BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.150 Serologic Genetic and Molecular Screening for Colorectal Cancer

Annual Effective Policy Date: April 1, 2026

Original Policy Date: September 2020

Related Policies:

2.01.84 - Chromoendoscopy as an Adjunct to Colonoscopy
2.04.29 - Analysis of Human DNA or RNA in Stool Samples as a Technique for Colorectal Cancer Screening
2.04.61 - Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
6.01.32 - Virtual Colonoscopy/Computed Tomography Colonography

Serologic Genetic and Molecular Screening for Colorectal Cancer

Description

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It is well established that early detection of colorectal cancer (CRC) reduces disease-related mortality. For patients at average risk for CRC, organizations such as the U.S. Preventive Services Task Force have recommended several options for colon cancer screening. Currently accepted screening options for CRC include colonoscopy or sigmoidoscopy, fecal occult blood testing, and fecal immunochemical testing. However, many individuals do not undergo recommended screening with fecal tests or colonoscopy. Approximately 75% of colorectal cancer deaths occur in people who are not up to date with cancer screening. A simpler screening blood test for genetic alterations associated with non-familial CRC may have the potential to encourage screening and decrease mortality if associated with increased screening compliance. Genetic testing is also being investigated to guide therapy.

SEPT9 Methylated DNA

ColoVantage (various manufacturers) blood tests for serum Septin9 (*SEPT9)* methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration (FDA) approval in April 2016 (Epi proColon is now marketed by New Day Diagnostics as ColoHealth™) Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage and Epi proColon/ColoHealth™ are both polymerase chain reaction (PCR) assays; however, performance characteristics vary across tests, presumably due to differences in methodology (eg, DNA preparation, PCR primers, probes).

Gene Expression Profiling

ColonSentry (Stage Zero Life Sciences) is a PCR assay that uses a blood sample to detect the expression of 7 genes found to be differentially expressed in CRC patients compared with controls[7,]: *ANXA3*, *CLEC4D*, *TNFAIP6*, *LMNB1*, *PRRG4*, *VNN1*, and *IL2RB*. The test is intended to stratify average-risk adults who are non-compliant with colonoscopy and/or fecal occult blood testing. "Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules."[8,] BeScreened-CRC (Beacon Biomedical) is a PCR assay that uses a blood sample to detect the expression of 3 protein biomarkers: teratocarcinoma derived growth factor-1 (TDGF-1, Cripto-1); carcinoembryonic antigen, a well-established biomarker associated with CRC; and an extracellular matrix protein involved in early stage tumor stroma changes.[9,]

OBJECTIVE

The objective of this evidence review is to determine whether serologic genetic or molecular screening for colorectal cancer improves the net health outcome.

POLICY STATEMENT

SEPT9 methylated DNA testing (e.g., ColoVantage, ColoHealth™) is considered **not medically necessary** for colorectal cancer screening.

Gene expression profiling (e.g., ColonSentry, BeScreened™ CRC) is considered **investigational** for colorectal cancer screening.

Epigenomic and genomic cell-free DNA (cfDNA) blood-based testing with Guardant Shield is considered **investigational** for all indications.

POLICY GUIDELINES

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

Plan Considerations

There may be individual exceptions whereby use of epigenomic and genomic blood-based cfDNA testing would be considered medically necessary (see Supplemental Information Section).

On a population level, it is imperative that use of epigenomic and genomic blood-based cfDNA testing be implemented in a manner that limits substitution. Substitution is shifting the screening method to epigenomic and genomic blood-based cfDNA testing among individuals who would be willing to use an established method, and could lead to more harm than benefit. Modeling studies of substitution effect assume 25-50% substitution, and suggest that epigenomic and genomic blood-based cfDNA testing would have to match the performance of established alternatives in order to avoid harms from significant substitution.[1,] Real world evidence and studies of patient adherence, however, suggest that substitution could be higher. [2,] [Graham-Adderton C, Guerra CE, Ngo-Metzger Q, et al.... ov 08 2025: 1-6. PMID 41164862]Plans choosing to employ the use of epigenomic and genomic blood-based cfDNA testing are thereby encouraged to consider use for individuals where patient-provider shared decision-making identifies that the individual is counseled on limited performance compared to other screening modalities; is unwilling to undergo screening by any other testing modality; and is committed to follow-up colonoscopy when the blood test is abnormal. Further, testing should be offered as part of a comprehensive

colon cancer screening program that optimizes follow-up including that programs offer such within 9 months and ensures that substitution is limited. (see Supplemental Information Section)

Guardant Shield

Cell-free DNA testing with Guardant Shield has not been directly compared with other colorectal cancer screening tests, but has sensitivity and specificity for the detection of CRC similar to stool-based tests and might be of higher uptake among individuals currently declining colorectal cancer screening (see Appendix Table 1). It is not known if higher uptake of a blood-based test will offset lower sensitivity for detection of advanced adenomas at a population level; yet, the right screening test is one that is utilized. Plans may thereby consider Guardant Shield as a screening technique for colorectal cancer, particularly for individuals declining other screening technologies, should they be amenable to receiving a diagnostic colonoscopy after a positive screen. That is, Shield needs to be offered as part of a comprehensive colon cancer screening program that optimizes follow-up of individuals choosing to use blood-based colorectal cancer screening (see Supplemental Information Section).

For the detection of precancerous adenomas or other polyps, technologies that allow visualization of the colorectal tract perform better than stool or blood-based tests. The performance of any liquid-based product is expected to be lower for the detection of precancerous lesions, as these early lesions generally do not release high amounts of DNA into the circulation. Other analytes outside of DNA-based markers may eventually prove to be useful for blood-based detection of precancerous lesions. Even for the stool-based tests, the majority of the test sensitivity comes from the fecal immunochemical component rather than the DNA contribution, indicating that other analytes outside of DNA may need to be assessed in future versions of tests.

The transformation of adenoma to carcinoma typically takes around 10 years, which is the basic screening interval for colonoscopy. However, other pathways of colorectal tumorigenesis have been described, such as the microsatellite instability pathway and the methylation pathway, and these do not have well-defined timeframes. A 3-year interval of the Guardant Shield test has been suggested in the publication of results of the pivotal study, but has not been tested.

Combination testing of blood-based cfDNA with other methods of colorectal cancer screening has not been studied.

Shield FDA labeling

The FDA-approved product label for the Shield test includes the following Precaution:

"Based on data from clinical studies, Shield has limited detection (55%-65%) of Stage I colorectal cancer and does not detect 87% of precancerous lesions. One out of 10 patients with a negative Shield result may have a precancer that would have been detected by a screening colonoscopy. Shield demonstrated high detection of Stages II, III, and IV colorectal cancer."

Other limitations listed in the label include, but are not limited to, the following:

- "The Shield test is not intended as a screening test for individuals who are at high risk for CRC."
- "Patients with a positive result should be followed by colonoscopy."
- "Patients with a negative result should continue participating in colorectal cancer screening programs, at the appropriate guideline recommended intervals."
- "The benefits and risks of programmatic colorectal screening (i.e., repeated testing over an established period of time) with Shield has not been studied.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic tests evaluated in this evidence review are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of these tests.

The Epi proColon test is the only *SEPT9* DNA test that has received FDA approval. It was approved in 2016 for use in average-risk patients who decline other screening methods. In 2024, the Epi proColon test was purchased by New Day Diagnostics and renamed ColoHealth™.

Guardant Health's Shield™ Blood Test was approved by the FDA in July 2024 for colorectal cancer (CRC) screening in adults aged 45 and older who are at average risk for the disease. The Molecular and Clinical Genetics Panel of the FDA"s Medical Devices Advisory Committee reviewed evidence for Shield and voted on three questions regarding the use of Shield. They voted 8 to 1 favorably that there is reasonable assurance Shield is safe, 6 to 3 favorably that there is reasonable assurance Shield is effective, and 7 to 2 favorably that the benefits of Shield outweigh its risks. The labeled indication is 'Shield is intended for colorectal cancer screening in individuals at average risk of the disease, age 45 years or older. Patients with a positive result should follow up with a colonoscopy. Shield is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals.' A prospective, longitudinal Post-Approval Study (PAS) to evaluate the longitudinal performance of Shield in an average risk population was required (NCT04136002).

RATIONALE

Summary of Evidence

For individuals who are being screened for CRC who receive SEPT9 methylated DNA screening for CRC, the evidence includes case-control, cross-sectional, and prospective diagnostic accuracy studies along with systematic reviews of those studies. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The Evaluation of *SEPT9* Biomarker Performance for Colorectal Cancer Screening (PRESEPT) prospective study estimated the sensitivity and specificity of Epi proColon detection of invasive adenocarcinoma at 48% and 92%, respectively. Other studies were generally low to fair quality. In systematic reviews, sensitivity ranged from 62% to 71% and pooled specificity ranged from 91% to 93%. Based on results from these studies, the clinical validity of Septin9 (*SEPT9)* methylated DNA screening is limited by the low sensitivity of the test. Optimal intervals for retesting are not known. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being screened for CRC who receive gene expression profiling screening for CRC, the evidence includes cross-sectional studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. Sensitivity in the 2 cross-sectional studies of ColonSentry ranged from 61% to 72% and specificity for detecting CRC was 70% to 77%. Based on results from these studies, the clinical validity of gene expression screening is limited by low sensitivity and low specificity. No published peer-reviewed evidence was identified for BeScreened-CRC. Optimal intervals for retesting are not known. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals at average risk of CRC who are being screened for CRC who receive epigenomic and genomic cell-free DNA (cfDNA) blood-based testing, the evidence includes cross-sectional studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. For one screening period, the cfDNA test performance exceeded the predefined acceptance criteria for regulatory approval and predefined criteria for Centers for Medicare & Medicaid Services (CMS) coverage, with sensitivity for CRC of 83% and specificity for non-advanced neoplasia of 90%. Although the cfDNA test has not been compared head-to-head with stool-based tests, these overall estimates of sensitivity and specificity for CRC appear similar to stool-based tests. However, the cfDNA test has lower sensitivity (13%) than colonoscopy and some alternative stool-based tests for the detection of advanced adenomas. Modeling studies conclude that 'blood-based' testing meeting CMS criteria would be clinically effective compared to no screening, but less clinically effective compared to fecal immunochemical test, multi-target stool DNA, and colonoscopy. Modeling studies also identify the potential harm if test substitution is not offset by increased screening participation among individuals refusing other screening modalities. Data evaluating a screening interval of 3 years are being collected as part of the Post-approval Study requirements. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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.

American Cancer Society

In 2018, the American Cancer Society recommended that "adults aged 45 years and older with an average risk of CRC [colorectal cancer] undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy."[24,] The stool-based tests listed as options are a fecal immunochemical test, fecal occult blood test, and multi-target stool DNA test. The Society noted that "...at this time, [methylated] S*EPT9* [Septin9] is not included in this guideline as an option for routine CRC screening for average-risk adults."

American College of Gastroenterology

The American College of Gastroenterology published updated guidelines in 2021 on CRC screening recommendations.[6,] Regarding blood-based tests, they made a conditional recommendation based on very low-quality of evidence stating the following: "We suggest against Septin 9 for CRC screening."

American College of Physicians

In 2019, based on its review of U.S. guidelines, the American College of Physicians issued a guidance statement on screening for CRC in average-risk adults.[25,] For average-risk adults ages 50 to 75 years, the College recommended using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy for screening. No recommendation for genetic or molecular testing of average-risk individuals was included. Updated guidance was issued in 2023, and recommended CRC tests mentioned were fecal immunochemical or high-sensitivity guaiac fecal occult blood tests, colonoscopy, flexible sigmoidoscopy, and fecal immunochemical tests.[26,] The College stated that "Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer."

American College of Gastroenterology

In 2025, the American Gastroenterological Association (AGA) published a clinical practice update focused on blood tests for CRC screening.[27,] The AGA notes that while such blood tests may increase screening participation due to their convenience, patients should know that a positive result necessitates a follow-up colonoscopy. Furthermore, although modeling shows that regular use of these tests is significantly better than no screening, they are less effective at preventing CRC and related deaths compared to standard screening methods. Therefore, these blood tests are best suited for individuals who decline standard CRC screening methods.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) (v.2.2025) guidelines on CRC screening state that blood-based screening modalities "should only be employed to screen individuals of average risk with the commitment to a follow-up colonoscopy for any abnormal result."[13,] Furthermore, blood-based cell-free DNA (bb-cfDNA)-based testing is recommended for every-3-year average-risk screening. The guideline also notes the following regarding bb-cfDNA testing:

- "Requires a single blood specimen to be tested
- Any abnormal result should lead to a referral for a colonoscopy as soon as possible and not later than within 9 months
- Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening

- Given its modest performance, particularly among advanced precancerous lesions, this test is only recommended for individuals who would not be willing to undergo screening through another modality."

U.S. Multi-Society Task Force on Colorectal Cancer

The U.S. Multi-Society Task Force (MSTF) on Colorectal Cancer represents the American College of Gastroenterology, the AGA, and the American Society for Gastrointestinal Endoscopy.[28,] In 2017, the Task Force's clinical guidelines stated that the advantage of *SEPT9* assays for CRC screening is convenience. The disadvantage is "markedly inferior performance characteristics compared with FIT [fecal immunochemical test]." The guidelines also stated that the best frequency for performing the test is unknown and that the task force recommended not using *SEPT9* assays for CRC screening. The MSTF published a focused update of the guidance in 2022.[29,] The updated guidance suggested CRC screening in average-risk individuals ages 45 to 49. The updated guidance did not address *SEPT9* assays.

U.S. Preventive Services Task Force Recommendations

In 2021, the U.S. Preventive Services Task Force (USPSTF) updated its recommendations for CRC screening in adults.[30,31,4,]It recommended screening for CRC starting at age 45 years and continuing until age 85 years. However, conclusions regarding the level of certainty and net benefit with screening varied by age groups. The USPSTF provided a Grade A recommendation for screening in adults aged 50 to 75 years (based on high certainty of a substantial net benefit), a Grade B recommendation for screening in adults aged 45 to 49 years (based on moderate certainty of a moderate net benefit), and a Grade C recommendation for selective screening in adults aged 76 to 85 years (based on moderate certainty of a small net benefit). The guideline states that "because of limited available evidence, the USPSTF recommendation does not include serum tests, urine tests, or capsule endoscopy for colorectal cancer screening." The evidence review supporting the recommendations included a search for studies of serum-based tests (eg, methylated *SEPT9* DNA tests) but concluded that the strength of evidence was low, based on a single case-control study.

Medicare National Coverage

NCD 210.3 (Colorectal Cancer Screening Tests) refers to blood-based biomarker tests:[32,]

"Effective for dates of service on or after January 19, 2021, a blood-based biomarker test is covered as an appropriate colorectal cancer screening test once every 3 years for Medicare beneficiaries when performed in a Clinical Laboratory Improvement Act (CLIA)-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

The patient is:

- age 50-85 years, and,
- asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test), and,
- at average risk of developing colorectal cancer (no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn"s Disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).

The blood-based biomarker screening test must have all of the following:

- Food and Drug Administration (FDA) market authorization with an indication for colorectal cancer screening; and,
- proven test performance characteristics for a blood-based screening test with both sensitivity greater than or equal to 74% and specificity greater than or equal to 90% in the detection of colorectal cancer compared to the recognized standard (accepted as colonoscopy at this time), as minimal threshold levels, based on the pivotal studies included in the FDA labeling.

Effective January 1, 2023, the minimum age for blood-based biomarker test is reduced to 45 years and older."

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2020	New Policy	Policy created with literature review through June 17, 2020. Screening for colorectal cancer using Sept9 methylated DNA is considered not medically necessary; gene profile testing is considered investigational.
September 2021	Replace policy	Policy updated with literature review through May 27, 2021; references added. Minor change to second gene expression profiling policy statement to add BeScreened as investigational.
September 2022	Replace policy	Policy updated with literature review through April 18, 2022; no references added. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through May 22, 2023; reference added. Policy statements unchanged.
July 2024	Replace policy	Policy updated with literature review through May 21, 2024; reference added. Policy statements unchanged.
September 2025	Replace policy	Policy updated with literature review through May 21, 2024; reference added. Policy statements unchanged. Reference policy scheduled for review October 2025.
March 2026	Replace policy	Policy updated with literature review through October 23, 2025; references added. PICOs separated and added separate PICO for Shield test. Position statement added: "Epigenomic and genomic cell-free DNA (cfDNA) blood-based testing with Guardant Shield is considered investigational for all indications.