2.04.150	Serologic Genetic and Molecular Screening for Colorectal Cancer		
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Section:	2.0 Medicine	**Page:**	Page 1 of 16

Policy Statement

I. *SEPT9* methylated DNA testing (e.g., ColoVantage®, Epi proColon®) is considered **investigational** for colorectal cancer screening.

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

See the Codes table for details.

Description

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. 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.

Summary of Evidence

For individuals who are being screened for colorectal cancer (CRC) who receive serologic molecular or genetic 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. Sensitivity in the 2 cross-sectional studies of ColonSentry ranged from 61% to 72% and specificity for detecting CRC were 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable

Related Policies

- General Approach to Evaluating the Utility of Genetic Panels
- General Approach to Genetic Testing

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

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.

Rationale

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. 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 CRC reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy. A simpler screening blood test may have the potential to encourage screening and decrease mortality if associated with increased screening compliance.

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. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage and Epi proColon are both polymerase chain reaction (PCR) assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., 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[1,]: *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."[2,] 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.[3,]

Table 1 lists tests assessed in this evidence review.

Table 1. Genetic and Molecular Diagnostic Tests Assessed This Evidence Review

Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Therapeutic	Future Risk
BeScreened-CRC	Beacon Biomedical	May 2021	●			
ColonSentry	Stage Zero Life Sciences	Aug 2015	●			
***SEPT9* methylated DNA**[a]	Several[b]	Oct 2014	●			

a. For example, ColoVantage and Epi proColon.
b. ARUP, Quest, Clinical Genomics and Epigenomics.

Literature Review

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 first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Colorectal Cancer Screening

Clinical Context and Test Purpose

The U.S. Preventive Services Task Force has recommended screening for colorectal cancer (CRC) starting at age 50 years and continuing until age 75 years but many adults do not receive screening for CRC.[4,] It is thought that less burdensome methods of screening could increase the number of adults screened and thereby improve outcomes.

Serum biomarkers that are shed from colorectal tumors have been identified and include Septin9 (*SEPT9*) hypermethylated DNA. 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.

ColonSentry is a polymerase chain reaction assay that uses a blood sample to detect the expression of 7 genes found to be differentially expressed in individuals with CRC compared with controls. The purpose of CRC screening using *SEPT9* methylated DNA testing and gene expression profiling in individuals who are indicated for CRC screening is to provide a testing option that is an alternative to or an improvement on existing tests used to detect CRC.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are being screened for CRC.

Intervention

The interventions of interest are *SEPT9* methylated DNA testing (e.g., ColoVantage, Epi proColon) and gene expression profiling (e.g. ColonSentry, BeScreened-CRC).

Comparators

The comparator of interest is the standard of care without genetic screening.

Outcomes

The outcomes of interest are overall survival (OS), disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up for CRC screening is weeks for the diagnosis of CRC to years for survival outcomes.

Study Selection Criteria

For the evaluation of clinical validity of serologic genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

SEPT9 Methylated DNA With ColoVantage and Epi proColon

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

The diagnostic performance of *SEPT9* methylation for colon cancer has been reported in meta-analyses. The systematic reviews identified from 2016 and 2017 included 14 to 39 studies (see Table 2). Pooled sensitivity ranged from 62% to 71% and pooled specificity ranged from 91% to 93% (see Table

3). The systematic review by Nian et al (2017) found that study designs (case-control vs cross-sectional), assays or kits used (Epi proColon vs other), country (Asia or other), sample sizes (n >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 2. 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 3). 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 negative predictive value (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 2. 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 to 2 Domains	>2 Domains
Harihan and Jenkins (2020)[7,]	19	7629	CC	Colonoscopy	6	8	5
Nian et al (2017)[5,]	25	9927	CC and CS	Colonoscopy	3	14	8
Li et al (2016)[8,]	39	3853 patients with CRC and 6431 controls	CC and CS	Colonoscopy	6	12	21
Yan et al (2016)[9,]	14	9870	CC and CS	Colonoscopy	0	13	1

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

Table 3. 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 et al (2017)[5,]	Various	71 (67 to 75)	92 (89 to 94)
Nian et al (2017)[5,]	Epi Procolon 2.0	75 (67 to 77)	93 (88 to 96)
Li et al (2016)[8,]	Various	62 (56 to 67)	91 (89 to 93)
Yan et al (2016)[9,]	Various	66 (64 to 69)	91 (90 to 91)
Yan et al (2016)[9,]	Epi Procolon	63 (58 to 67)	91 (90 to 92)

CI: confidence interval.

The evidence review for the 2016 U.S. Preventive Services Task Force update on CRC screening included studies on blood tests for methylated *SEPT9* DNA. 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 only study found to meet these inclusion criteria was the Evaluation of SEPT9 Biomarker Performance for Colorectal Cancer Screening (PRESEPT) (described below).

PRESEPT (Church et al [2014]) was an international prospective screening study of the first-generation Epi proColon test (see Table 4).[10,] Of 1516 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 (PPV), and NPV for the detection of invasive adenocarcinoma are shown in Table 5. Sensitivity for any adenoma was 48% and advanced adenoma was 11%.

Table 4. Study Characteristics

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Church et al (2014)[10,]	Patients ≥50 y at average risk and scheduled for colonoscopy	Prospective random sampling from 7941 patients at 32 sites	Colonoscopy	6 to 16 days before colonoscopy	Yes

Table 5. Study Results

Study	Initial N	Final N	Excluded Samples	Clinical Validity (95% Confidence Interval), %			
				Sensitivity	Specificity	PPV	NPV
Church et al (2014)[10,]	1516	1510	6	48.2 (32.4 to 63.6)	91.5 (89.7 to 93.1)	5	100

NPV: negative predictive value; PPV: positive predictive value.

Tables 6 and 7 display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Church et al (2014)[10,]		3. First-generation test			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Church et al (2014)[10,]	2. Not randomly sampled					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of

samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported

Nonrandomized Studies

Song et al (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.[11,] All 1347 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.

Clinically Useful

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

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 randomized controlled trials (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 (e.g., 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.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the sensitivity of *SEPT9* methylated DNA is low, a chain of evidence establishing the clinical utility of *SEPT9* methylated DNA cannot be established.

Subsection Summary: Colorectal Cancer Screening With *SEPT9* Methylated DNA Testing

The evidence for the clinical validity of CRC screening includes case-control studies and prospective screening studies. Systematic reviews have reported that the sensitivity of testing ranges from 62% to 75% and the specificity from 91% to 93%. Studies were generally of low to fair quality. The prospective PRESEPT study with average-risk patients scheduled for colonoscopy estimated the sensitivity of Epi proColon for detection of invasive adenocarcinoma to be 48% and for an advanced adenoma to be 11%. Based on results from these studies, the clinical validity of *SEPT9* methylated DNA screening is limited by low sensitivity and low positive predictive value of the test.

Detection of only half of preclinical cancers and a small proportion of advanced adenomas limits the clinical utility of the test. 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.

Gene Expression Profiling With ColonSentry

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Observational Studies

Two case-control studies have been identified with ColonSentry. Marshall et al (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.[12,] Through logistic regression and bootstrapping (subsampling with replacement) in a training set of 232 samples, 7 genes were selected for further development. In a subsequent test set of 410 samples (208 controls, 202 patients with CRC), sensitivity, specificity, PPV, and NPV were determined (see Tables 8 and 9). Yip et al (2010) conducted a similar cross-sectional study of 210 blood samples from patients in Malaysia.[1,] The Malaysian population has different ethnic groups with different CRC incidences and CRC in Asian populations is more likely to be nonpolypoid (ie, flat or depressed) compared with Western populations in whom the test was developed.

Sensitivity for the 2 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 [CI], 0.70 to 0.82).

Table 8. Study Characteristics

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests
Marshall et al (2010)[12,]	202 patients with CRC and 208 controls	Case-control	NA	NA
Yip et al (2010)[1,]	99 patients with CRC and 111 controls	Case-control	NA	NA

CRC: colorectal cancer; NA: not applicable.

Table 9. Study Results

Study	Initial N	Final N	Excluded Samples	AUC (95% CI)	Clinical Validity (95% CI), %			
					Sensitivity	Specificity	PPV	NPV
Marshall et al (2010)[12,]	410			0.80 (0.76 to 0.84)	72	70	70	72
Yip et al (2010)[1,]	200				61	77		

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

Tables 10 and 11 display notable limitations in relevance and design and conduct. Because of its 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 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Marshall et al (2010)[12,]	4. Included patients with CRC and healthy controls				
Yip et al (2010)[1,]	4. Included patients with CRC and healthy controls				

CRC: colorectal cancer.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b]Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 11. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Marshall et al (2010)[12,]	2. Selection not random					
Yip et al (2010)[1,]	2. Selection not random					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b]Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c]Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinically Useful

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

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.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence supporting the use of ColonSentry for predicting CRC risk cannot be constructed due to lack of clinical validity.

Subsection Summary: Colorectal Screening With ColonSentry

ColonSentry is intended to stratify patients with average CRC risk who are averse to current screening approaches to identify those at increased risk and therefore choose a less-invasive screening method. However, 2 cross-sectional studies are insufficient to demonstrate the risk predictive ability of the test; i.e., clinical validity has not been established. Sensitivity for the 2 studies 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 with ColonSentry is limited by low sensitivity and low specificity. Direct and indirect evidence of clinical utility is currently lacking.

Colorectal Screening with BeScreened-CRC

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

No published peer-reviewed evidence was identified.

Clinically Useful

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

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 BeScreened-CRC were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence supporting the use of BeScreened-CRC for predicting CRC risk cannot be constructed due to lack of evidence.

Subsection Summary: Colorectal Screening With BeScreened-CRC

BeScreened-CRC is intended for individuals who are averse to current screening approaches to identify those at increased risk and therefore choose a less-invasive screening method. No published peer-reviewed evidence was identified; therefore, evidence of clinical validity and clinical utility is currently lacking.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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." [13,] 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.[14,] 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.[15,] 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.[16,] The College stated that "Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer."

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) (v.1.2024) guidelines on CRC screening state that "A blood test that detects circulating methylated *SEPT9* DNA has been U.S. Food and Drug Administration approved for CRC screening for those who refuse other screening modalities…the interval for repeating testing is unknown/unclear".[17,]

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.[18,] 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.

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.[19,20,] 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 (e.g., methylated *SEPT9* DNA tests) but concluded that the strength of evidence was low, based on a single case-control study.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03218423[a]	Performance of Epi proColon in Repeated Testing in the Intended Use Population (PERT)	4500	Jan 2024 (unknown)
NCT04136002[a]	Evaluation of the ctDNA LUNAR Test in an Average Patient Screening Episode (ECLIPSE)	40000	Dec 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result
	0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas
	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), cell-free 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)
	81327	SEPT9 (Septin9) (e.g., colorectal cancer) promoter methylation analysis
HCPCS	G0327	Colorectal cancer screening; blood-based biomarker

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/01/2020	New policy.
09/01/2021	Annual review. Policy statement, guidelines and literature updated. Coding update.
09/01/2022	Annual review. No change to policy statement. Literature review updated.
09/01/2023	Annual review. No change to policy statement. Policy guidelines and literature review updated.
10/01/2025	Policy reactivated. Previously archived from 10/01/2024 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.

- The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Serologic Genetic and Molecular Screening for Colorectal Cancer 2.04.150** **Policy Statement:** I. *SEPT9* methylated DNA testing (e.g., ColoVantage®, Epi proColon®) is considered **investigational** for colorectal cancer screening. II. Gene expression profiling (e.g., ColonSentry®, BeScreened™-CRC) is considered **investigational** for colorectal cancer screening.