# Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/25**
**(See policy history boxes for previous effective dates)**

# Title: Analysis of Human FIT-DNA (i.e., ColoGuard®) and FIT-RNA (i.e., Colosense®) in Stool Samples as a Technique for Colorectal Cancer Screening

## Description/Background

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.

### FIT DNA Testing

Screening stool or fecal DNA (Cologuard™) testing detects molecular markers of altered DNA that are contained in the cells shed by colorectal cancer and pre-malignant colorectal polyps. DNA tests are designed to detect very small amounts of DNA markers to identify colorectal cancer or pre-malignant colorectal neoplasia. 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 DNA test combines FIT and DNA analysis and is referred to as FIT-DNA in this review, though other publications also use the terms stool DNA (sDNA)-FIT and multitarget stool DNA (mt-sDNA).

Cologuard™ is a proprietary in vitro diagnostic multitarget FIT-DNA test which uses a device which incorporates both DNA and fecal immunochemical test techniques and is designed to analyze individuals stool samples for markers associated with the presence of colorectal cancer and pre-malignant colorectal neoplasia.

Cologuard Plus™ (Exact Sciences Laboratories, LLC) is a multianalyte assays with algorithmic analyses test for colorectal screening. Cologuard Plus is a multitarget test that detects 3 novel methylated DNA markers including LASS4, LRRC4 and PPP2R5C along with fecal hemoglobin. Fecal hemoglobin is detected using a quantitative enzyme-linked immunosorbent assay. An algorithm incorporates results of DNA methylation and hemoglobin assays to generate a qualitative positive or negative result.

**FIT-RNA Testing**

ColoSense is an RNA-based stool test which analyzes 8 RNA biomarkers (GAPDH, ACY1, AREG, TNFRSF10B, CDH1, EGLN2, KRAS SMAD4) associated with CRC, along with an individuals smoking history and a fecal immunochemical test. The multi-target stool RNA (mt-sRNA) test is engineered for the stabilization and qualitative detection of RNA signals. RNA biomarkers are purported to provide a dynamic view of disease activity, not subject to age-related methylation patterns that can lead to variability in test performance across different age groups ColoSense is intended for the qualitative detection of colorectal neoplasia-associated RNA markers and for the presence of occult hemoglobin in human stool. Indications include use as a screening tool for adults 45 years of age or older who are at typical average risk for developing CRC. ColoSense is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

The U.S. Preventive Services Task Force recommendations for colorectal screening include DNA-FIT testing every 1 to 3 years as an option for adults 45 to 75 years of age.(1) RNA-FIT testing is not among the tests that the U.S. Preventative Services Task Force recommend for screening of colorectal cancer.

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## 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) 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 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 (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

## Medical Policy Statement

FIT-DNA (i.e., ColoGuard® ColoGuard Plus) analysis of stool samples, using FDA approved tests, is considered established as a screening technique for colorectal cancer for individuals at average risk who are 45 years of age and older and not been screened by another colorectal cancer screening method within the last year.

FIT-RNA (i.e., ColoSense®) analysis of stool samples is considered established as a screening technique for colorectal cancer for individuals at average risk who are 45 years of age and older and have not been screened by another colorectal cancer screening method within the last year.

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## Inclusionary and Exclusionary Guidelines

**Inclusions:**

Screening of members who are 45-75 years old must meet **both** of the following criteria:

- At average risk for colon cancer
- Asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in the stools, positive guaiac fecal occult blood test or fecal immunochemical test)

The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history.

- Adults in this age group who have never been screened for colorectal cancer are more likely to benefit.
- Screening would be most appropriate among adults who meet **both** of the following indications:
    - Are healthy enough to undergo treatment if colorectal cancer is detected
    - Do not have co-morbid conditions that would significantly limit their life expectancy

Repeat studies, are appropriate at 3-year intervals in individuals, who remain at average risk and meet all of the above requirements

**Exclusions:**

- DNA or RNA testing is not indicated in the following: *(list may not be all inclusive)*
    - Symptomatic individuals
    - Personal history of adenomatous polyps
    - Personal history of colorectal cancer
    - History of inflammatory bowel disease
    - Family history of colorectal cancer or adenomatous polyps in a parent or other first degree relative, particularly when the age of cancer onset is 45 years or less.
    - Familial adenomatous polyposis
    - Lynch Syndrome
- Combination testing of DNA or RNA analysis stool samples with other methods of colorectal cancer screening within a year

Because colonoscopy offers specific advantages as a colon cancer screening tool, providers should ideally discuss this as 1 of the options for screening with their patients, so an informed decision can be made.

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## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

### *Established codes:*

81528 0421U 0464U

### *Other codes (investigational, not medically necessary, etc.):*

N/A

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## Rationale

**FECAL IMMUNOCHEMICAL DNA OR RNA TESTING**

For patients at average risk for colorectal cancer (CRC), organizations such as the U.S. Preventive Services Task Force recommend 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 on 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. 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 PICOs were used to select literature to inform this review.

***Populations***

The relevant population of interest are 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. These tests are approved by the Food and Drug Administration, which combine FIT and DNA or RNA analysis (FIT-DNA). 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)<br>75%–93% (≥6 mm adenomas) | ---- | 89% (≥10 mm adenomas)<br>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)<br>86% (≥6 mm adenomas) | ---- | 94% (≥10 mm adenomas)<br>88% (≥6 mm adenomas) |
| High-sensitivity guaiac-based test | Annually | 50%–75% | 7%–21% (advanced neoplasia)<br>6%–17% (advanced adenoma) | 96%–98% | 96%–99% (advanced neoplasia)<br>96%–99% (advanced adenoma) |
| Quantitative FIT (using OC-Sensor) | Annually | 74% | 25% (advanced neoplasia)<br>23% (advanced adenoma) | 94% | 96% (advanced neoplasia)<br>96% (advanced adenoma) |
| Quantitative FIT (using OC-Light) | Annually | 81% | 27% (advanced neoplasia)<br>28% (advanced adenoma) | 93% | 95% (advanced neoplasia)<br>94% (advanced adenoma) |
| mt-sDNA test[4] | Every 3 years | 93% | 47% (advanced neoplasia)<br>43% (advanced adenoma) | 85% | 89% (advanced neoplasia)<br>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 45. The FDA approved the use of Cologuard for individuals aged 45 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.(9) The studies all used colonoscopy as the reference standard. When pooled, FIT-DNA had a sensitivity of 93% (95% confidence interval [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% to55.0%; $I^2$=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 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 U.S. Food and Drug Administration (FDA) approval of this fecal 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 colorectal cancer and cancer precursors. In 9989 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, sensitivity of the FIT-DNA did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of fecal DNA testing was higher for distal lesions than for proximal lesions. FIT-DNA sensitivity increased as lesion size increased. The specificity of the FIT-DNA was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, specificity of FIT-DNA test was 89.8% versus 94.9% for FIT. For identification of patients 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 (2-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 individuals 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 individuals 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.(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 to1.9).

**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 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 3. 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)
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 life years gained (LYG), number of colonoscopies, and adverse events for men and women 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 25-26 deaths compared to 42-45 cases and 25-26 deaths with FIT-DNA per 1000 individuals. Assuming reported adherence, colonoscopy averted 34 cases and 20 deaths compared to 16- 25 cases and 10-16 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 65-70% would be necessary for any stool-based screening modality to match the benefits of colonoscopy. However, a major limitation of this study is 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 life years gained (LYG; 0.022 life years) and CRCs prevented (n=1068), and the lowest total cost.(25) Modeling for FIT-DNA every year or every other year found 0.011 life years gained, 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.

**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 a 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.(5,28)

**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 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.

**SUMMARY OF EVIDENCE**
For individuals who are asymptomatic and at average risk of CRC who receive FIT-DNA, the evidence includes screening studies comparing the original and next generation version of the FIT-DNA (using colonoscopy as the reference standard) to fit alone, 2 systematic reviews of screening studies, and 2 modeling studies. Relevant outcomes are overall survival, disease-specific survival. The screening studies have reported that both the original and the next-generation FIT-DNA tests have higher sensitivity and lower specificity than FIT. There are no studies directly assessing health outcomes such as overall survival or disease-specific survival. The screening interval for the test has not been confirmed nor is there evidence on the adherence of the test at a recommended screening interval. Effective screening for CRC requires a screening program with established screening intervals and appropriate follow-up for positive tests. Clinical utility of FIT-DNA is based on modeling studies. These studies have demonstrated that the diagnostic characteristics of FIT-DNA are consistent with decreases in CRC mortality that are in the range of other accepted modalities. FIT-DNA every 3 years is less effective than most other accepted screening strategies, while FIT-DNA every year is close to the efficacy of colonoscopy every 10 years. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at average risk of colorectal cancer (CRC) who receive fecal immunochemical testing (FIT)-RNA, the evidence includes a screening study

comparing the FIT-RNA (using colonoscopy as the reference standard) to FIT alone. Relevant outcomes are overall survival and disease-specific survival. The screening study reported that the FIT-RNA test has higher sensitivity and lower specificity than FIT. There are no studies directly assessing health outcomes such as overall survival or disease-specific survival. The screening interval for the test has not been confirmed nor is there evidence on the adherence of the test at a recommended screening interval. Effective screening for CRC requires a screening program with established screening intervals and appropriate follow-up for positive tests. Clinical utility of FIT-RNA is based on the similar performance characteristics of FIT-RNA compared to FIT-DNA so that FIT-DNA modeling studies are also of relevance for FIT-RNA. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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## Supplemental Information

### PRACTICE GUIDELINES AND POSITION STATEMENTS

#### National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines for colorectal cancer screening includes the use of FIT-DNA based testing to screen patients with an average risk for colon cancer.(26) 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 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, and the American Society for Gastrointestinal Endoscopy (2017) provided recommendations for colorectal cancer screening.(29) The recommended first tier tests for individuals with average risk were colonoscopy every 10 years, and for individuals who decline colonoscopy, annual fecal immunochemical testing (FIT). Recommended second tier tests in patients who declined the first-tier tests were computed tomography (CT) 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 “CT colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low quality evidence, or flexible sigmoidoscopy every 5 to 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

The American Cancer Society (2020) updated its guidelines for CRC screening for average-risk adults.(31) For people at average risk, the ACS recommends regular screening for colorectal cancer should begin at age 45. No preference is given to either a high sensitivity stool-based test or a direct visual examination. 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

The U.S. Preventive Services Task Force (USPSTF [2021]) updated its 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 1 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<br>• 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 | • Harms from screening with FIT-DNA arise from colonoscopy to follow-up abnormal FIT-DNA results |

| | | |
|---|---|---|
| | • Modeling suggests that screening every 3 years does not provide a favorable balance of benefits and harms compared with other stool-based screening options (annual FIT or FIT-DNA every 1 or 2 years)<br>• Insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative follow-up colonoscopy<br>• No direct evidence evaluating the effect of FIT-DNA on colorectal cancer mortality | • Can be done with a single stool sample but involves collecting an entire bowel movement<br>• Requires good adherence over multiple rounds of testing<br>• Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home) |

FIT: fecal immunochemical testing.

## ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently 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 (recruiting) |
| NCT04336397 | Randomized Controlled Trial of the Stool DNA Test to Improve Colorectal Cancer Screening Among Alaska Native People | 1,540 | Mar 2025 |
| ***Unpublished*** | | | |
| NCT02419716[a] | A Longitudinal Study of Cologuard™ in an Average Risk Population Assessing a 3 Year Test Interval | 2,404 | Mar 2020 (completed) |

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

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## Government Regulations
## National:

"NCD for **Colorectal Cancer Screening Tests** (210.3)," Effective Date 1/1/23, Implementation Date 2/27/23 Pub number 100-3; v. 7.

*The Cologuard™ - Multitarget Stool DNA (sDNA) Test (effective October 9, 2014)*

The Cologuard™ test is covered once every 3 years for Medicare beneficiaries who meet all of the following criteria:

- Age 50 to 85 years,
- Asymptomatic (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), and
- At average risk of developing colorectal cancer (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).

*Nationally Non-Covered Indications*

All other indications for colorectal cancer screening not otherwise specified in the Act and regulations, or otherwise specified above remain nationally non-covered. Non-coverage specifically includes:

- All screening sDNA tests, effective April 28, 2008, through October 8, 2014. Effective for dates of service on or after October 9, 2014, all other screening sDNA tests not otherwise specified above remain nationally non-covered.

As noted in the Centers for Medicare & Medicaid Services decision memo, the optimal screening interval for Cologuard is unknown. In the interim, Centers for Medicare & Medicaid Services has indicated it will cover Cologuard every 3 years as previously specified and would reevaluate the screening interval after the FDA post-approval study is completed.

### Local:

There is no Local Coverage Determination for fecal DNA analysis for colorectal cancer screening.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

- CPT Category III Codes – Noncovered Services
- Genetic Testing – Experimental/Investigational Status
- Miscellaneous and Genetic and Molecular Diagnostic Tests
- Serologic Genetic and Molecular Screening for Colorectal Cancer

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/28/25, the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 10/6/03 | 10/6/03 | 10/6/03 | Joint medical policy established |
| 2/2/04 | 2/2/04 | 3/1/04 | S code received – effective April 1, 2004 |
| 6/15/05 | 6/15/05 | 5/18/05 | Routine maintenance |
| 1/1/07 | 11/1/06 | 9/24/06 | Routine maintenance |
| 1/1/08 | 10/16/07 | 11/11/07 | Routine maintenance |
| 3/1/09 | 12/1/09 | 12/21/08 | Routine maintenance |
| 9/1/10 | 6/15/10 | 6/29/10 | Routine maintenance |
| 3/1/12 | 12/13/11 | 12/21/11 | Routine maintenance |
| 5/1/13 | 2/19/13 | 3/4/13 | Routine maintenance; incorporated BCBSA's policy; title changed from "Fecal DNA Analysis for Colorectal Cancer Screening" to current title. |
| 3/1/15 | 12/9/14 | 12/29/14 | Routine maintenance; updated Medicare NCD coverage information for Cologuard™; codes 81479 and G0464 added to policy; references updated |
| 3/1/16 | 12/10/15 | 12/10/15 | • Routine maintenance<br>• Added procedure code 81528; deleted S3890, G0464 and unlisted procedure code 81479<br>• References updated<br>• U.S. Preventative Services Task Force recommendation updated<br>• National Guidelines updated to reflect Version 1.2015 |
| 11/1/16 | 8/16/16 | 8/16/16 | • Routine maintenance |
| 3/1/17 | 1/27/17 | 12/31/16 | • Change in policy status from experimental/investigational to established. |
| 3/1/17 | 4/18/17 | 4/18/17 | • Updated NCCN guidelines<br>• Added age 50-75 to inclusions |

| | | | |
|---|---|---|---|
| | | | • Added USPSTF recommendations for age 76-85 years old to inclusions<br>• Updated MPS statement |
| 3/1/18 | 12/12/17 | 12/12/17 | • Routine maintenance<br>• USPSTF Tier 2 recommendations added |
| 3/1/19 | 12/11/18 | 12/11/18 | • Routine maintenance |
| 7/1/19 | 4/16/19 | | • Routine maintenance |
| 7/1/20 | 4/14/20 | | • Routine maintenance |
| 7/1/21 | 4/20/21 | | • Routine maintenance |
| 7/1/21 | 6/15/21 | | • Added USPSTF updated recommendations (May) to allow for screening to begin at age 45 |
| 7/1/22 | 4/19/22 | | • Routine maintenance |
| 7/1/23 | 4/18/23 | | • Routine maintenance (slp)<br>• Vendor managed: Avalon |
| 7/1/24 | 4/16/24 | | • Routine maintenance (slp)<br>• Vendor managed: Avalon<br>• Title updated from: Analysis of Human DNA in Stool for CRC |
| 7/1/25 | 4/16/25 | | • Routine maintenance (slp)<br>• Vendor managed: Avalon PPO; JVHL for HMO LOB only (0464U)<br>• Title updated from: Analysis of Human FIT-DNA (i.e., ColoGuard) in Stool Samples as a Technique for CRC<br>• ColoGuard Plus (0464U) added as EST |

Next Review Date: 2nd Qtr, 2026

# BLUE CARE NETWORK BENEFIT COVERAGE POLICY: ANALYSIS OF HUMAN FIT-DNA (I.E., COLOGUARD®) AND FIT-RNA (I.E., COLOSENSE®) IN STOOL SAMPLES AS A TECHNIQUE FOR COLORECTAL CANCER SCREENING

## I. Coverage Determination:

| | |
|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | Covered; criteria apply |
| **BCNA (Medicare Advantage)** | Refer to the Medicare information under the Government Regulations section of this policy. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.