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

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

**Effective**: November 1, 2020

**Next Review:** August 2021
**Last Review:** September 2020

## 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 Cologuard®, which may be considered medically necessary.

Fecal DNA testing using any test other than Cologuard® 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 and BRAF Variant Analysis in Metastatic Colorectal Cancer, Genetic Testing, Policy No. 13
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. Multigene Expression Assay for Predicting Recurrence in Colon Cancer, Genetic Testing, Policy No. 22
5. Serologic Genetic and Molecular Screening for Colorectal Cancer, Genetic Testing, Policy No. 86
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 cancer 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

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.[1] 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.[2] 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

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.[3] 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.[4] 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.[5] 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.[6,7]

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.[8,9]

## PRACTICE GUIDELINE SUMMARY

### U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF)

The USPSTF guidelines for colon cancer screening were updated in 2016.[10] The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years (Grade A). The recommendation statement reviews seven different screening strategies including FIT-DNA. Regarding comparisons or preferences between the seven different methods mentioned: "The USPSTF found no head-to-head studies demonstrating that any of the screening strategies it considered are more effective than others, although the tests have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations…. The screening tests are not presented in any preferred or ranked order…." In addition, the USPFTF further states that the risks and benefits of different screening methods vary and references a table outlining different screening strategies. According to these recommendations, for adults aged 76 to 85 years, the screening decision is an individual one and should take into account the patient's overall health and prior screening history (Grade C).

### NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

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.[11] These guidelines specifically reference Cologuard® and do not mention other tests.

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

The U.S. Multi-Society Task Force on Colorectal Cancer, which represents the American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy, released evidence-based screening recommendations in 2017. These recommendations list fecal DNA testing every three years as a second-tier testing option.[12] Cologuard® is the only specific test referenced.

### 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.

## SUMMARY

There is not enough research to show that stool DNA testing with any test other than Cologuard® 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® is considered investigational.

## REFERENCES

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Detection: A Systematic Review. *Clin Transl Gastroenterol*. 2016;7(6):e175. PMID: 27253514
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14. BlueCross BlueShield Association Medical Policy Reference Manual "Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening " Policy No. 2.04.29

## CODES

| Codes | Number | Description |
|---|---|---|
| CPT | 81479 | Unlisted molecular pathology procedure |
| HCPCS | None | |

***Date of Origin:*** *October 2012*