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

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

**Effective**: May 1, 2026

**Next Review:** August 2026
**Last Review:** March 2026

**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 or RNA from shed colorectal cancer cells isolated from stool samples.

## MEDICAL POLICY CRITERIA

**Note:** This policy does not address fecal DNA testing with the Cologuard® (CPT 81528) or Cologuard Plus® (HCPCS 0464U) test, which may be considered medically necessary.

Fecal DNA or RNA testing using any test other than Cologuard® or Cologuard Plus®, including but not limited to the Colosense™, 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.

Cologaurd plus is an expanded version of the Cologaurd stool test (both Exact Science, Inc) using enhanced technology and additional molecular markers to improve sensitivity for detecting advanced cancerous lesions. The Cologuard plus utilizes a re-engineered DNA panel - focusing on select DNA methylation markers (LASS4, PPP2R5C, LRRC4 and ZDHHC1) in an aim to increase specificity and reduce false positives while maintaining sensitivity. The Cologaurd plus is also referred to as a multi-target stool based DNA test (mt-sDNA) or next generation FIT-DNA. The original Cologuard and the next generation Cologuard Plus both received FDA approval (August 2014 and October 2024, respectively).

The ColoSense test (Geneoscopy, Inc) is multi-target stool based RNA test (mt-sRNA) which analyzes 8 RNA biomarkers (GAPDH, ACY1, AREG, TNFRSF10B, CDH1, EGLN2, KRAS SMAD4) associated with colorectal cancer (CRC), along with an individuals smoking history and a fecal immunochemical test (FIT) and may also be referred to as FIT-RNA. The ColoSense received FDA approval in May 2024.

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 multi-target DNA (sDNA) 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.

### REGULATORY STATUS

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.

ColoSense (Geneoscopy, Inc) was approved by the FDA in May 2024: (P230001) Intended for the detection of colorectal neoplasia associated RNA markers and for the presence of occult hemoglobin in human stool. ColoSense is for use with the ColoSense Collection Kit, the ColoSense Test Kit, the ColoSense Software, and the following instruments: Polymedco Immunochemical Fecal Occult Blood Test (iFOBT) Analyzer; bioMerieux EMAG Nucleic Acid Extraction System; and Bio-Rad QXDx Droplet Digital Polymerase Chain Reaction (ddPCR) System. ColoSense is a single-site test performed at Geneoscopy, Inc. A positive ColoSense result may indicate the presence of colorectal cancer (CRC), advanced adenomas (AA) or serrated precancerous lesions (SPL) and should be followed by a colonoscopy. ColoSense is indicated as a screening test for adults, 45 years of age or older, who are at average-risk for developing CRC. ColoSense is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

## EVIDENCE SUMMARY

### MULTI TARGETED STOOL DNA TESTS: OTHER THAN COLOGUARD OR COLOGUARD PLUS

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.[1] 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.[2] 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.[3] 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.[4, 5]

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.[6, 7]

## MULTI TARGETED STOOL RNA TESTS (COLSENSE)

### Cohort Studies

Barnell (2023) reported results of the pivotal study (CRC-PREVENT; NCT04739722) of the FIT-RNA (Colosense) test.[8] CRC-PREVENT prospectively enrolled 14,263 participants ages 45 and older (mean, 55 years) who were willing to undergo a colonoscopy from 49 US states using decentralized recruitment through a online social media platform from 2021 to 2022. Stool samples were collected prior to participants completing a colonoscopy at their local endoscopy center. The reference standard was colonoscopy results, which were based on histopathological review of all lesions either biopsied or resected during the colonoscopy, or negative results by colonoscopy. Participants were navigated to complete a routine colonoscopy at a local endoscopy center. 68% of participants did not have a colonoscopy scheduled prior to enrollment and many required assistance with obtaining a colonoscopy appointment at a local endoscopy center. 8920 participants were included in the analysis in the publication. Thirty four percent had a prior or current history of smoking. Overall, the sensitivity of the FIT-RNA test for CRC was 94% (95% CI, 81 to 99) and for advanced adenomas (AA) was 46% (95% CI, 42 to 50). Overall, specificity for the FIT-RNA test was 87% (95% CI, 86 to 88). The primary outcome for regulatory approval reported in the Summary of Safety and Effectiveness Data (SSED) was the sensitivity and specificity in the average risk population (n=7,763), excluding 526 enrolled participants with first-degree relatives with CRC. In the average risk population, the CRC sensitivity of the FIT-RNA test was 93% (95% CI, 76 to 99) and the AA sensitivity was 45% (95% CI, 41 to 49). The specificity of the FIT-RNA test in the average risk population was 86% (95% CI, 85 to 86). Sensitivity for CRC and AA was greater for the FIT-RNA test compared to FIT alone but the FIT-RNA test had lower specificity compared to FIT.

### Section Summary

In a head-to-head comparison of the FIT-RNA test (Colosense) to FIT alone (using colonoscopy as the reference standard). The FIT-RNA test had higher sensitivity for both CRC detection and cancer precursor detection, but lower specificity than FIT. The FIT-RNA test (Colosense) has not been directly compared to the original FIT-DNA (Cologuard). There are no studies directly assessing health outcomes such as overall survival or disease-specific

survival. The screening interval for the test has not been confirmed nor is there evidence on the adherence of the test at a recommended screening interval

## 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.[9] 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. This guideline does not address the FIT-RNA tests.

### NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer screening (V2.2025) discuss multi-target stool DNA (mt-sDNA) and multi-target stool RNA testing as a potential screening option for average-risk individuals.[10] For the screening of individuals at average risk, these guidelines state: "It is recommended that screening for persons at average risk begin at 45 years of age after available options have been discussed. Currently, recommended options include: colonoscopy every 10 years; flexible sigmoidoscopy every 5-10 years; annual high-sensitivity guaiac-based testing for FIT, or mt-sDNA based testing or mt-sRNA based testing or blood-based cfDNA testing (every 3 years); or CT colonography every five years.

The NCCN CRC screening panel recommends the inclusion of the mt-sRNA based testing as another potential screening modality in individuals at average risk. And they acknowledge that data to help determine how the mt-sRNA testing may fit into an overall screening program as limited.

### 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.[11] 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.[12] 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.[13] 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.[14] 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". They do not address stool RNA tests.

### 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.[15] 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.[16] 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 or RNA testing with any test other than Cologuard® or Cologuard® Plus, including but not limited to the ColoSense™ is an effective

way to screen for colon cancer and can improve health outcomes for patients. Therefore, stool DNA or RNA testing using any test other than Cologuard® or Cologuard® Plus, including but not limited to the ColoSense™ 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 |
| | 81479 | Unlisted molecular pathology procedure |
| HCPCS | None | |

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