Medical Policy

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

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

DESCRIPTION

Detection of DNA 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 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).

OBJECTIVE

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

BACKGROUND

Colorectal Cancer

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

REGULATORY STATUS

On August 12, 2014, Cologuard® (Exact Sciences Corporation) 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 years (P130017). Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and of occult hemoglobin in human stool.[1,] A positive result may indicate the presence of CRC 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 average risk adults aged ≥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,]

POLICY

A. DNA analysis of stool samples using Cologuard™ may be considered **medically necessary** as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 45 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval:
   1. Guaiac-based fecal occult blood test in the past year, **OR**
   2. Fecal immunochemical test in the past year, **OR**
   3. Multitargeted stool DNA test in the past 3 years, **OR**
   4. Colonoscopy in the past 10 years, **OR**
   5. CT colonography in the past 5 years, **OR**
   6. Flexible sigmoidoscopy in the past 5 years.

B. In individuals who are considered candidates for Cologuard™ screening, repeat testing at intervals of every 3 years may be considered **medically necessary**.

C. DNA analysis of stool samples is considered **experimental / investigational** when the criteria above are not met and for all other indications including post colorectal cancer diagnosis surveillance.

D. If medical documentation is not provided which supports medical necessity, DNA analysis of stool samples using Cologuard™ is considered **not medically necessary**.

E. All other screening stool DNA tests are considered **experimental / investigational**.

POLICY GUIDELINES

A. Average risk of developing colorectal cancer include those individuals who have no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer.

B. Asymptomatic individuals include those who have no signs or symptoms of colorectal disease including, but not limited to, lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test.

C. Individuals with an estimated life expectancy of less than 10 years should not be screened for colorectal cancer.

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

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 26, 2021.

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

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

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

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

Clinical Context and Test Purpose
The purpose of stool DNA testing in patients who are at average risk of CRC is to inform a decision whether to proceed to colonoscopy.

The question addressed in this evidence review is this: Does testing of stool DNA improve the net health outcome for asymptomatic individuals at average risk of CRC who are undergoing routine CRC screening?

The following PICO was 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 U.S. Food and Drug Administration (FDA), 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 patients of average risk undergoing colonoscopy, this is every 10 years beginning at age 50 years. The FDA approved the use of this test for patients aged 45 years and older in September 2019. CRC screening with Cologuard may be needed more frequently.

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

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

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 conducted by Lin et al (2021)[4,] (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[5,], Redwood 2016[6,] and Cooper 2018[7,] 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.[4,] 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% to 55.0%; I^2=0%) and specificity was 89% (95% CI, 87.0% to 92.0%; I^2=88.8%) based on 4 studies. Pooled sensitivity and specificity for detection of advanced adenoma, based on 3 studies, was 43% (95% CI, 40.0% to 46.0%; I^2=0%) and 89% (95% CI, 86.0% to 92.0%; I^2=87.8%).

Cohort Studies

Preliminary studies of the FIT-DNA (Cologuard) were conducted by Ahlquist et al (2012)[8,9,] and Lidgard et al (2013).[10,] This multitarget 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. Because it includes a FIT in its algorithm, it is actually a combined stool DNA and FIT. 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.[8,] Another smaller study of this same test showed a sensitivity of 87% for detecting CRC and 82% sensitivity for detecting adenomas.[9,] 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 nonadvanced adenomas (<1 cm). In the case group, 93 subjects had CRC, 84 had advanced adenoma 1 cm or larger, and 30 had sessile serrated adenoma 1 cm or larger. In the control group, 155 subjects had nonadvanced 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%, FIT-DNA identified 84 (98% sensitivity) of 86 CRCs and 41 (56% sensitivity) of 73 advanced adenoma cases.[10,] These preliminary studies all evaluated stool DNA using preassembled samples of study subjects with and without cancer or colonic lesions. For diagnostic characteristics of tests evaluated in these types of study, samples might have been biased.

A large-scale evaluation of FIT-DNA (Cologuard) in a screening population was published by Imperiale et al (2014), who compared FIT-DNA with colonoscopy in 12,000 asymptomatic adults between the ages of 50 and 84 years (mean age, 64 years) at average risk for CRC.[5,] The results of this study supported the initial FDA approval of this FIT-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 CRC and cancer precursors. In 9,989 evaluable subjects, FIT-DNA sensitivity for cancer was 92.3% (95% CI , 83.0% to 97.5%) and for FIT it was 73.8% (95% CI, 61.5% to 84.0%). For advanced precancerous lesion, FIT-DNA test sensitivity was 42.4% (95% CI, 38.9% to 46.0%) and for FIT it was 23.8% (95% CI, 20.8% to 27.0%). In analyses of specific types of lesions, the sensitivity of FIT-DNA did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of FIT-DNA testing was higher for distal lesions than for proximal lesions. FIT-DNA sensitivity increased as lesion size increased. The specificity of FIT-DNA was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, the specificity of FIT-DNA was 86.6% (95% CI, 85.9% to 87.2%) and 94.9% (95% CI, 94.4% to 95.3%) for FIT. For identification of patients only with negative colonoscopy, specificity of FIT-DNA was 89.8% (95% CI, 88.9% to 90.7%) and 96.4% (95% CI, 95.8% to 96.9%) for FIT.

Following FDA approval for use of FIT-DNA (Cologuard) in asymptomatic adults aged 45 to 49 years, Imperiale et al (2021) published results from a screening study that included 983 adults aged 45 to 49 years (mean age, 48 years) at average risk of CRC.[11,] 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.

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.[6,] 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.[7,] 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 (see Table 3).[12,]

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.[13,] Of 1,216 participants, 206 had a positive FIT-DNA test and a negative colonoscopy. After a median 5 years follow up, individuals with discordant results (positive FIT-DNA test, negative colonoscopy) showed a nonsignificant trend towards increased risk of aerodigestive cancer relative to individuals with concordant results (negative FIT-DNA, negative colonoscopy; adjusted risk ratio, 2.2; 95% CI, 0.8 to 6.2), but the rate of aerodigestive cancer in the discordant group was lower than the expected rate based on the National Cancer Institute's Surveillance, Epidemiology and End Result (SEER) data (risk ratio, 0.8; 95% CI, 0.3 to 1.9).

Chain of Evidence
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.

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).[14,] Screening outcomes from various screening strategies beginning at age 45 years were estimated and compared. FIT-DNA was evaluated in these models using both a yearly screening strategy and an every 3 year strategy. The modeling results suggested that FIT-DNA screening produces outcomes within the range of other screening strategies. In terms of life-years gained according to screening strategy, FIT-DNA every 3 years is at the lower range of effectiveness, only higher than flexible sigmoidoscopy, and testing every year is at the higher range of effectiveness, only lower than colonoscopy every 10 years. In terms of complications or lifetime burden as expressed as colonoscopies, the modeling results found FIT-DNA to be in the range of other CRC screening strategies, with every year screening having higher complication and colonoscopy rates than every 3 year screening. Both measures of harm were estimated to be lower with FIT-DNA testing than the screening strategy of colonoscopy every 10 years.

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

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

Adapted from Knudsen et al (2021)[14,]
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 aged 50 years or older over their lifetime.[15,] Modeling was conducted under 100% adherence rates and reported adherence rates at the population level. Adherence rates of 42.6% were assumed for FIT-DNA screening every 3 years and adherence to colonoscopy screening every 10 years was modeled on data from the National Health Interview Survey suggesting that 62.4% of individuals become up to date with screening within a 10-year period. With 100% adherence, colonoscopy averted 46 CRC cases and 25 to 26 deaths compared to 42 to 45 cases and 25 to 26 deaths with FIT-DNA per 1000 individuals. Assuming reported adherence, colonoscopy averted 34 cases and 20 deaths compared to 16 to 25 cases and 10 to 16 deaths with FIT-DNA per 1000 individuals. LYG were

proportional to the effectiveness of each strategy. Adverse events were more frequent for colonoscopy (3.7 per 1000 screened). Colonoscopy was found to have a larger benefit when compared to other screening methods including FIT-DNA. The authors note that screening adherence rates higher than 65% to 70% would be necessary for any stool-based screening modality to match the benefits of colonoscopy. However, a major limitation of this study 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%.[16,] 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.[17,]

A comparative effectiveness modeling study by Barzi et al (2017) found that colonoscopy was the most effective screening strategy with the highest LYG (0.022 life years) and CRCs prevented (n=1,068), and the lowest total cost.[18,] Modeling for FIT-DNA every year or every other year found 0.011 LYG, 647 CRCs prevented, and a higher total cost. The main reason for the difference in CRCs prevented was due to the detection of precancerous polyps. The study found that if the sensitivity of FIT-DNA for adenomas increased, it could surpass the sensitivity of colonoscopy. An unexpected consequence of a positive FIT-DNA test may be to improve the quality of the subsequent colonoscopy.[19,]

Another modeling study, by Berger et al (2016), sponsored by the manufacturer of Cologuard, showed similar findings.[20,] 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.[21,] The report found the Imperiale et al (2014) study[5,] 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 CRC 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 than for 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), a systematic review of the screening studies, and modeling studies. Relevant outcomes are overall survival and 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
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines (v.2. 2021) for colorectal cancer (CRC) screening includes the use of fecal immunochemical testing (FIT)-DNA to screen patients with an average risk for colon cancer.[22,] Following a negative test, the recommendation is to rescreen with any modality after 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 CRC screening.[23,] The recommended first-tier tests for individuals with average risk were colonoscopy every 10 years, and for individuals who decline colonoscopy, annual FIT. Recommended second-tier tests in patients who declined the first-tier tests were computed tomography colonography every 5 years, FIT-DNA every 3 years, or flexible sigmoidoscopy every 5 to 10 years. Capsule colonoscopy was listed as a third-tier test. The task force recommended, "[computed tomography] colonography every 5 years or FIT-fecal

DNA every 3 years (strong recommendation, low-quality evidence), or flexible sigmoidoscopy every 5-10 years (strong recommendation, high-quality evidence) in patients who refuse colonoscopy and FIT."

American Cancer Society

In 2018, the American Cancer Society updated its guidelines for CRC screening for average-risk adults.[24,] Regular screening with either a structural examination (i.e., colonoscopy) or a high-sensitivity stool-based test is recommended to start in adults who are age 45 years and older (qualified recommendation) or who are age 50 years and older (strong recommendation). Recommendations for screening with stool-based tests include FIT repeated every year, high-sensitivity guaiac-based fecal occult blood test repeated every year, or multitarget stool DNA test repeated every 3 years.

U.S. Preventive Services Task Force Recommendations

In 2021, the U.S. Preventive Services Task Force (USPSTF) published updated recommendations for CRC screening in asymptomatic, average risk adults (defined as no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorders that predispose them to a high lifetime risk of CRC [such as Lynch syndrome or familial adenomatous polyposis]).[25,] The USPSTF recommended universal screening for average risk adults aged 45 to 49 years (B recommendation) and for adults aged 50 to 75 years (A recommendation). For adults aged 76 to 85 years, the USPSTF recommends selective screening due to the small magnitude of net benefit (C Recommendation). The USPSTF reviewed evidence for 6 screening strategies, including FIT-DNA. They do not recommend one screening strategy over another and noted the lack of direct evidence on clinical outcomes when comparing screening strategies. Clinical considerations noted for FIT-DNA testing appear in Table 2.

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

Recommended screening interval	Efficacy	Other considerations
1 to 3 years	• Improved sensitivity compared with FIT per 1-time application of screening test • Specificity is lower than that of FIT, resulting in more false-positive results, more follow-up colonoscopies, and more associated adverse events per FIT-DNA screening test compared with per FIT test • Modeling suggests that screening every 3 years does not provide a favorable balance of	• Harms from screening with FIT-DNA arise from colonoscopy to follow up abnormal FIT-DNA results • Can be done with a single stool sample but involves collecting an entire bowel movement • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)

Recommended screening interval	Efficacy	Other considerations
	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	

FIT: fecal immunochemical testing

Ongoing and Unpublished Clinical Trials

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

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04144738[a]	Clinical Validation of An Optimized Multi-Target Stool DNA (Mt-sDNA 2.0) Test, for Colorectal Cancer Screening "BLUE-C"	12,500	Apr 2022
NCT04124406[a]	Voyage: Real-World Impact of the Multi-target Stool DNA Test on CRC Screening and Mortality	150,000	Dec 2029
Unpublished			
NCT02419716[a]	A Longitudinal Study of Cologuard in an Average Risk Population Assessing a 3 Year Test Interval	2,404	Mar 2020
NCT01647776	Screening and Risk Factors of Colon Neoplasia	3,315	Aug 2016

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

CODING

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

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

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

CPT/HCPCS	
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

ICD-10 DIAGNOSES	
C18.0-C18.9	Malignant neoplasm of colon code range
C19	Malignant neoplasm of rectosigmoid junction
Z12.10-Z12.13	Encounter for screening for malignant neoplasm of intestinal tract code range
Z15.09	Genetic susceptibility to other malignant neoplasm
Z80.0	Family history of malignant neoplasm of digestive organs

REVISIONS	
08-08-2016	Policy added to the bcbsks.com web site on 07-07-2016 with an effective date of 08-08-2016.
01-01-2017	Updated Description section.
	In Policy section: ▪ Removed entire previous policy statement, "DNA analysis of stool samples is considered experimental / investigational as a screening technique for colorectal cancer in patients at average-to-high risk of colorectal cancer." ▪ Added " A. DNA analysis of stool samples using Cologuard™ may be considered medically necessary as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 50 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval: 1. Guaiac-based fecal occult blood test in the past year, or 2. Fecal immunochemical test in the past year, or 3. Multitargeted stool DNA test in the past 3 years, or Colonoscopy in the past 10 years, or 4. CT colonography in the past 5 years, or 5. Flexible sigmoidoscopy in the past 5 years. B. In individuals who are considered candidates for Cologuard™ screening, repeat testing at intervals of every 3 years may be considered medically necessary. C. DNA analysis of stool samples is considered experimental / investigational when the criteria above are not met and

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	for all other indications including post colorectal diagnosis surveillance. D. All other screening stool DNA tests are considered experimental / investigational." ▪ Added "Policy Guidelines 1. Average risk of developing colorectal cancer include those individuals who have no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer. 2. Asymptomatic individuals include those who have no signs or symptoms of colorectal disease including, but not limited to, lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes: Z12.10, Z12.11, Z12.12.
	Updated References section.
12-20-2017	Updated Description section.
	In Policy section: ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
01-04-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-02-2020	Updated Description section
	Updated Rationale section
	Updated Reference section
09-22-2021	In Policy section: ▪ A. Age range 45 years to 75 years change
01-04-2022	Updated Description Section
	Updated Rationale Section
	Updated Codes Section ▪ Added ICD 10 codes C18.0-C18.9, C19, Z15.09, Z80.0
	Updated References Section

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