Regence

Medical Policy Manual Genetic Testing, Policy No. 86

Serologic Genetic and Molecular Screening for Colorectal Cancer

Effective: October 1, 2024

Next Review: May 2025
Last Review: September 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

Certain genes are differentially methylated in colorectal cancer tissues. Blood tests designed to measure methylated DNA and other genomic changes in circulating tumor cells have been proposed as a method to screen for colorectal cancer or to detect disease recurrence. Gene expression testing in blood has also been investigated for colorectal cancer screening.

MEDICAL POLICY CRITERIA

Note: This policy does not address fecal DNA testing or gene expression testing in tumor tissue for cancer recurrence (see Cross References).

I. Blood testing for methylated DNA, with or without gene variant testing, (including but not limited to ColoScape™, ColoVantage®, Colvera®, Epi proColon®, and Shield™) is considered **investigational** for colorectal cancer screening or recurrence monitoring.

II. Gene expression profiling (e.g., ColonSentry®) is considered **investigational** for colorectal cancer screening.

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

CROSS REFERENCES

1. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
2. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
3. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory Policy, No. 46
4. Multianalyte and Gene Expression Assays for Predicting Recurrence in Colon Cancer, Laboratory, Policy No. 76

BACKGROUND

COLORECTAL CANCER

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.[1] The diagnostic performance characteristics of the currently accepted screening options (i.e., colonoscopy, sigmoidoscopy, fecal tests) 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. Early detection of colorectal cancer (CRC) reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy.

The U.S. Preventive Services Task Force has recommended screening for CRC for adults between 45 and 75 years of age,[1] but many adults do not receive screening for CRC. It is thought that less burdensome methods of screening could increase the number of adults screened and thereby improve outcomes.

The National Comprehensive Cancer Network (NCCN) recommendations for recurrence monitoring after colon cancer treatment include colonoscopy, and other lab and imaging tests based on the initial pathologic stage.[2]

SEPT9 METHYLATED DNA

ColoVantage® (various manufacturers) blood tests for serum *SEPT9* methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon® (Epigenomics) received U.S. Food and Drug Administration approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage® and Epi proColon® are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology.

BCAT1 AND *IKZF1* METHYLATED DNA

Colvera® (ClinicalGenomics) is a serum test for methylated *BCAT1* and *IKZF1* in circulating tumor DNA. The test is marketed as a surveillance method to detect recurrent colon cancer or measure residual disease following treatment.

CELL-FREE DNA TO DETECT EPIGENOMIC MODIFICATIONS

Shield™ (Guardant Health) extracts cell-free (cf) DNA from blood to assess for epigenetic and genomic alterations simultaneously in DNA that has shed from neoplastic lesions. The test assesses for circulating tumor (ct) DNA variants that are known to occur in cancer, and detects epigenetic modifications, including altered methylation patterns and changes in fragment size distribution that may be associated with malignant transformation.

GENE EXPRESSION PROFILING

ColonSentry® (Stage Zero Life Sciences) is a PCR assay that uses a blood sample to detect the expression of seven genes found to be differentially expressed in CRC patients compared with controls[3]: *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."[4]

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. Food and Drug Administration (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.

EVIDENCE SUMMARY

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 focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

COLORECTAL CANCER SCREENING WITH *SEPT9* METHYLATED DNA TESTING (COLOVANTAGE®, EPI PROCOLON®)

Serum biomarkers that are shed from colorectal tumors have been identified and include Septin 9 hypermethylated DNA (*SEPT9*). The Septin 9 protein is involved in cell division, migration, and apoptosis and acts as a tumor suppressor; when hypermethylated, expression of *SEPT9* is reduced.

Clinical Validity

The diagnostic performance of *SEPT9* methylation for colon cancer has been reported in meta-analyses. The systematic reviews identified from 2016 and 2017 included from 14 to 39 studies (see Table 1). Pooled sensitivity ranged from 62% to 71% and pooled specificity ranged from 91% to 93% (see Table 2). The systematic review by Nian (2017) found that study designs (case-control vs. cross-sectional), assays or kits used (Epi proColon® vs. other), country (Asia or other), sample sizes (>300 or <300), and risk of bias of included studies all contributed to heterogeneity.[5] Most included studies were case-control with the exclusion of difficult to diagnose patients, which may lead to a spectrum bias and overestimation of diagnostic accuracy. Reviewers included 20 studies of Epi proColon® test 1.0, 2.0, or a combination of the two. When only looking at studies of Epi proColon® 2.0, sensitivity was 75% compared with 71% in the overall analysis, with a specificity of 93% (see Table 2). Sensitivity and specificity may be additionally affected by the specific algorithm used, with the 1/3 algorithm resulting in higher sensitivity and the 2/3 algorithm resulting in higher specificity.[6] A 2020 systematic review of Epi proColon® 2.0 by Hariharan and Jenkins found high specificity (92%) and NPV (99.9%) for CRC so that a negative test would rule out CRC.[7] However, a test with sensitivity of 69% would accurately diagnose only 21 of 30 CRC cases in a sample of 10,000 people at average risk. Sensitivity for precancerous lesions would be lower.

Table 1. Systematic Review Characteristics

Study	Studies Included	N	Study Designs Included	Study Reference Standards Included	11-Item QUADAS Quality Assessment		
					No. of Studies Rated as High or Unclear Risk of Bias		
					No Domains	1-2 Domains	>2 Domains
Harihan and Jenkins (2020)[7]	19	7,629	CC	Colonoscopy	6	8	5
Nian (2017)[5]	25	9,927	CC and CS	Colonoscopy	3	14	8
Li (2016)[8]	39			Colonoscopy	6	12	21
Yan (2016)[9]	14	9,870	CC and CS	Colonoscopy	0	13	1

CC: case-control; CRC: colorectal cancer; CS: cross-sectional.

Table 2. Systematic Review Results

Study	Test	Sensitivity (95% CI, %)	Specificity (95% CI, %)
Harihan and Jenkins (2020)[7]	Epi proColon® 2.0	69 (62 to 75)	92 (89 to 95)
Nian (2017)[5]	Various	71 (67 to 75)	92 (89 to 94)
Nian (2017)[5]	Epi proColon® 2.0	75 (67 to 77)	93 (88 to 96)
Li (2016)[8]	Various	62 (56 to 67)	91 (89 to 93)
Yan (2016)[9]	Various	66 (64 to 69)	91 (90 to 91)
Yan (2016)[9]	Epi proColon®	63 (58 to 67)	91 (90 to 92)

CI: confidence interval.

The evidence review for the 2021 U.S. Preventive Services Task Force update on CRC screening included studies on blood tests for methylated *SEPT9* DNA.[10] The inclusion criteria were fair- or good-quality English-language studies, asymptomatic screening populations, age of 40 years or older, and at average risk for CRC or not selected for inclusion based on CRC

risk factors. The Evaluation of *SEPT9* Biomarker Performance for Colorectal Cancer Screening (PRESEPT) met these inclusion criteria.

PRESEPT, published by Church (2014) was an international prospective screening study of the first-generation Epi proColon® test (see Table 3).[11] Of 1,516 patients selected for laboratory analysis, colonoscopy identified 53 (3%) patients with invasive adenocarcinoma, 315 (21%) with advanced adenoma, and 210 (14%) with nonadvanced adenoma. The overall sensitivity, specificity, positive predictive value, and negative predictive value for the detection of invasive adenocarcinoma are shown in Table 4. Sensitivity for any adenoma was 48% and advanced adenoma was 11%.

Table 3. Study Characteristics

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Church (2014)[11]	Patients ≥50 years of age at average risk and scheduled for colonoscopy	Prospective random sampling from 7,941 patients at 32 sites	Colonoscopy	6-16 days before colonoscopy	Yes

Table 4. Study Results

Study	Initial N	Final N	Excluded Samples	Clinical Validity (95% CI, %)			
				Sensitivity	Specificity	PPV	NPV
Church (2014)[11]	1,516	1,510	6	48.2 (32.4 to 63.6)	91.5 (89.7 to 93.1)	5	100

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

Song (2018) conducted a prospective study of the colorectal tumor detection rate from methylated *SEPT9* levels by Epi proColon® 2.0 using the 2/3 algorithm.[12] All 1,347 individuals who met criteria and were to undergo colonoscopy provided a blood sample prior to evaluation of clinical status. The level of methylated *SEPT9* increased as the severity of disease increased, and the detection rate increased with disease severity. The detection rate was less than 20% for serrated adenoma and tubular adenoma, 41% for tubulovillous adenoma, 54% for stage I CRC, and then increased to 84% as the stage of CRC increased to stage IV CRC. Results suggested potential utility for monitoring treatment response but limited utility as a screening tool.

Clinical Utility

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 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 RCTs.

Studies comparing survival outcomes in patients who undergo CRC screening with *SEPT9* methylated DNA testing or with standard screening were not identified. Such comparative studies with clinically meaningful outcomes, such as survival, are necessary to demonstrate incremental improvement in the net health outcome compared with current standard screening

approaches (fecal immunochemical test, colonoscopy) and to address lead-time bias for cancers identified through the screening.

There is a need for further studies evaluating survival outcomes in patients screened with *SEPT9* methylated DNA testing (ColoVantage®, Epi proColon®) who have refused established screening methods. Because the evidence on clinical validity has reported that the test has a lower sensitivity than other screening methods, the clinical utility is uncertain. If the test is restricted only to patients who would otherwise not be screened, outcomes might be improved. However, if the test is used as a substitute for other screening tests that have higher sensitivity, outcomes may be worse.

COLORECTAL CANCER RECURRENCE MONITORING WITH *BCAT1* AND *IKZF1* METHYLATED DNA TESTING (COLVERA®)

The *BCAT1* and *IKZF2* genes are hypermethylated in colorectal tumor tissue. The Colvera® assay measures levels of these methylated genes in blood and has been proposed as a method for detecting cancer recurrence following treatment.

Clinical Validity

Evidence on the use of the Colvera® test to predict or detect CRC recurrence is limited to observational cohort studies of CRC patients undergoing surveillance for disease recurrence.[13-16] These manufacturer-sponsored studies have found significant associations between test results and cancer recurrence, with two studies reporting sensitivities of 63% and 66% and specificities of 91.5% and 97.9%.[15, 16] These studies generally lacked long-term follow-up, with median follow-ups of less than two years. Additional limitations included differing surveillance protocols, timing of blood draws, and recurrence definitions between studies.

Clinical Utility

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 RCTs.

No studies examining the clinical utility of Colvera® were identified.

COLORECTAL CANCER SCREENING USING CELL-FREE DNA TO DETECT EPIGENOMIC MODIFICATIONS

Cf-DNA sequencing is enriched with DNA shed from neoplastic lesions in order to detect circulating tumor (ct) DNA from malignant and precancerous colorectal lesions.

Clinical Validity

Chung (2024) published a prospective validation study (“Evaluation of ctDNA LUNAR Assay In an Average Patients Screening Encounter; ECLIPSE study) involving 7861 people aged 45 to 84 years, at average risk for colorectal cancer.[17] The primary study outcomes were the sensitivity for colorectal cancer and specificity for advanced neoplasia compared to colonoscopy. The secondary outcome was sensitivity for advanced precancerous lesions. Out of 65 participants with a colonoscopy-detected colon cancer, 54 had a positive cfDNA test and 11 had a negative cfDNA test. The sensitivity of the cfDNA test was 83.1% (95% confidence

interval [CI], 72.2 to 90.3). Of participants without cancer or precancerous lesions on colonoscopy, 10.4% had a positive cfDNA blood test. Therefore, the specificity of the test for advanced neoplasia was 89.6% (95% CI, 88.8 to 90.3). Advanced precancerous lesions were identified on colonoscopy in 1116 participants. Of those, 147 (13.2%) had a positive cfDNA test, indicating a 13.2% sensitivity for advanced precancerous lesions (95% CI, 11.3 to 15.3). The authors note that while the sensitivity and specificity of the test met FDA acceptance criteria used for other approved colorectal cancer screening tests, non-invasive tests that reliably detect advanced precancerous lesions remain elusive.

Clinical Utility

No studies evaluating the clinical utility of cfDNA-based colorectal cancer screening tests were identified.

GENE EXPRESSION PROFILING (COLONSENTRY®)

Clinical Validity

Two case-control studies have been identified with ColonSentry®. Marshall (2010) conducted a genome-wide association study in 189 whole blood samples (98 controls, 91 patients with CRC) and identified 45 differentially expressed gene biomarker candidates using microarray hybridization.[18] Through logistic regression and bootstrapping (subsampling with replacement) in a training set of 232 samples, seven genes were selected for further development. In a subsequent test set of 410 samples (208 controls, 202 patients with CRC), sensitivity, specificity, positive predictive value, and negative predictive value were determined (see Tables 5 and 6). Yip (2010) conducted a similar cross-sectional study of 210 blood samples from patients in Malaysia.[3] The Malaysian population has different ethnic groups with different CRC incidences and CRC in Asian populations is more likely to be nonpolypoid (i.e., flat or depressed) compared with Western populations in whom the test was developed. Sensitivity for the two studies ranged from 61% to 72% and specificity for detecting CRC were 70% to 77%. The area under the curve was 0.76 (95% confidence interval 0.70 to 0.82). Because of the cross-sectional design, follow-up of controls to determine which strata developed CRC was not reported, limiting conclusions drawn about the accuracy of the test for risk prediction.

Table 5. Study Characteristics

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests
Marshall (2010)[18]	202 patients with CRC and 208 controls	Case-control	NA	NA
Yip (2010)[3]	99 patients with CRC and 111 controls	Case-control	NA	NA

Table 6. Study Results

Study	Initial N	Final N	Excluded Samples	AUC (95% CI)	Clinical Validity (95% CI, %)			
					Sensitivity	Specificity	PPV	NPV
Marshall (2010)[18]	410			0.80 (0.76 to 0.84)	72	70	70	72
Yip (2010)[3]	200				61	77		

AUC: area under the curve; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

Clinical Utility

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 RCTs.

No studies examining the clinical utility of ColonSentry® were identified.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

Current NCCN (v.1.2024) guidelines on colorectal cancer (CRC) screening state that "A blood test that detects circulating methylated *SEPT9* DNA has been FDA-approved for CRC screening for those who refuse other screening modalities. Based on current data, the panel concludes that the interval for repeating testing is unclear".[19] These guidelines do not discuss screening using gene expression testing or cfDNA.

NCCN guidelines for colon cancer (v.3.2024) state, “Circulating tumor DNA (ctDNA) is emerging as a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results.”[2]

AMERICAN CANCER SOCIETY

The American Cancer Society Guideline for Colorectal Cancer Screening (2024) “recommends that people at average risk of colorectal cancer start regular screening at age 45.”[20] The guideline includes stool-based tests and visual (structural) exams of the colon and rectum. The use of blood tests as a colorectal cancer screening tool are not addressed.

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2021, the American College of Gastroenterology (ACG) published Clinical Guidelines: Colorectal Cancer Screening.[21] The ACG strongly recommends colonoscopy and fecal immunochemical testing (FIT) testing as the primary screening modalities for CRC. For people who are unable or unwilling to undergo colonoscopy, the ACG conditionally recommends consideration of flexible sigmoidoscopy, multitarget DNA test, CT colonography, or colon capsule. The ACG suggests against Septin 9 for CRC screening.

AMERICAN COLLEGE OF PHYSICIANS

In 2023, based on its review of U.S. guidelines, the American College of Physicians issued an updated guidance statement on screening for CRC in average risk adults.[22] For average-risk adults ages 50 to 75 years, the College recommended using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy for screening. The guideline states that clinicians should not use serum screening tests for colorectal cancer.

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

The U.S. Multi-Society Task Force on Colorectal Cancer represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.[23] In 2022, the Task Force updated its clinical guidelines. The guidelines recommend offering CRC screening to all average risk individuals between 45-49.

The guidelines do not address the use of SEPT9 or other blood tests for methylated DNA for CRC screening.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

In 2021, the U.S. Preventive Services Task Force updated its recommendations for CRC screening in adults.[1] It recommended screening for CRC starting at age 45 years and continuing until age 75 years. The 2021 recommendations differ from the 2016 and 2008 recommendations in that current guidance does not emphasize specific screening approaches but highlights evidence that CRC screening may substantially reduce deaths from the disease among adults ages 45 to 50 years, based on an increased incidence of CRC in this group. The USPSTF recommendation for CRC "does not include serum tests, urine tests, or capsule endoscopy for colorectal cancer screening because of the limited available evidence on these tests" and because of the availability of other effective methods (i.e., the recommended screening strategies).

SUMMARY

There is not enough research to show that screening for colorectal cancer using blood tests for circulating tumor DNA or methylated DNA (including but not limited to *SEPT9*, *BCAT1,* and *IKZF1*), with or without gene variant testing, can improve health outcomes for patients. Blood-based colorectal screening testing has been shown to detect fewer cancers than other existing screening methods, and there are no studies that have evaluated outcomes for patients screened using blood-based tests compared to those screened with other tests. Current clinical practice guidelines do not recommend blood-based testing to screen for colorectal cancer. Therefore, this testing, including but not limited to the use of ColoScape™, ColoVantage®, Epi proColon®, or Shield™ is considered investigational.

There is not enough research to show that blood testing for methylated DNA, including *BCAT1* and *IKZF1,* can improve health outcomes for patients undergoing surveillance for recurrent colorectal cancer. There are no studies that have evaluated whether the results of methylated DNA testing can lead to improved survival compared to other forms of surveillance. In addition, current clinical practice guidelines do not recommend this testing. Therefore, testing for colorectal cancer recurrence using blood tests for methylated DNA, including but not limited to the use of Colvera®, is considered investigational.

There is not enough research to show that screening for colorectal cancer using gene expression tests can improve health outcomes for patients. There are no studies that have compared outcomes for patients managed with and without the test. In addition, current clinical practice guidelines do not recommend gene expression testing to screen for colorectal cancer. Therefore, this testing, including but not limited to ColonSentry®, is considered investigational.

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CODES

Codes	Number	Description
CPT	0229U	*BCAT1* (Branched chain amino acid transaminase 1) or *IKZF1* (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
	0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer
	0453U	Oncology (colorectal cancer), cellfree DNA (cfDNA), methylation based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)
	0496U	Oncology (colorectal), cell-free DNA, 8 genes for mutations, 7 genes for methylation by real-time RT-PCR, and 4 proteins by enzyme-linked immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk
	0501U	Oncology (colorectal), blood, quantitative measurement of cellfree DNA (cfDNA)
	81327	*SEPT9* (Septin9) (eg, colorectal cancer) promoter methylation analysis
HCPCS	G0327	Colorectal cancer screening; blood-based biomarker

Date of Origin: *May 2021*