**Medical Policy Manual** Genetic Testing, Policy No. 12

# *Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening*

**Effective**: October 1, 2024

**Next Review:** August 2025
**Last Review:** August 2024

## IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION

Tumor-associated gene variants and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Since cancer cells are shed into stool, screening tests have been developed that detect these genetic alterations in the DNA from shed colorectal cancer cells isolated from stool samples.

## MEDICAL POLICY CRITERIA

**Note:** This policy does not address fecal DNA testing with the standard Cologuard® test (CPT 81528), which may be considered medically necessary.

Fecal DNA testing using any test other than Cologuard®, including but not limited to the Colosense™ and Cologuard® Plus tests, is considered **investigational** for all indications.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## CROSS REFERENCES

1. Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes,

Genetic Testing, Policy No. 06
2. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. Serologic Genetic and Molecular Screening for Colorectal Cancer, Genetic Testing, Policy No. 86
5. Multigene and Gene Expression Assays for Predicting Recurrence in Colon Cancer, Laboratory, Policy No. 76
6. Confocal Laser Endomicroscopy, Medicine, Policy No. 151

## BACKGROUND

Numerous cellular genetic alterations have been associated with colorectal cancer. In the proposed multistep model of carcinogenesis, the tumor suppressor gene p53 (*TP53*) and the proto-oncogene *KRAS* are most frequently altered. Variants in APC (adenomatous polyposis coli) genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. Colorectal cancer is also associated with deoxyribonucleic acid (DNA) replication errors in microsatellite sequences (termed microsatellite instability or MSI) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) and in a subgroup of patients with sporadic colon carcinoma.

Several tests have been marketed, including the PreGen-Plus™ test (LabCorp) which includes testing for 21 different variants in the p53, APC, and *KRAS* genes, along with the BAT-26 MSI marker and a marker called the DNA Integrity Assay (DIA®). PreGen-Plus has not been cleared by the U.S. Food and Drug Administration (FDA). Another test, ColoSure™, was developed by OncoMethylome and detects aberrant methylation of the vimentin (*VIM*) gene. This test is offered as a laboratory-developed test, not subject to FDA regulation.

## EVIDENCE SUMMARY

The important outcome of interest in cancer screening is a reduction in the mortality and morbidity due to cancer. This is ideally determined with randomized clinical trials. However, for colon cancer screening, many of the recommended tests have not been evaluated with clinical trials. 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 regarding the natural history of the progression of precursors to cancer. Modelling studies have evaluated the robustness and quantity of health benefit of various screening tests when clinical trial evidence is lacking.

Lacking direct evidence of screening in reducing cancer mortality, the critical parameters in the evaluation of a screening test 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. The diagnostic performance characteristics of the currently accepted screening options (i.e, fecal occult blood testing [FOBT], fecal immunochemical testing [FIT], flexible sigmoidoscopy, double contrast barium enema) have been established using colonoscopy as the criterion standard. Modelling studies and clinical trial evidence on some of the screening modalities have allowed some confidence on the effectiveness of currently recommended cancer screening modalities.

For patients at average to moderate 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, and the detection of cancer-associated DNA may be superior to current stool tests for the detection of cancer and cancer precursors.

Currently, there are no studies of stool DNA testing for screening of individuals at high risk of colorectal cancer.

## SYSTEMATIC REVIEWS

Garg (2023) published a meta-analysis to evaluate the performance of FIT and FIT-DNA testing for SSP detection rate (SSPDR) in patients (n = 482, 405) undergoing colonoscopy for follow up of positive noninvasive tests.[1] The outcome was overall colonoscopy detection of any SSPs and advanced serrated polyps (ASP: SSP ≥ 10 mm and/or dysplasia). Results Included were 482,405 patients (52.4% females) with a mean age of 62.3 ± 4.4 years from 23 studies. The pooled SSPDR for all positive stool-based tests was 5.3% and higher for FIT-DNA (15.0%, 95% confidence interval [CI] 8.3-25.7) versus FIT (4.1%, 95% CI 3.0-5.6; p = 0.0002). The overall pooled ASP detection rate was 1.4% (95% CI 0.81-2.3) and higher for FIT-DNA (3.8 %, 95% CI 1.7-8.6) compared with FIT (0.71%, 95% CI 0.36-1.4; p < 0.01). SSPDR with FIT-DNA was also significantly higher than FIT when the FIT cutoff was >10 µg/g and in FIT-positive patients in studies conducted in North America (p < 0.05).

Dolatkhah (2022) published a systematic review (SR) and meta-analysis assessing the sensitivity and specificity of FIT-DNA compared to colonoscopy.[2] Data were pooled from 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 I2 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 (2021) (used to inform the U.S. Preventive Services Task Force 2021 CRC screening recommendation statement) pooled data from one good- and three fair-quality studies assessing the accuracy of CRC screening with FIT-DNA testing.[3] 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%; I2=0%) and a specificity of 85% (95% CI, 84.0% to 86.0%; I2=37.3%) for detection of CRC, based on 3 studies. For advanced neoplasia, sensitivity was 47% (95% CI, 44.0% to 55.0%; I2=0%) and specificity was 89% (95% CI, 87.0% to 92.0%; I2=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%; I2=0%) and 89% (95% CI, 86.0% to 92.0%; I2=87.8%).

Gachabayov (2021) reported a systematic review and meta-analysis of the accuracy of stool DNA methylation testing for the detection of CRC.[4] A total of 46 studies with 16,149 patients met inclusion criteria. Combinations of genes provided higher sensitivity compared to single genes (80.8% vs. 57.8%) with no significant decrease in specificity (87.8% vs. 92.1%). The most accurate single gene was *SDC2*, which had a sensitivity of 83.1% and a specificity of 91.2%.

A systematic review conducted by Niedermaier (2016) evaluated FITs in combination with stool tests compared to FIT alone. The systematic review included 18 total studies.[5] Only one of the prospective studies was conducted in an asymptomatic screening population. A variety of stool-based tests were used in combination with FIT including fecal DNA or RNA, stool proteins other than hemoglobin (Hb), haptoglobin (Hp), or the HbHp complex, or tissue from the colonic mucosa. Many of the studies had methodological limitations with risk of bias including selective reporting. The authors concluded that the addition of stool-based tests to FIT may improve performance compared to FIT alone. However, no definitive conclusions can be drawn, and additional research is needed in true screening settings to evaluate performance of FIT in combination with other stool tests.

Raut (2020) published a systematic review of fecal DNA methylation markers for the detection of colorectal cancer, which included 27 studies reporting stage-specific associations or performances of these markers for detecting colorectal neoplasms.[6] Stage-specific associations or sensitivities were only reported for two markers, hypermethylation of *GATA4* and *VIM*, and the authors noted that “most studies were underpowered and limited by their case-control design.”

**NONRANDOMIZED STUDIES**

Imperiale (2023) published a longitudinal cohort study evaluating a 3-year interval for the multitarget stool DNA test (mt-sDNA) for CRC screening.[7] 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 three value for CRC was 0% (95% CI, -3.62% to 1.02%; p = 1.0); the PSI for advanced precancerous lesions was 9.3% (95% CI, 1.83 to 17.63; two-sided p = 0.01).The observed 3-year colorectal cancer yield was lower than expected (one-sided p = 0.09), while the yield for advanced precancerous lesions was higher than expected (two-sided p = 0.009). The detection of advanced precancerous lesions increased and was statistically significant after repeat mt-sDNA screening at a 3-year interval.

Anderson (2022) published a retrospective study 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.[8] 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).

Following FDA approval for use of FIT-DNA (Cologuard®) in asymptomatic adults aged 45 to 49 years, Imperiale (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.[9] 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.

Mo (2021) reported results of a multidimensional analysis of stool samples from patients with CRC (n=108), colorectal adenoma (n=18), or no cancer (n=36).[10] The analysis of stool samples included FIT, stool DNA tests for methylation of three genes (*Septin9*, *NDRG4*, *BMP3*), variants in three genes (*KRAS*, *BRAF*, *PI3KCA*) using next generation sequencing, and detection of stool bacteria level of Fusobacterium nucleatum and Parvimonas micra using qPCR. The FIT and sDNA tests together had a sensitivity of 81.5% for CRC (AUC 0.93, higher than FIT alone, p=0.017) and 27.8% for adenoma with 94.4% specificity. Sensitivity of the multidimensional test to detect CRC was 84.6% for stage II 91.9% for stage III CRC, which was relatively higher (88.2%) than that of patients with stage I (60.0%) and stage IV (75.0%) (p=0.024).

Other, smaller studies have assessed the accuracy of FIT-DNA in special populations. Cooper (2018) compared the sensitivity of FIT-DNA and FIT using colonoscopy as the reference standard in 265 Black and 495 White participants.[11] 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%. Redwood (2016) included 661 asymptomatic, Alaska natives undergoing screening or surveillance colonoscopy, using colonoscopy as a reference standard.[12] 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.

A study by Imperiale (2004) prospectively evaluated the PreGen-Plus™ test, which is no longer available but was used to support prior practice recommendations regarding fecal DNA cancer screening.[13] Another previously marketed test, ColoSure™, has not been evaluated in a large screening study.

Two studies allow calculation of the performance characteristics of the assay for the hypermethylated vimentin (hV) gene. In a study by Itzkowitz (2007), separately assembled groups of patients with colorectal cancer (n=40) and patients with normal colonoscopy (n=122) were tested with hV.[14] Sensitivity was 72% and specificity was 87%. In a second study by Itzkowitz (2008), separately assembled groups of patients with CRC (n=82) and patients with normal colonoscopy (n=363) were tested with hV and a two-site DNA integrity assay.[15] The purpose of the study was to calculate diagnostic performance characteristics of this combined test, but the results are also presented for hV alone. Using data-derived cutoff values, the sensitivity for cancer was 77% and the specificity was 83%. Other studies of hypermethylated vimentin using different assays have shown sensitivities of 38% and 41% for detecting colorectal cancer.[16, 17]

Additional studies have been published that evaluate the performance of various other types of fecal DNA tests, however there is a lack of evidence regarding the clinical utility of such tests.[18, 19]

## PRACTICE GUIDELINE SUMMARY

### U.S. PREVENTIVE SERVICES TASK FORCE

The U.S. Preventive Services Task Force (USPSTF) guidelines for colorectal cancer screening were updated in 2021.[20] The USPSTF recommends screening for colorectal cancer for adults age 45 to 49 years (Grade B) and adults age 50 to 75 years (Grade A). The guidelines also recommend selectively screening adults aged 76 to 85 years, dependent on the patient's overall health, prior screening history, and preferences (Grade C). The recommendation statement reviews seven different screening strategies including FIT-DNA. Regarding comparisons or preferences between the seven different methods mentioned: "Recommendations regarding which screening tests to use, or if there is a hierarchy of preferred screening tests, will depend on the decisionmaker's criteria for sufficiency of evidence and weighing the net benefit." In addition, the USPFTF further states that the risks and benefits of different screening methods vary and includes a table outlining different screening modalities and recommended frequency of testing.

### NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer screening discuss FIT-DNA-based testing as a potential screening option for average-risk individuals.[21] These guidelines specifically reference Cologuard® and do not mention other tests.

### THE U.S. MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER

A U.S. Multi-Society task force representing the American College of Gastroenterology, the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (2017) provided recommendations for CRC screening.[22] The recommended first-tier tests for individuals with average risk were colonoscopy every 10 years, and for individuals who decline colonoscopy, annual FIT. Recommended second-tier tests in patients who declined the first-tier tests were computed tomography colonography every 5 years, FIT-DNA every 3 years, or flexible sigmoidoscopy every 5 to 10 years. Capsule colonoscopy was listed as a third-tier test. The task force recommended, "[computed tomography] colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low-quality evidence), or flexible sigmoidoscopy every 5-10 years (strong recommendation, high-quality evidence) in patients who refuse colonoscopy and FIT." In 2022, a focused update to the 2017 CRC screening recommendations from the task force was published that addressed the age to begin and stop CRC screening in average-risk individuals.[23] The task force now suggests CRC screening in average-risk individuals aged 45 to 49 years. Unchanged from 2017 are the following recommendations: a) offer CRC screening to all average-risk individuals aged 50 to 75 years, b) consider starting or continuing screening for individuals aged 76 to 85 years on an individualized basis (depending on patient and disease factors), and c) screening is not recommended after age 85 years.

### AMERICAN CANCER SOCIETY

In 2018, the American Cancer Society updated its guidelines for CRC screening for average-risk adults.[24] Regular screening with either a structural examination (i.e., colonoscopy) or high-sensitivity stool-based test is recommended to start in adults who are 45 years and older (qualified recommendation) or who are 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 three 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.[25] 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 (AGA)

The AGA (2023) published a Clinical Practice Update on Risk Stratification for Colorectal Cancer Screening and Post-Polypectomy Surveillance: Expert Review.[26] The authors recommend the following best practices: Screening options for individuals at average risk for CRC should include colonoscopy, fecal immunochemical test, flexible sigmoidoscopy plus fecal immunochemical test, multitarget stool DNA fecal immunochemical test, and computed tomography colonography, based on availability and individual preference; and, colonoscopy should be the screening strategy used for individuals at increased CRC risk. Note: these guidelines are based on expert review and did not include a systematic evidence review.

In 2022, the AGA published a clinical practice update commentary that reviewed the evidence on noninvasive CRC screening options.[27] 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.

## SUMMARY

There is not enough research to show that stool DNA testing with any test other than Cologuard®, including but not limited to the Colosense™ and Cologuard® Plus tests, is an effective way to screen for colon cancer and can improve health outcomes for patients. Therefore, stool DNA testing using any test other than Cologuard®, including but not limited to the Colosense™ and Cologuard® Plus tests, is considered investigational.

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## CODES

| Codes | Number | Description |
|---|---|---|
| CPT | 0421U | Oncology (colorectal) screening, quantitative real-time target and signal amplification of 8 RNA markers (GAPDH, SMAD4, ACY1, AREG, CDH1, KRAS, TNFRSF10B, EGLN2) and fecal hemoglobin, algorithm reported as a positive or negative for colorectal cancer risk |
| | 0464U | Oncology (colorectal) screening, quantitative real-time target and signal amplification, methylated DNA markers, including LASS4, LRRC4 and PPP2R5C, a reference marker ZDHHC1, and a protein marker (fecal hemoglobin), utilizing stool, algorithm reported as a positive or negative result |
| | 81479 | Unlisted molecular pathology procedure |
| HCPCS | None | |

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