinical Guidelines: Colorectal Cancer Screening 2021. *Official journal of the American College of Gastroenterology | ACG*, *116*(3), 458-479. https://doi.org/10.14309/ajg.0000000000001122

USPSTF. (2017). *About the USPSTF*. USPSTF. Retrieved 11/14 from https://www.uspreventiveservicestaskforce.org/Page/Name/about-the-uspstf

USPSTF. (2021a). Colorectal Cancer: Screening. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening

USPSTF. (2021b). *USPSTF Final Recommendation Statement*. https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/colorectal-cancer-screening

Wolf, A. M. D., Fontham, E. T. H., Church, T. R., Flowers, C. R., Guerra, C. E., LaMonte, S. J., Etzioni, R., McKenna, M. T., Oeffinger, K. C., Shih, Y.-C. T., Walter, L. C., Andrews, K. S., Brawley, O. W., Brooks, D., Fedewa, S. A., Manassaram-Baptiste, D., Siegel, R. L., Wender, R. C., & Smith, R. A. (2018). Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA: A Cancer Journal for Clinicians*, *68*(4), 250-281. https://doi.org/10.3322/caac.21457

IX. Revision History

Revision Date	Summary of Changes
09/15/2023	Initial Effective Date Committee approved: 06/12/2023 DCH approved: 09/15/2023