BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.150 Serologic Genetic and Molecular Screening for Colorectal Cancer

Effective Policy Date: October 1, 2023

Original Policy Date: September 2020

Related Policies:

2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.10 - Identification of Microorganisms Using Nucleic Acid Probes
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2 and TMB)

Serologic Genetic and Molecular Screening for Colorectal Cancer

Description

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It is well established that early detection of colorectal cancer (CRC) reduces disease-related mortality. For patients at average risk for CRC, organizations such as the U.S. Preventive Services Task Force have recommended several options for colon cancer screening. Currently accepted screening options for CRC include colonoscopy or sigmoidoscopy, fecal occult blood testing, and fecal immunochemical testing. However, many individuals do not undergo recommended screening with fecal tests or colonoscopy. 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.

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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 (eg, DNA preparation, PCR primers, probes).

Gene Expression Profiling

ColonSentry (Stage Zero Life Sciences) is a PCR assay that uses a blood sample to detect the expression of 7 genes found to be differentially expressed in CRC patients compared with controls[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.

OBJECTIVE

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

POLICY STATEMENT

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

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

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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.

BENEFIT APPLICATION

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

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

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

FDA REGULATORY STATUS

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

The Epi proColon test is the only *SEPT9* DNA test that has received FDA approval. It was approved in 2016 for use in average-risk patients who decline other screening methods.

RATIONALE

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.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Cancer Society

In 2018, the American Cancer Society recommended that "adults aged 45 years and older with an average risk of CRC [colorectal cancer] undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy." [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.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) (v.1.2023) 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".[16,]

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.[17,] 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.[18,19,] 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,

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or capsule endoscopy for colorectal cancer screening." The evidence review supporting the recommendations included a search for studies of serum-based tests (eg, methylated *SEPT9* DNA tests) but concluded that the strength of evidence was low, based on a single case-control study.

Medicare National Coverage

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.

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

Date	Action	Description
September 2020	New Policy	Policy created with literature review through June 17, 2020. Screening for colorectal cancer using Sept9 methylated DNA is considered not medically necessary; gene profile testing is considered investigational.
September 2021	Replace policy	Policy updated with literature review through May 27, 2021; references added. Minor change to second gene expression profiling policy statement to add BeScreened as investigational.
September 2022	Replace policy	Policy updated with literature review through April 18, 2022; no references added. Policy statements unchanged.
September 2023	Replace policy	Policy updated with literature review through May 22, 2023; reference added. Policy statements unchanged.

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