Medical Policy

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Title: Analysis of Human DNA or RNA in Stool Samples as a Technique for Colorectal Cancer Screening

Professional / Institutional
Original Effective Date: August 8, 2016
Latest Review Date: March 13, 2025
Current Effective Date: March 13, 2025

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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic and at average risk of colorectal cancer	Interventions of interest are: • FIT-DNA testing	Comparators of interest are: • Established tests for colorectal cancer screening	Relevant outcomes include: • Overall survival • Disease-specific survival
Individuals: • Who are asymptomatic and at average risk of colorectal cancer	Interventions of interest are: • FIT-RNA testing	Comparators of interest are: • Established tests for colorectal cancer screening	Relevant outcomes include: • Overall survival • Disease-specific survival

DESCRIPTION

Detection of DNA or RNA abnormalities associated with colorectal cancer (CRC) in stool samples has been proposed as a screening test for CRC. This technology is another potential alternative to currently available screening approaches such as fecal occult blood testing, fecal immunochemical testing (FIT), and colonoscopy. The currently available stool tests combine FIT

and DNA or RNA analysis and are referred to as FIT-DNA or FIT-RNA in this review, though other publications use terms such as stool DNA (sDNA)-FIT, multitarget stool DNA (mt-sDNA) or multitarget stool RNA (mt-sRNA) test.

OBJECTIVE

The objective of this evidence review is to evaluate whether testing of stool DNA or RNA improves the net health outcome for asymptomatic individuals at average risk of CRC who are undergoing routine CRC screening.

BACKGROUND

Colorectal Cancer

Several cellular genetic alterations have been associated with colorectal cancer (CRC). In the proposed multistep model of carcinogenesis, the tumor suppressor gene *p53* and the proto-oncogene *KRAS* are most frequently altered. Variants in adenomatous polyposis coli genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. CRC is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis CRC) and in subgroups of patients with sporadic colon carcinoma. Tumor-associated gene variants and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Because cancer cells are shed into the stool, tests have been developed to detect these genetic alterations in the DNA from shed CRC cells isolated from stool samples.

REGULATORY STATUS

Table 1. FDA Approved Colorectal Cancer Screening Tests Evaluating DNA or RNA in Stool Samples

Device	Manufacturer	Original Date Approved	Pivotal study	Original PMA number	PAS identifier(s)	Indication(s)
Cologuard™	Exact Sciences Corporation	Aug 2014	NCT01260168	P130017	P130017 S029/ PAS001; clinicaltrials.gov registry not listed	'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)

Device	Manufacturer	Original Date Approved	Pivotal study	Original PMA number	PAS identifier(s)	Indication(s)
						and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 45 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.'
Cologuard Plus™	Exact Sciences Corporation	Oct 2024	NCT04144738	P230043	NA	'intended for the detection of colorectal neoplasia-associated DNA markers and for the presence of occult hemoglobin in human stool. The Cologuard Plus test is performed on samples collected using the Cologuard Plus Collection Kit. A positive result may indicate the presence of colorectal cancer (CRC) or advanced precancerous lesions (APL) and should be followed by colonoscopy. The Cologuard Plus test is indicated to screen adults 45 years or older, who are at average risk

Device	Manufacturer	Original Date Approved	Pivotal study	Original PMA number	PAS identifier(s)	Indication(s)
						for CRC. The Cologuard Plus test is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.'
Colosense®	Geneoscopy, Inc	May 2024	NCT04739722	P230001	P230001 / PAS001; NCT04739722	'intended for the detection of colorectal neoplasia associated RNA markers and for the presence of occult hemoglobin in human stool. ColoSense is for use with the ColoSense Collection Kit, the ColoSense Test Kit, the ColoSense Software, and the following instruments: Polymedco Immunochemical Fecal Occult Blood Test (iFOBT) Analyzer; bioMerieux EMAG Nucleic Acid Extraction System; and Bio-Rad QXDx Droplet Digital Polymerase Chain Reaction (ddPCR) System. ColoSense is a single-site test performed at Geneoscopy, Inc. A positive ColoSense result may indicate the presence of colorectal cancer

Device	Manufacturer	Original Date Approved	Pivotal study	Original PMA number	PAS identifier(s)	Indication(s)
						(CRC), advanced adenomas (AA) or serrated precancerous lesions (SPL) and should be followed by a colonoscopy. ColoSense is 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.

PMA: Premarket Approval; PAS: Post-approval Study

POLICY

A. DNA or RNA analysis of stool samples can be considered **medically necessary** as a screening technique for colorectal cancer in individuals at average risk of colorectal cancer who have not been screened by another colorectal cancer screening method within the last year.

B. Combination testing of DNA or RNA analysis of stool samples with other methods of colorectal cancer screening within a year is **experimental / investigational**.

C. DNA or RNA analysis of stool samples is considered **experimental / investigational** for all other indications.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 12, 2024.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Fecal Immunochemical-DNA or RNA Testing

For individuals at average risk for colorectal cancer (CRC), organizations such as the U.S Preventive Services Task Force have recommended several options for colon cancer screening. Advocates of DNA testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations compared with imaging or direct visualization screening strategies, and tests that detect cancer-associated DNA in the stool may be superior to current stool tests for the detection of cancer and cancer precursors.

The diagnostic performance characteristics of the currently accepted screening options (i.e., fecal occult blood testing, fecal immunochemical testing [FIT], flexible sigmoidoscopy, double-contrast barium enema) have been established using colonoscopy as the criterion standard. Modeling studies and clinical trial evidence on some of the screening modalities have allowed some confidence in the effectiveness of several cancer screening modalities. The efficacy of these tests is supported by numerous studies evaluating the diagnostic characteristics of the test for detecting cancer and cancer precursors along with a well-developed body of knowledge on the natural history of the progression of cancer precursors to cancer.

Clinical Context and Test Purpose
The U.S.Preventive Services Task Force has recommended screening for colorectal cancer (CRC) starting at age 45 years and continuing until age 75 years.[1,] The purpose of stool DNA testing in individuals who are at average risk of CRC is to inform a decision regarding whether to proceed to colonoscopy.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals aged 45 to 84 years at average risk of CRC.

The incidence of CRC varies by sex and race. Male have higher incidence than females. Non-Hispanic American Indian or Alaska Native persons and non-Hispanic Black persons have the highest incidence.[2,]

Interventions
The tests being considered are Cologuard, Cologuard Plus and Colosense, tests approved by the U.S. Food and Drug Administration (FDA), which combine FIT and DNA or RNA analysis (FIT-DNA; FIT-RNA). A stool sample is collected at home, prepared in a collection kit, and shipped to the manufacturer for analysis.

Cologuard
Cologuard detects 3 independent categories of biomarkers: 1) epigenetic changes in the form of gene promoter region methylation (N-Myc Downstream-Regulated Gene 4 [NDRG4] and Bone Morphogenetic Protein 3 [BMP3]); 2) 7 specific gene mutations in V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog [KRAS]; 3) non-DNA based, occult hemoglobin.[3,]

Cologuard Plus
Cologuard Plus expands the original Cologuard by incorporating a new molecular panel (methylated DNA markers ceramide synthase 4 gene [LASS4], leucine-rich repeat-containing protein 4 gene [LRRC4], serine–threonine protein phosphatase 2A 56-kDa regulatory subunit gamma isoform gene [PPP2R5C], and reference marker zinc finger DHHC-type containing 1 gene [ZDHHC1].[4,] The goal of the additional biomarkers was to increase specificity without decreasing sensitivity compared to the original Cologuard.

Colosense
ColoSense evaluates 8 stool-derived eukaryotic ribonucleic acid (seRNA) markers [(Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH), Aminoacylase 1 (ACY1), Amphiregulin

(AREG), TNF Receptor Superfamily Member 10B (TNFRSF10B), Cadherin 1 (CDH1), Egl-9 Family Hypoxia Inducible Factor 2 (EGLN2), Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), Suppressor of Mothers against Decapentaplegic (SMAD) Family Member 4 (SMAD4)] and an occult hemoglobin assay result fecal immunochemical test (FIT)/iFOBT. A single ColoSense result is provided based on combined results of the RNA markers, hemoglobin, and smoking status.[5,]

Comparators

The following test is currently the reference standard for CRC screening: colonoscopy every 10 years.

Table 2 shows the NCCN descriptions of modalities for CRC screening.[6,]

Table 2. NCCN CRC Screening Modality and Schedule

Screening Test[1]	**Recommended Testing Interval[2]**	**Sensitivity**		**Specificity**	
		Colon Cancer		Colon Cancer	
Colonoscopy	Every 10 years	94.7%	89%–95% (≥10 mm adenomas) 75%–93% (≥6 mm adenomas)	----	89% (≥10 mm adenomas) 94% (≥6 mm adenomas)
Flexible sigmoidoscopy[3]	Every 5–10 years	58%–75%	72%–86%	----	92%
CT colonography	Every 5 years	86%–100%	89% (≥10 mm adenomas) 86% (≥6 mm adenomas)	----	94% (≥10 mm adenomas) 88% (≥6 mm adenomas)
High-sensitivity guaiac-based test	Annually	50%–75%	7%–21% (advanced neoplasia) 6%–17% (advanced adenoma)	96%–98%	96%–99% (advanced neoplasia) 96%–99% (advanced adenoma)
Quantitative FIT (using OC-Sensor)	Annually	74%	25% (advanced neoplasia) 23% (advanced adenoma)	94%	96% (advanced neoplasia) 96% (advanced adenoma)
Quantitative FIT (using OC-Light)	Annually	81%	27% (advanced neoplasia) 28% (advanced adenoma)	93%	95% (advanced neoplasia) 94% (advanced adenoma)
mt-sDNA test[4]	Every 3 years	93%	47% (advanced neoplasia)	85%	89% (advanced neoplasia)

Screening Test[1]	Recommended Testing Interval[2]	Sensitivity		Specificity	
			43% (advanced adenoma)		89% (advanced adenoma)

[1]A blood test that detects circulating methylated SEPT9 DNA has been FDA-approved for CRC screening for those who refuse other screening modalities. Based on current
data, the panel concludes that the interval for repeating testing is unknown/unclear. The panel will continue to review this strategy and monitor data as they emerge.
[2]Frequency based upon normal (negative) results.
[3]Data for the sensitivity and specificity of flexible sigmoidoscopy are for the entire colon and are based on the completion of colonoscopy for those found to have a distal colon lesion on flexible sigmoidoscopy.
[4]Optimal FIT thresholds will vary across screening programs, taking into consideration available colonoscopy resources to investigate abnormal results, including false positive tests.

Outcomes

The outcome of interest in cancer screening is a reduction in mortality and morbidity due to cancer. This is ideally determined by randomized controlled trials; however, for colon cancer screening, many of the recommended tests have not been evaluated with clinical trials. When lacking direct evidence that a screening test reduces cancer mortality, the critical parameters in the evaluation are the diagnostic performance characteristics (i.e., sensitivity, specificity, positive and negative predictive value) compared with a criterion standard, the proposed frequency of screening, and the follow-up management of test results. Modeling studies have evaluated the robustness and quantity of health benefits of various screening tests when clinical trial evidence is lacking.

The time of interest is during standard-interval screening. For individuals of average risk undergoing colonoscopy, this is every 10 years beginning at age 50 years. The FDA approved the use of Cologuard for individuals aged 45 years and older in September 2019. CRC screening with Cologuard may be needed more frequently.

Study Selection Criteria

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

REVIEW OF EVIDENCE

COLOGUARD AND COLOGUARD PLUS

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

A systematic review and meta-analysis conducted by Dolatkhah et al (2022) assessed the sensitivity and specificity of FIT-DNA compared to colonoscopy.[7,] Data were pooled from 11 studies, including the Redwood 2016[8,], Imperiale 2014[9,], Lidgard 2013[10,], and Ahlquist 2012[11,] studies. Outcomes evaluated were detection of CRC and any precancerous lesions. The meta-analyses of FIT-DNA found a combined sensitivity of 89% (95% confidence interval [CI], 76% to 96%), 51% (95% CI, 39% to 63%), and 76% (95% CI, 61% to 86%) for the detection of CRC, advanced adenoma, and combined CRC and advanced adenoma, respectively. The overall specificity was 91% (95% CI, 86% to 95%), 89% (95% CI, 84% to 92%), and 90% (95% CI, 87% to 93%) for the detection of CRC, advanced adenoma, and combined CRC and advanced adenoma, respectively. The I^2 was 100 for the CRC subgroup, 99 for advanced adenoma, and 100 for combined CRC and advanced adenoma. The sensitivity and specificity of FIT-DNA, while indicating its diagnostic accuracy, were lower than colonoscopy for CRC and diagnosis of advanced adenoma.

A systematic review conducted by Lin et al (2021)[12,] (used to inform the U.S. Preventive Services Task Force 2021 CRC screening recommendation statement) pooled data from 1 good- and 3 fair-quality studies (including the Imperiale 2014[9,], Redwood 2016[8,] and Cooper 2018[13,] studies discussed below) assessing the accuracy of CRC screening with FIT-DNA testing. The Imperiale 2014 study accounted for ≥80% of the data included in the pooled analyses.[12,] The studies all used colonoscopy as the reference standard. When pooled, FIT-DNA had a sensitivity of 93% (95% CI , 87.0% to 100%; I^2=0%) and a specificity of 85% (95% CI, 84.0% to 86.0%; I^2=37.3%) for detection of CRC, based on 3 studies. For advanced neoplasia, sensitivity was 47% (95% CI, 44.0% to 55.0%; I^2=0%) and specificity was 89% (95% CI, 87.0% to 92.0%; I^2=88.8%) based on 4 studies. Pooled sensitivity and specificity for detection of advanced adenoma, based on 3 studies, were 43% (95% CI, 40.0% to 46.0%; I^2=0%) and 89% (95% CI, 86.0% to 92.0%; I^2=87.8%), respectively.

COHORT STUDIES

Cologuard

A large-scale evaluation of FIT-DNA (Cologuard) in a screening population was published by Imperiale et al (2014), who compared FIT-DNA with colonoscopy in 12,000 asymptomatic adults between the ages of 50 and 84 years (mean age, 64 years) at average risk for CRC.[9,] The results of this study supported the initial FDA approval of this FIT-DNA test (Cologuard) in August 2014.[3,] All enrolled subjects were scheduled to undergo a screening colonoscopy. Stool specimens were collected and tested no more than 90 days before the screening colonoscopy. Screening colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of FIT-DNA for detecting CRC and cancer precursors. In 9,989 evaluable subjects, FIT-DNA sensitivity for cancer was 92.3% (95% CI, 83.0% to 97.5%), and for FIT it was 73.8% (95% CI, 61.5% to 84.0%). For advanced precancerous lesion, FIT-DNA test sensitivity was 42.4% (95% CI, 38.9% to 46.0%), and for FIT it was 23.8% (95% CI, 20.8% to 27.0%). In analyses of specific types of lesions, the sensitivity of FIT-DNA did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of FIT-DNA testing was higher for distal lesions than for proximal lesions. FIT-DNA sensitivity increased as lesion size increased. The specificity of FIT-DNA was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, the specificity of FIT-DNA was 86.6% (95% CI, 85.9% to 87.2%) and 94.9% (95% CI, 94.4% to

95.3%) for FIT. For identification of patients only with negative colonoscopy, specificity of FIT-DNA was 89.8% (95% CI, 88.9% to 90.7%), and 96.4% (95% CI, 95.8% to 96.9%) for FIT. Following FDA approval for use of FIT-DNA (Cologuard) in asymptomatic adults aged 45 to 49 years, Imperiale et al (2021) published results from a screening study that included 983 adults aged 45 to 49 years (mean age, 48 years) at average risk of CRC.[14,] Among 816 participants who had evaluable FIT-DNA and colonoscopy results, 49 participants (6%) were found to have advanced precancerous lesions; no cases of CRC were detected. Sensitivity of FIT-DNA was 32.7% (95% CI, 19.9% to 47.5%) for detection of advanced precancerous lesions and 7.1% (95% CI, 4.3% to 11.0%) for detection of nonadvanced adenoma. When analyzed according to lesion type, FIT-DNA was most sensitive for villous growth pattern adenomas (60%; 95% CI, 26.2% to 87.8%). Specificity was 96.3% (95% CI, 94.3% to 97.8%) in participants with a negative colonoscopy, and 95.2% (95% CI, 93.4% to 96.6%) in those with non-advanced adenomas, non-neoplastic findings, and negative results on colonoscopy. FIT testing without DNA analysis was not included in the study.

Imperiale et al (2023) also published a longitudinal cohort study evaluating a 3-year interval for the multitarget stool DNA test (mt-sDNA) for CRC screening.[15,] Participants enrolled in the study had a valid baseline mt-sDNA result (N=2044); those with a negative baseline test (n=1760) were followed up to 3 years and asked to undergo repeat mt-sDNA testing and colonoscopy. Patients contributed to the baseline intention to screen (ITS) analysis population if they were mt-sDNA positive at baseline and had an evaluable colonoscopy result or if they were mt-sDNA negative at baseline, had a valid mt-sDNA test result at year 3, and evaluable colonoscopy result. Following attrition, the ITS cohort at year 3 included 591 of 1,760 patients with valid mt-sDNA and colonoscopy results; 122 of these patients were mt-sDNA positive. The Predictive Summary Index (PSI) year 3 value for CRC was 0% (95% CI, -3.62% to 1.02%; p=1); the PSI for advanced precancerous lesions was 9.3% (95% CI, 1.83 to 17.63; two-sided p=.01).The observed 3-year colorectal cancer yield was lower than expected (one-sided p=.09), while the yield for advanced precancerous lesions was higher than expected (two-sided p=.009). The detection of advanced precancerous lesions increased and was statistically significant after repeat mt-sDNA screening at a 3-year interval.

Other, smaller studies have assessed the accuracy of FIT-DNA in special populations. Redwood et al (2016) included 661 asymptomatic, Alaska natives undergoing screening or surveillance colonoscopy, using colonoscopy as a reference standard.[8,] Sensitivity for CRC was 100% for FIT-DNA, and 85% for FIT. For screening-relevant neoplasms (defined as adenoma or sessile serrated adenoma or polyp ≥1 cm, any adenoma with ≥25% villous component, or cancer), sensitivity was 49% for FIT-DNA and 28% for FIT. Cooper et al (2018) compared the sensitivity of FIT-DNA and FIT using colonoscopy as the reference standard in 265 Black and 495 White participants.[13,] FIT-DNA was associated with sensitivities of 50% in Black participants and 39% in White participants for identifying advanced lesions; corresponding sensitivities for FIT were 35% and 33%.

Cologuard Plus

Imperiale et al (2024) reported results of the pivotal study (BLUE-C; NCT04144738) of the next generation FIT-DNA test (Cologuard Plus).[16,] BLUE-C prospectively enrolled 26,758 asymptomatic persons 40 years of age or older (mean, 63 years) who were scheduled to or planned to undergo screening colonoscopy at 186 sites across the United States between 2019 and 2023. Stool specimens were obtained before colonoscopy. Submitted tissue specimens, colonoscopy reports,

histopathological reports, and relevant post-colonoscopy follow-up procedures or imaging reports were reviewed centrally by independent pathologists and were considered to be the reference standard. Central readers were unaware of the results of the stool tests. An independent FIT test was conducted by a separate central laboratory. Of 26,758 enrolled participants, 20,176 (75%) had results included in the primary analysis. 62 adults ages 40 to 44 were enrolled but not included in the primary analysis. The most common exclusions were incomplete screening colonoscopy (8%), unusable stool sample (3%), and nonreceipt of stool sample (3%). 60% of participants identified as White; 16% as Hispanic or Latino; 13% as Black or African American; and 9% as Asian. 32% of the participants had a previous colonoscopy (>9 years prior to enrollment) and 4% had a prior FIT-DNA test. The Cologuard Plus FIT-DNA test sensitivity for CRC was 94% (95% CI, 87 to 98). In subgroup analyses, sensitivity for CRC was greater than 90% for all age categories. The sensitivity for advanced precancerous lesions (APL) was 43% (95% CI, 41 to 46). Specificity for the Cologuard Plus FIT-DNA test was 91% (95% CI, 90 to 91). Sensitivity for CRC and APL was greater for the Cologuard Plus test compared to FIT but Cologuard Plus had lower specificity compared to FIT for advanced neoplasia. A sensitivity analysis using multiple imputation for missing data was performed and reported to yield results consistent with primary results.[16,4,]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There are no studies evaluating the direct health outcomes of a longitudinal screening program using Cologuard or Cologuard Plus. Voyage, a prospective cohort study with a planned enrollment of 150,000 individuals designed to address the real-world impact of Cologuard on CRC screening and mortality, is currently underway, but study completion is not expected until 2029 (see Table 3).[17,]

A study was conducted by Anderson et al (2022) using data from the New Hampshire Colonoscopy Registry to evaluate colonoscopy outcomes between age-, sex-, and risk-matched patients with and without a preceding positive FIT-DNA test.[18,] The investigators found that individuals in the positive FIT-DNA group (n=306) were significantly more likely than the colonoscopy-only cohort (n=918) to have CRC (1.3% vs. 0.4%) or advanced noncancerous neoplasia (27.1% vs. 8.2%; p<.0001). Colorectal neoplasia was found in 68.0% of individuals who underwent colonoscopy after a positive FIT-DNA test versus 42.3% of individuals with colonoscopy alone (p<.0001).

A retrospective cohort study conducted by Berger et al (2020) provides some limited evidence on the clinical implications of a false-positive FIT-DNA test.[19,] Of 1,216 participants, 206 had a positive FIT-DNA test and a negative colonoscopy. After a median 5 years follow up, individuals with discordant results (positive FIT-DNA test, negative colonoscopy) showed a nonsignificant trend towards increased risk of aerodigestive cancer relative to individuals with concordant

results (negative FIT-DNA, negative colonoscopy; adjusted risk ratio, 2.2; 95% CI, 0.8 to 6.2), but the rate of aerodigestive cancer in the discordant group was lower than the expected rate based on the National Cancer Institute's Surveillance, Epidemiology and End Result (SEER) data (risk ratio, 0.8; 95% CI, 0.3 to 1.9).

Chain of Evidence

Fendrick et al (2022) compared the life-years gained (LYG) per screening colonoscopy and follow-up colonoscopy after a positive stool-based test (FIT-DNA or FIT).[20,] Modeling was used to estimate CRC outcomes from screening and follow-up colonoscopies versus no screening in a simulated population of average-risk individuals aged 45 to 75 years. The LYG/colonoscopy per 1000 individuals was 0.09 for screening colonoscopy and 0.29 for follow-up colonoscopy. The number of CRC cases and CRC deaths averted per colonoscopy were 0.01 and 0.01 for screening colonoscopy, respectively, and 0.04 and 0.02 for follow-up colonoscopy, respectively.

Knudsen et al (2021) compared different CRC screening strategies using microsimulation modeling techniques to inform the U.S. Preventive Services Task Force CRC screening recommendations (see Table 1).[21,] Screening outcomes from various screening strategies beginning at age 45 years were estimated and compared. FIT-DNA was evaluated in these models using both a yearly screening strategy and an every 3 year strategy. The modeling results suggested that FIT-DNA screening produces outcomes within the range of other screening strategies. In terms of life-years gained according to screening strategy, FIT-DNA every 3 years is at the lower range of effectiveness, only higher than flexible sigmoidoscopy, and testing every year is at the higher range of effectiveness, only lower than colonoscopy every 10 years. In terms of complications or lifetime burden as expressed as colonoscopies, the modeling results found FIT-DNA to be in the range of other CRC screening strategies, with every year screening having higher complication and colonoscopy rates than every 3 year screening. Both measures of harm were estimated to be lower with FIT-DNA testing than the screening strategy of colonoscopy every 10 years.

Table 1. Outcomes of Colorectal Cancer Screening Strategies Over a Lifetime, in Order of Life-Years, Gained

Screening Method and Screening Interval	Life-Years Gained per 1000 Screened	CRC Deaths Averted per 1000 Screened	Complications of Screening and Follow-Up per 1000 Screened	Lifetime No. of Colonoscopies per 1000 Screened
Flexible sigmoidoscopy, 5 y	286	32	11	1839
FIT-DNA, 3 y	303	25	10	1661
CT colonography, 5 y	317	27	11	1751
FIT, 1 y	318	26	10	1682
Flexible sigmoidoscopy, 10 y + FIT, 1 y	332	27	13	2223
FIT-DNA, 1 y	333	28	12	2532
Colonoscopy, 10 y	337	28	16	4248

Adapted from Knudsen et al (2021)[21,]
CRC: colorectal cancer; CT: computed tomography; FIT: fecal immunochemical testing.

D'Andrea et al (2020) compared different CRC screening strategies using microsimulation modeling techniques to quantify CRC incidence and mortality, incremental LYG, number of colonoscopies, and adverse events for men and women aged 50 years or older over their lifetime.[22,] Modeling was conducted under 100% adherence rates and reported adherence rates at the population level. Adherence rates of 42.6% were assumed for FIT-DNA screening every 3 years, and adherence to colonoscopy screening every 10 years was modeled on data from the National Health Interview Survey suggesting that 62.4% of individuals become up to date with screening within a 10-year period. With 100% adherence, colonoscopy averted 46 CRC cases and 25 to 26 deaths, compared to 42 to 45 cases and 25 to 26 deaths with FIT-DNA per 1000 individuals. Assuming reported adherence, colonoscopy averted 34 cases and 20 deaths, compared to 16 to 25 cases and 10 to 16 deaths with FIT-DNA per 1000 individuals. LYG were proportional to the effectiveness of each strategy. Adverse events were more frequent for colonoscopy (3.7 per 1000 screened). Colonoscopy was found to have a larger benefit when compared to other screening methods including FIT-DNA. The authors note that screening adherence rates higher than 65% to 70% would be necessary for any stool-based screening modality to match the benefits of colonoscopy. However, a major limitation of this study was that the population adherence rate for FIT-DNA was assumed to be similar to FIT, which underestimates recently observed adherence rates. A cross-sectional screening study in a large, national sample of Medicare beneficiaries (N=368,494) by Weiser et al (2020) reported a real-world FIT-DNA adherence rate of 71%.[23,] Kisiel et al (2020) note that existing modeling strategies may additionally be limited by input assumptions that fail to account for aspects of neoplasia and adenoma progression, adenoma detection rates, and other patient, polyp, and provider characteristics that may impact simulated outcomes of lifetime screening and surveillance.[24,]

A comparative effectiveness modeling study by Barzi et al (2017) found that colonoscopy was the most effective screening strategy with the highest LYG (0.022 life years) and CRCs prevented (n=1,068), and the lowest total cost.[25,] Modeling for FIT-DNA every year or every other year found 0.011 LYG, 647 CRCs prevented, and a higher total cost. The main reason for the difference in CRCs prevented was due to the detection of precancerous polyps. The study found that, if the sensitivity of FIT-DNA for adenomas increased, it could surpass the sensitivity of colonoscopy. An unexpected consequence of a positive FIT-DNA test may be to improve the quality of the subsequent colonoscopy.[26,]

Another modeling study, by Berger et al (2016), sponsored by the manufacturer of Cologuard, showed similar findings.[27,] Compared with colonoscopy every 10 years, yearly FIT-DNA was estimated to produce similar reductions in CRC incidence and mortality. Every 3-year and every 5-year testing produced less reduction in CRC incidence and mortality. Colonoscopy every 10 years was estimated to decrease CRC incidence by 65%, whereas FIT-DNA every 3 years reduced CRC incidence by 57%, and FIT-DNA every 5 years reduced CRC incidence by 52%.

Updated modeling studies of health outcomes including Cologuard Plus have not yet been published. The modeling studies described in the previous paragraphs assume performance characteristics (sensitivity and specificity) for FIT-DNA from the original Cologuard test. Given that the performance characteristics of the next generation FIT-DNA test (Cologuard Plus) appear similar with respect to sensitivity and perhaps better with respect to specificity, the expected

clinical outcomes would be at least as good with the new FIT-DNA test compared to the original FIT-DNA test.

Section Summary: Fecal Immunochemical-DNA Testing: Cologuard and Cologuard Plus

Studies have demonstrated the higher sensitivity of FIT-DNA compared to FIT for both CRC detection and cancer precursor detection, but lower specificity. Modeling studies comparing different screening strategies have demonstrated that the diagnostic characteristics of FIT-DNA as shown in the existing studies are consistent with decreases in CRC mortality that are in the range of other accepted screening modalities. In terms of LYG, FIT-DNA every year is estimated to be close to, but not as effective as, colonoscopy every 10 years, while testing every 3 years is estimated to be less effective than most of the other accepted screening strategies. Estimates of harms and burdens are in the range of other screening strategies. Interpretation of modeling studies may be limited by their input assumptions.

As with the original FIT-DNA, in a head-to-head comparison of the new next generation FIT-DNA test to FIT alone including almost 19,000 participants, the new FIT-DNA test had higher sensitivity for both CRC detection and cancer precursor detection, but lower specificity. Although the next generation FIT-DNA test has not been directly compared to the original FIT-DNA, the new test appears to have similar sensitivity for CRC and cancer precursor detection while having higher specificity compared to the original test.

COLOSENSE

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Cohort Studies

Barnell et al (2023) reported results of the pivotal study (CRC-PREVENT; NCT04739722) of the FIT-RNA (Colosense) test.[28,] CRC-PREVENT prospectively enrolled 14,263 participants ages 45 and older (mean, 55 years) who were willing to undergo a colonoscopy from 49 US states using decentralized recruitment through an online social media platform from 2021 to 2022. Stool samples were collected prior to participants completing a colonoscopy at their local endoscopy center. The reference standard was colonoscopy results, which were based on histopathological review of all lesions either biopsied or resected during the colonoscopy, or negative results by colonoscopy. Participants were navigated to complete a routine colonoscopy at a local endoscopy center. 68% of participants did not have a colonoscopy scheduled prior to enrollment and many required assistance with obtaining a colonoscopy appointment at a local endoscopy center. 8920 participants were included in the analysis in the publication. The most common exclusions were: 2179 did not submit a valid stool sample; 852 had insufficient RNA; 1263 did not complete a colonoscopy; and 297 had inadequate colonoscopy preparation. 60% of participants were women. 4% of participants identified as Asian, 11% as Black or African American, 7% as Hispanic or Latino, and 84% as White. 34% had a prior or current history of smoking. Overall, the sensitivity of the FIT-RNA test for CRC was 94% (95% CI, 81 to 99) and for advanced adenomas (AA) was 46% (95% CI, 42 to 50). Overall, specificity for the FIT-RNA test was 87% (95% CI, 86 to 88). The primary outcome for regulatory approval reported in the Summary of Safety and Effectiveness Data (SSED) was the sensitivity and specificity in the average risk

population (n=7,763), excluding 526 enrolled participants with first-degree relatives with CRC. In the average risk population, the CRC sensitivity of the FIT-RNA test was 93% (95% CI, 76 to 99) and the AA sensitivity was 45% (95% CI, 41 to 49). The specificity of the FIT-RNA test in the average risk population was 86% (95% CI, 85 to 86). Sensitivity for CRC and AA was greater for the FIT-RNA test compared to FIT alone but the FIT-RNA test had lower specificity compared to FIT.[28,5,]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There are no studies evaluating the direct health outcomes of a longitudinal screening program using Colosense.

Chain of Evidence
Updated modeling studies of health outcomes incorporating the FIT-RNA test have not yet been published. The modeling studies described in the previous section assume performance characteristics (sensitivity and specificity) for FIT-DNA from the original Cologuard test. Given that the performance characteristics of the FIT-RNA test (Colosense) appear similar with respect to sensitivity and specificity, the expected clinical outcomes would be similar with the FIT-RNA test compared to the original FIT-DNA test.

Section Summary: Fecal Immunochemical-DNA Testing: Colosense
In a head-to-head comparison of the FIT-RNA test (Colosense) to FIT alone including almost 8000 participants, the FIT-RNA test had higher sensitivity for both CRC detection and cancer precursor detection, but lower specificity. Although the FIT-RNA test (Colosense) has not been directly compared to the original FIT-DNA (Cologuard), the FIT-RNA test appears to have similar sensitivity for CRC and cancer precursor detection as well as similar specificity for CRC.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guideline (v.1.2024) for colorectal cancer (CRC) screening includes the use of fecal immunochemical testing (FIT)-DNA to screen patients with an average risk for colon cancer. [6,] Following a negative test, the recommendation is to rescreen with any modality in 3 years. Use of FIT-DNA is not described for the screening of high-risk individuals. Follow-up colonoscopy is recommended within 9 months after a positive test.

Multi-Society Task Force on Colorectal Cancer

A U.S. Multi-Society task force representing the American College of Gastroenterology, the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (2017) provided recommendations for CRC screening.[29,] The recommended first-tier tests for individuals with average risk were colonoscopy every 10 years, and for individuals who decline colonoscopy, annual FIT. Recommended second-tier tests in patients who declined the first-tier tests were computed tomography colonography every 5 years, FIT-DNA every 3 years, or flexible sigmoidoscopy every 5 to 10 years. Capsule colonoscopy was listed as a third-tier test. The task force recommended, "[computed tomography] colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low-quality evidence), or flexible sigmoidoscopy every 5-10 years (strong recommendation, high-quality evidence) in patients who refuse colonoscopy and FIT." In 2022, a focused update to the 2017 CRC screening recommendations from the task force was published that addressed the age to begin and stop CRC screening in average-risk individuals.[30,] The task force now suggests CRC screening in average-risk individuals aged 45 to 49 years. Unchanged from 2017 are the following recommendations: a) offer CRC screening to all average-risk individuals aged 50 to 75 years, b) consider starting or continuing screening for individuals aged 76 to 85 years on an individualized basis (depending on patient and disease factors), and c) screening is not recommended after age 85 years.

American Cancer Society

In 2018, the American Cancer Society updated its guidelines for CRC screening for average-risk adults.[31,] Regular screening with either a structural examination (i.e., colonoscopy) or a high-sensitivity stool-based test is recommended to start in adults who are age 45 years and older (qualified recommendation) or who are age 50 years and older (strong recommendation). Recommendations for screening with stool-based tests include FIT repeated every year, high-sensitivity guaiac-based fecal occult blood test repeated every year, or multitarget stool DNA test repeated every 3 years.

American College of Physicians

In 2023, the American College of Physicians (ACP) released updated guidance on screening for CRC in asymptomatic, average-risk adults.[32,] The ACP stated that "Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer". A guidance statement of approved tests is as follows: "Clinicians should select among a fecal immunochemical or high-sensitivity guaiac fecal occult blood test every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus a fecal immunochemical test every 2 years as a screening test for colorectal cancer".

American Gastroenterological Association

In 2022, the AGA published a clinical practice update commentary that reviewed the evidence on noninvasive CRC screening options.[33,] Similar to the U.S. Multi-Society task force, the ACG recommends FIT-DNA every 3 years as an average-risk option for CRC screening. The

commentary compares this recommendation to that of the U.S. Preventive Services Task Force (USPSTF), which recommends FIT-DNA every 1 to 3 years.

In 2023, the AGA published a clinical practice update reviewing risk stratification for CRC screening and post-polypectomy surveillance.[34,] Similar to other guidelines, the following best practice advice was provided: "Screening options for individuals at average risk for CRC should include colonoscopy, fecal immunochemical test (FIT), flexible sigmoidoscopy plus FIT, multitarget stool DNA test, and computed tomography colonography, based on availability and individual preference."

U.S. Preventive Services Task Force Recommendations

In 2021, the U.S. Preventive Services Task Force published updated recommendations for CRC screening in asymptomatic, average risk adults (defined as no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorders that predispose them to a high lifetime risk of CRC [such as Lynch syndrome or familial adenomatous polyposis]).[1,] The USPSTF recommended universal screening for average risk adults aged 45 to 49 years (B recommendation) and for adults aged 50 to 75 years (A recommendation). For adults aged 76 to 85 years, the USPSTF recommends selective screening due to the small magnitude of net benefit (C Recommendation). The USPSTF reviewed evidence for 6 screening strategies, including FIT-DNA. They do not recommend one screening strategy over another, and noted the lack of direct evidence on clinical outcomes when comparing screening strategies. Clinical considerations noted for FIT-DNA testing appear in Table 2.

Table 2. U.S. Preventative Services Task Force Considerations for Fecal Immunochemical-DNA Testing

Recommended screening interval	Efficacy	Other considerations
1 to 3 years	• 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 FIT-DNA screening test compared with per FIT test • Modeling suggests that screening every 3 years does not provide a favorable balance of benefits and harms compared with other stool-based screening options	• Harms from screening with FIT-DNA arise from colonoscopy to follow-up abnormal FIT-DNA 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)

Recommended screening interval	Efficacy	Other considerations
	(annual FIT or FIT-DNA every 1 or 2 years) • Insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative follow-up colonoscopy • No direct evidence evaluating the effect of FIT-DNA on colorectal cancer mortality	

FIT: fecal immunochemical testing.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04739722[a]	Multitarget Stool RNA Test (ColoSense) for Colorectal Cancer Screening	14,263	Jan 2024
NCT04124406[a]	Voyage: Real-World Impact of the Multi-target Stool DNA Test on CRC Screening and Mortality	150,000	Dec 2029
NCT04336397	Randomized Controlled Trial of the Stool DNA Test to Improve Colorectal Cancer Screening Among Alaska Native People	1,540	Sept 2024
Unpublished			
NCT02419716[a]	A Longitudinal Study of Cologuard in an Average Risk Population Assessing a 3 Year Test Interval	2,404	Mar 2020

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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
0421U	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 8 RNA markers (GAPDH, SMAD4, ACY1, AREG, CDH1, KRAS, TNFRSF10B, EGLN2) and fecal hemoglobin, algorithm reported as a positive or negative for colorectal cancer risk

REVISIONS	
08-08-2016	Policy added to the bcbsks.com web site on 07-07-2016 with an effective date of 08-08-2016.
01-01-2017	Updated Description section.
	In Policy section: ▪ Removed entire previous policy statement, "DNA analysis of stool samples is considered experimental / investigational as a screening technique for colorectal cancer in patients at average-to-high risk of colorectal cancer." ▪ Added " A. DNA analysis of stool samples using Cologuard™ may be considered medically necessary as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 50 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval: 1. Guaiac-based fecal occult blood test in the past year, or 2. Fecal immunochemical test in the past year, or 3. Multitargeted stool DNA test in the past 3 years, or Colonoscopy in the past 10 years, or 4. CT colonography in the past 5 years, or 5. Flexible sigmoidoscopy in the past 5 years. B. In individuals who are considered candidates for Cologuard™ screening, repeat testing at intervals of every 3 years may be considered medically necessary. C. DNA analysis of stool samples is considered experimental / investigational when the criteria above are not met and for all other indications including post colorectal diagnosis surveillance. D. All other screening stool DNA tests are considered experimental / investigational." ▪ Added "Policy Guidelines 1. Average risk of developing colorectal cancer include those individuals who have no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer. 2.

REVISIONS	
	Asymptomatic individuals include those who have no signs or symptoms of colorectal disease including, but not limited to, lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes: Z12.10, Z12.11, Z12.12.
	Updated References section.
12-20-2017	Updated Description section.
	In Policy section: ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
01-04-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-02-2020	Updated Description section
	Updated Rationale section
	Updated Reference section
09-22-2021	In Policy section: ▪ A. Age range 45 years to 75 years change
01-04-2022	Updated Description Section
	Updated Rationale Section
	Updated Codes Section ▪ Added ICD 10 codes C18.0-C18.9, C19, Z15.09, Z80.0
	Updated References Section
12-29-2022	Updated Description Section
	Updated Rationale Section
	Updated Reference Section
01-05-2024	Updated Description Section
	Updated Rationale Section
	Updated Codes Section ▪ Removed ICD-10 Codes
	Updated References Section
Posted 02-11-2025 Effective 03-13-2025	Updated Title ▪ Added" "RNA" to the title "Analysis of Human DNA or RNA in Stool Samples as a Technique for Colorectal Cancer Screening"
	Updated Description Section
	Update Policy Section ▪ Removed: A. DNA analysis of stool samples using Cologuard™ may be considered medically necessary as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 45 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval: 1. Guaiac-based fecal occult blood test in the past year, OR 2. Fecal immunochemical test in the past year, OR 3. Multitargeted stool DNA test in the past 3 years, OR 4. Colonoscopy in the past 10 years, OR 5. CT colonography in the past 5 years, OR 6. Flexible sigmoidoscopy in the past 5 years. B. In individuals who are considered candidates for Cologuard™ screening, repeat testing at intervals of every 3 years may be considered medically necessary.

REVISIONS	
	C. DNA analysis of stool samples is considered experimental / investigational when the criteria above are not met and for all other indications including post colorectal cancer diagnosis surveillance. D. If medical documentation is not provided which supports medical necessity, DNA analysis of stool samples using Cologuard™ is considered not medically necessary. E. All other screening stool DNA or tests are considered experimental / investigational. ▪ Added: A. DNA or RNA analysis of stool samples can be considered medically necessary as a screening technique for colorectal cancer in individuals at average risk of colorectal cancer who have not been screened by another colorectal cancer screening method within the last year. B. Combination testing of DNA or RNA analysis of stool samples with other methods of colorectal cancer screening within a year is experimental / investigational. C. DNA or RNA analysis of stool samples is considered experimental / investigational for all other indications.
	Updated Policy Guidelines ▪ Removed policy guidelines: A. Average risk of developing colorectal cancer include those individuals who have no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer. B. Asymptomatic individuals include those who have no signs or symptoms of colorectal disease including, but not limited to, lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test. C. Individuals with an estimated life expectancy of less than 10 years should not be screened for colorectal cancer.
	Updated Rationale Section
	Updated Coding Section ▪ Added 0421U
	Updated Reference Section

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