FEP Medical Policy Manual

FEP 2.04.150 Serologic Genetic and Molecular Screening for Colorectal Cancer

Effective Policy Date: October 1, 2020
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 - KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer

Serologic Genetic and Molecular Screening for Colorectal Cancer

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 colorectal cancer 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.

SEPT9 Methylated DNA

ColoVantage (various manufacturers) blood tests for serum SEPT9 methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (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 controls1: 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."

Table 1 lists tests assessed in this review.

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

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Date Added</th>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Therapeutic</th>
<th>Future Risk</th>
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<tbody>
<tr>
<td>ColonSentry®</td>
<td>Stage Zero Life Sciences</td>
<td>Aug 2015</td>
<td>⚫</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SEPT9 methylated DNAa</td>
<td>Severalb</td>
<td>Oct 2014</td>
<td></td>
<td>⚫</td>
<td></td>
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</tbody>
</table>

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 (eg, ColoVantage, Epi proColon) is considered **not medically necessary** for colorectal cancer screening.

Gene expression profiling (eg, ColonSentry) is considered **investigational** for colorectal cancer screening.

POLICY GUIDELINES

Genetic Counseling

Genetic counseling is primarily aimed at patients 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

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. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

The Epi proColon test is the only SEPT9 DNA test that has received FDA approval (P130001). 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 colorectal cancer, 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 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. 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. The evidence is insufficient to determine the effects of the technologies on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current NCCN (v.2.2020) guidelines on colorectal cancer (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. It is not recommended for routine screening. The interval for repeating testing is unknown." 12

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 College noted that "...at this time, mSEPT9 is not included in this guideline as an option for routine CRC screening for average-risk adults."

American College of Physicians

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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. 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.

**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. 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 2016, the U.S. Preventive Services Task Force updated its recommendations for CRC screening in adults. It recommended screening for CRC starting at age 50 years and continuing until age 75 years. The 2016 recommendations differ from the 2008 recommendations in that current guidance does not emphasize specific screening approaches but highlights evidence that CRC screening substantially reduces deaths from the disease among adults ages 50 to 75 years and not enough adults in the U.S. are using effective preventive interventions. The evidence review supporting the recommendations included a search for studies of blood tests for methylated SEPT9 DNA but concluded that the test "currently has limited evidence evaluating its use."

**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.

**REFERENCES**


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

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>September 2020</td>
<td>New Policy</td>
<td>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.</td>
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</table>

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