Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Serologic Genetic and Molecular Screening for Colorectal Cancer

Description/Background

Colorectal Cancer

For individuals 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 colonic neoplasia reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy.

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)

Test Description: FirstSight^{CRC}

FirstSight™ liquid biopsy (CellMax Life) is a proprietary lab test that which selectively captures and identifies precancerous adenomas and cancer cells that are shed into the blood via the lower gastrointestinal tract. High cell preservation and detection rates of precancerous cells are enabled by using a patented technology consisting of a microfluidic chip with a proprietary nano layer for cell capture; high-affinity antibodies; a unique biomimetic process to effectively wash away unwanted cells, while retaining circulating tumor cells; and a special air-foam release technology to gently release the captured cells. An algorithm is used for high throughput image analysis and reproducibility. Results are reported as “positive” or “negative”.(20)

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	●			
FirstSight^{CRC}	CellMax Life	Oct 2020	●			
SEPT9 methylated DNA[a]	Several[b]	Oct 2014	●			

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

Cell-Free DNA

Shield™ (Guardant Health) is a cell-free DNA (cfDNA) test to detect genomic (somatic mutations) and epigenomic alterations (methylation and fragmentation patterns) associated with colorectal cancer from whole blood samples collected from individuals at average risk for CRC. The results are combined using proprietary bioinformatics algorithms to generate a final qualitative test result of “Positive” or “Negative.” Patients with a positive result may have CRC or advanced adenomas and should be followed by colonoscopy.

The comparator of interest for cfDNA is the gold standard of care for CRC screening (i.e., colonoscopy).
For 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 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 basis of screening intervals for colonoscopy. However, other pathways of colorectal tumorigenesis have been described, such as microsatellite instability pathway and 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.

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. **Note:** Two studies were presented to the FDA for approval. The highest sensitivity obtained by Epi proColon was 72.2% and the highest specificity was 80.8%.

Shield (Guardant Health, Inc) received FDA PMA (2024) as a qualitative, in vitro diagnostic test intended to detect colorectal cancer derived alterations in cell-free DNA. 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 be followed by colonoscopy. Shield is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals. Approval of Shield is contingent upon post-approval study data being submitted for ongoing evaluation of longitudinal performance in an average risk population. **Note:** Overall sensitivity of the cfDNA test for the detection of colorectal cancer was 83.1%. Specificity was found to be 89.6% for nonadvanced adenomas, non-neoplastic findings and negative colonoscopy.

Medical Policy Statement

The following types of testing are considered experimental/investigational for colorectal cancer screening:

- Serologic genetic testing (i.e., SEPT9 methylated DNA testing [ColoVantage®, Epi proColon®])
- Molecular testing (i.e., gene expression profiling [ColonSentry®, BeScreened™ CRC, FirstSight™]
- cfDNA blood test (e.g., Shield [Guardant Health, Inc.])

There is insufficient scientific evidence on the analytical and clinical validity as well as clinical utility of these tests on patient management and outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81327	81479	0163U	0498U	0499U	0501U
0537U	G0327				

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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 45 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 CRC individuals 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	1-2 Domains	>2 Domains
Harihan and Jenkins (2020)	19	7629	CC	Colonoscopy	6	8	5
Nian et al (2017)	25	9927	CC and CS	Colonoscopy	3	14	8
Li et al (2016)	39	3853 patients with CRC and 6431 controls	CC and CS	Colonoscopy	6	12	21
Yan et al (2016)	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)	Epi Procolon 2.0	69 (62 to 75)	92 (89 to 95)
Nian et al (2017)	Various	71 (67 to 75)	92 (89 to 94)
Nian et al (2017)	Epi Procolon 2.0	75 (67 to 77)	93 (88 to 96)
Li et al (2016)	Various	62 (56 to 67)	91 (89 to 93)
Yan et al (2016)	Various	66 (64 to 69)	91 (90 to 91)
Yan et al (2016)	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)	Patients ≥50 y at average risk and scheduled for colonoscopy	Prospective random sampling from 7941 patients at 32 sites	Colonoscopy	6-16 d 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)	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)		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)	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 (i.e., 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 (i.e., 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% 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)	202 patients with CRC and 208 controls	Case-control	NA	NA
Yip et al (2010)	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)	410			0.80 (0.76 to 0.84)	72	70	70	72
Yip et al (2010)	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)	4. Included patients with CRC and healthy controls				

Yip et al (2010)	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)	2. Selection not random					
Yip et al (2010)	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 (i.e., 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.

Cell-Free DNA Testing with Shield

Guardant Shield
The pivotal study of the cfDNA test was described in the FDA Summary of Safety and Effectiveness document and a publication by Chung et al (2024). The ECLIPSE study was a multicenter (265 US sites), prospective, non-randomized, observational study including 7,861

participants ages 45 to 84 years who were of average risk for CRC. Individuals who were eligible for CRC screening and intended to undergo colonoscopy were enrolled in the study between 2019 and 2022. Blood samples were collected prior to the participant undergoing standard of care colonoscopy. Central pathology reviews were conducted for lesion classification; the lesion of greatest clinical significance was used to classify into histopathology categories. The primary outcomes were sensitivity for CRC and specificity for non-advanced neoplasia compared to colonoscopy/histopathology. The predefined acceptance criteria was a lower bound of the 95% confidence interval of >65% for sensitivity and a lower bound for the 95% confidence interval of specificity of >85%. The secondary outcome was sensitivity for advanced adenoma. The test performance exceeded the predefined acceptance criteria for the primary outcomes with sensitivity for CRC of 83% and specificity for non-advanced neoplasia of 90%. The sensitivity for advanced adenoma was 13%. The FDA included a requirement for a Post-Approval study (PAS; NCT04136002) that will gather data on the cumulative false-positive and true-positive rates over 3 years, among other outcomes.

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.

Zhou et al (2022) summarized the techniques currently applied to liquid biopsy and described the different circulating biomarkers in body fluids and their clinical potential for precision therapy of CRC. Although authors agreed that liquid biopsy (e.g. cfDNA, ctDNA, exomes, tumor educated-platelet) has the potential to be used in the future, the current limitations of liquid biopsy include: (1) low concentration rates of Circulating tumor cells (CTC) in a 1 ml blood sample in comparison to the thousands of cells that may be present in the blood stream; (2) a lack of standardization of isolation, enrichment and detection of samples and testing. Each approach had its own limitations by way of applying different technology and thus diverse sensitivities and specificities were noted; (3) a need for multicenter, larger, longer-term studies to confirm efficacy. CTC detection is uncommon and challenging in early-stage CRC therefore, an ideal screening tool should have the advantages of reproducibility and high efficiency, as well as high sensitivity and specificity. Different detection methods of liquid biopsy were found to have different detection rates. Authors concluded that CTC testing for early diagnosis remains limited. Molecular mechanisms are currently insufficient and not completely understood at this time. Standardized methods are needed to enhance CTC detection in early malignancies. Authors recommended that attention should be devoted to improving technical assays to accelerate the rate of CTC detection in the future.

Subsection Summary: Cell-Free DNA in Screening for Colorectal Cancer
Literature is limited in the use of cfDNA efficacy when used to screen for CRC. One article which compared various tests for liquid biopsy found that standardization is lacking which caused a difference in specificity and sensitivity. Evidence of clinical utility is currently lacking.

FirstSight™

Review of Evidence
No full-length, peer-reviewed studies of the DNA Methylation Pathway Profile were identified.

Section Summary: DNA Methylation Pathway Profile
No studies were identified that evaluated this test. Factors that support a chain of evidence for prognostic or diagnostic utility are lacking.

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 OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The 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 *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 colorectal cancer (CRC) who receive gene expression profiling screening for CRC, the evidence includes cross-sectional studies. Relevant outcomes are overall survival (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 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. 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 colorectal cancer (CRC) who are being screened for CRC who receive cell-free DNA (cfDNA) blood-based testing, the evidence includes cross-sectional studies. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, change in disease status, and morbid events. Cell-free DNA testing with Guardant Shield has not been directly compared with the gold standard (colonoscopy) or other colorectal cancer screening tests. For a test to be clinically valid, it must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). 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. For a test to display clinical utility, the

results inform management decisions that improve the net health outcome of care including the administration of correct therapy or more effective therapy, and/or the avoidance of unnecessary therapy or testing. With the FDA approval, data evaluating a screening interval of 3 years are being collected as part of the Post-approval Study requirements. The National Comprehensive Cancer Network only supports the use of ctDNA testing a part of a clinical trial. 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

American Cancer Society
In 2018, the American Cancer Society has recommended that "adults aged 45 y and older with an average risk of CRC 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 NCCN 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 unknown/unclear."(17)

No other recommendations are made for any type of circulating-cell free DNA (cfDNA) testing.

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.

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	4500	Jan 2024 (unknown)
NCT04136002[a]	Evaluation of the ctDNA LUNAR Test in an Average Patient Screening Episode (ECLIPSE)	40,000	Dec 2025

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

Government Regulations
National:

Colorectal Cancer Screening Tests. Pub: 100-3; Section: 210.3; Version 6. Effective 1/1/23.

Blood-based Biomarker Tests (effective January 19, 2021)

Blood-based DNA testing detects molecular markers of altered DNA that are contained in the cells shed into the blood by colorectal cancer and pre-malignant colorectal epithelial neoplasia.

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. (See Regulatory section for more information)

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

Local:

Billing and Coding: MolDX: *SEPT9* Gene Test (A55206). Effective Date: 2/16/17. Revision Date: 11/30/23.

The MolDX team has determined that a Septin 9 methylation analysis test for colorectal cancer detection is not a Medicare covered service. Screening in the absence of signs and symptoms of an illness or injury is not defined as a Medicare benefit.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening
- Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)
- CPT Category III Codes – Noncovered Services

- Genetic Testing – Experimental/Investigational Status
- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer (e.g., ColoPrint, Conon PRS, GeneFx, OncoDefender, Oncotype Dx Colon Cancer Test)
- Miscellaneous and Genetic and Molecular Diagnostic Tests

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through December 10, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/22	2/15/22		Joint policy established
5/1/23	2/21/23		Routine maintenance (slp) Vendor Managed: N/A
5/1/24	2/20/25		Routine maintenance (slp) Vendor managed: N/A
5/1/25	2/18/25		• Routine maintenance (slp) • Vendor managed: N/A • G0327, 0498U, 0499U, 0501U, 0537U added as EI • Shield (Guardant Health Inc) added as EI

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: SEROLOGIC GENETIC AND MOLECULAR SCREENING FOR COLORECTAL CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*