Medical Policy

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***Current Policy Effective Date: 7/1/24**
(See policy history boxes for previous effective dates)

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

Description/Background

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.

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 (APC) 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:

On August 12, 2014, Cologuard® (Exact Sciences) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as an automated fecal DNA testing product for use in average risk adults aged 50 to 84 (P130017). Cologuard® is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool.(1) A positive result may indicate the presence of colorectal cancer or advanced adenoma and should be followed by diagnostic colonoscopy. On September 20, 2019, the FDA approved the expansion of the Cologuard® label to include adults ages ≥45 years.(2) Cologuard® is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. On August 26, 2020, the FDA approved the post approval study (PAS) protocol titled: "A Real-World Study of Patients Under the Age of 50 Screened for Colorectal Cancer (CRC) Using Cologuard® in the U.S. (Tidal)."(3)

Medical Policy Statement

The safety and effectiveness of FIT-DNA (i.e., ColoGuard®) 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.

FIT-DNA (i.e., ColoGuard®) analysis of stool samples for all other indications is considered experimental/investigational.

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:

- The test 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

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.

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

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

N/A

Rationale

FECAL IMMUNOCHEMICAL DNA 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 purpose of stool DNA testing in individuals who are at average risk of CRC is to inform a decision 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.

Interventions

The test being considered is Cologuard, the only test approved by the Food and Drug Administration, which combines FIT and DNA analysis (FIT-DNA). A stool sample is collected at home, prepared in a collection kit, and shipped to the manufacturer for analysis.

Comparators

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

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.

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.(4) Data were pooled from 11 studies, including the Redwood 2016,(5) Imperiale 2014,(6) Lidgard 2013,(7) and Ahlquist 2012,(8) studies discussed in the subsequent sections. 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),(9) (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.(6) Redwood 2016,(5) and Cooper 2018, (10) 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
Preliminary studies of the FIT-DNA (Cologuard) were conducted by Ahlquist et al (2012) (11,8) and Lidgard et al (2013).(7) This multi-target FIT-DNA consists of quantitative measurements of molecular assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS,* β-actin, and hemoglobin in a logistic-regression algorithm. Since the test includes a FIT in its algorithm, it is actually a combined stool DNA and FIT test. In a study of 252 patients with CRC, 133 patients with adenomas of 1 cm or larger and 293 subjects with normal colonoscopy, the test detected 85% of colon cancer cases and 54% of subjects with adenomas, with 90% specificity.(11) Another smaller study of this same test showed a sensitivity of 87% for detecting CRC and 82% sensitivity for detecting adenomas.(8) In the Lidgard et al (2013) study, of 1003 patients, there were 207 cases with CRC or advanced adenomas (>1 cm), and 796 control patients with no polyps or non-advanced adenomas (<1 cm). In the case group, 93 subjects had CRC, 84 had advanced adenoma (≥ 1 cm) and 30 had sessile serrated adenoma (≥ 1 cm). In the control group, 155 subjects had non-advanced adenomas and 641 had no colonic lesions. Using a logistic regression algorithm that incorporates 11 markers into a single regression score and a fixed specificity of 90%, the FIT-

DNA identified 84 of 86 (98% sensitivity) CRCs and 41 of 73 (56% sensitivity) advanced adenoma cases.(10) These preliminary studies all evaluated stool DNA using pre-assembled samples of study subjects with and without cancer or colonic lesions. For diagnostic characteristics of tests evaluated in these types of study samples may be biased.

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.(6) The results of this study supported the U.S. Food and Drug Administration (FDA) approval of this fecal DNA test (Cologuard™) in August 2014. 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.(12) 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.(13) 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.(5) 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.(10) 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%.

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. 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.(14)

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.(15) 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.(16) 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

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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).(17) 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).(18) 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 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)
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.(19) 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 and colleagues (2020) reported a real-world FIT-DNA adherence rate of 71%.(20) 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.(21)

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.(22) 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.(23)

Another modeling study, by Berger et al (2016), sponsored by the manufacturer of Cologuard, showed similar findings.(24) 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%.

A TEC Special Report (2014) evaluated FIT-DNA for CRC screening.(25) The report found the Imperiale et al (2014) study (6) to be of good quality but noted that while FIT-DNA had higher sensitivity than FIT for various types of colorectal lesions, these results represented the diagnostic characteristics of the FIT-DNA in a single-time cross-sectional study. How these study results would translate to reduced colorectal mortality in a longitudinal screening program has not been directly assessed. The optimal screening interval is unknown.

Section Summary: Fecal Immunochemical-DNA Testing

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.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic and at average risk of CRC who receive FIT-DNA, the evidence includes a number of small studies comparing FIT-DNA (in early stages of development) with colonoscopy, screening studies comparing the final version of the FIT-DNA (using colonoscopy as the reference standard), 2 systematic reviews of screening studies, and 2 modeling studies. Relevant outcomes are overall survival, disease-specific survival. The screening studies have reported that FIT-DNA 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 test characteristics of FIT-DNA show the potential of the test to be an effective CRC screening test, but there is uncertainty about other aspects of it. The screening interval for the test has not been firmly established 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.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.1.2023) 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 6 to 10 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.(27) 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.(28) 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.(29) 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.(30) 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.(31) 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.

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]).(32) 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 • 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 (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	• 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)

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			
NCT04144738[a]	Clinical Validation of An Optimized Multi-Target Stool DNA (Mt-sDNA 2.0) Test, for Colorectal Cancer Screening "BLUE-C"	26,758	Mar 2023
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.

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.

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.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 2/6/24, 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 • Added procedure code 81528; deleted S3890, G0464 and unlisted procedure code 81479 • References updated • U.S. Preventative Services Task Force recommendation updated • 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 • Added age 50-75 to inclusions

			• Added USPSTF recommendations for age 76-85 years old to inclusions • Updated MPS statement
3/1/18	12/12/17	12/12/17	• Routine maintenance • 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) • Vendor managed: Avalon
7/1/24	4/16/24		• Routine maintenance (slp) • Vendor managed: Avalon • Title updated from: Analysis of Human DNA in Stool for CRC

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ANALYSIS OF HUMAN FIT-DNA (I.E., COLOGUARD®) 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.