Sept9 Methylation Analysis for Colorectal Cancer

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
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<th>Procedure addressed by this guideline</th>
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What is Sept9 methylation analysis for colorectal cancer

Definition

Colorectal cancer (CRC) is one of the most common types of cancers, with over 145,000 new cases identified each year in the United States. It typically affects adults over 55 years old, with a median age at diagnosis of 67 years.

- Screening programs for CRC allow for its early detection. The earlier CRC is caught, the better chance a person has of surviving. Five year survival rates are 89.9% for localized cancer, 71.3% for cancer that has spread regionally, and 14.2% for CRC with distant metastasis.

- Standard recommended screening for CRC includes guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), multitargeted stool DNA test (FIT-DNA), colonoscopy, CT colonography, and flexible sigmoidoscopy. Screening begins at age 50 years and continues until at least age 75 for people at average risk for CRC.

- Although several screening tests have been endorsed and found to be cost-effective, compliance with CRC screening recommendations is limited. According to 2010 data from the Centers for Disease Control and Prevention (CDC), the percentage of adults over 50 years who reported their CRC screening was up to date ranged from 58.92% to 75.03%, depending on the state. The CDC estimates that 28 million Americans are not up-to-date on CRC screening.

- Two tests designed to detect colorectal cancer by analyzing Sept9 methylation will be addressed in this guideline: Epi proColon and ColoVantage.

- The Epi proColon Test (Epigenomics) is a Septin 9 assay that measures the presence of methylated Septin 9 DNA in a blood sample. It is intended to identify early stage colorectal cancer. It offers an alternative to current screening options.
• The ColoVantage Test (Quest Diagnostics) is a Septin 9 assay that measures the presence of methylated Septin 9 DNA in a blood sample. This test “aids in the detection of colorectal cancer in patients non-adherent to current testing approaches.”

Test information

• Both Epi proColon and ColoVantage are performed on a blood sample. No bowel preparation or dietary or medication restrictions are required to complete either test.

• Both tests measure methylation of Septin 9 DNA. Tumors may have increased methylation of Septin 9. When tumor DNA is shed into the bloodstream, this increase in methylation of Septin 9 may be found in the blood.

• Epi proColon provides a qualitative result: positive or negative. People who receive positive results should be referred for a diagnostic colonoscopy. Those with negative results can continue with standard CRC screening recommendations.

Guidelines and evidence

• There are currently no US guidelines that specifically address the use of either Epi proColon or ColoVantage testing.

• Current CRC cancer screening guidelines from the U.S. Preventive Services Task Force (USPSTF, 2016) recommend the use of gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, and flexible sigmoidoscopy for individuals ages 50 years to 75 years at average risk of colorectal cancer. These guidelines specifically state the following regarding Septin DNA testing:
  o “Although a serology test to detect methylated SEPT9 DNA was included in the systematic evidence review, this screening method currently has limited evidence evaluating its use (a single published test characteristic study met inclusion criteria, which found it had a sensitivity to detect colorectal cancer of <50%). It is therefore not included in this table.”

• For other age groups, the USPSTF guidelines recommend the following:
  o “For older adults aged 76 to 85 years, the benefits of screening for colorectal cancer decline, and the risk of experiencing serious associated harms increases. The most important consideration for clinicians and patients in this age group is whether the patient has previously been screened. Patients in this age group who have never been screened for colorectal cancer are more likely to benefit than those who have been previously screened.”
  o “Screening [in adults aged 76 to 85 years] would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy.”
The USPSTF does not recommend routine screening for colorectal cancer in adults 86 years and older. In this age group, competing causes of mortality preclude a mortality benefit that would outweigh the harms.²

The U.S. Food and Drug Administration approved Epi proColon in 2016 as an in vitro diagnostic.⁶

- The Epi proColon test is indicated to screen adults of either sex, 50 years or older, defined as average risk for CRC, who have been offered and have a history of not completing CRC screening.
- The Epi proColon test is not intended to replace colorectal cancer screening tests that are recommended by appropriate guidelines (e.g., 2008 USPSTF guidelines) such as colonoscopy, sigmoidoscopy and high sensitivity fecal occult blood testing.
- The Epi proColon test is not intended for patients who are willing and able to undergo routine colorectal cancer screening tests that are recommended by appropriate guidelines.
- Tests that are available and recommended in the USPSTF 2008 CRC screening guidelines should be offered and declined prior to offering the Epi proColon test.

The National Comprehensive Cancer Network guidelines on colorectal cancer screening (version 2.2019) include the following footnote regarding methylated SEPT9 DNA testing:⁷

- A blood test that detects circulating methylated SEPT9 DNA has been FDA-approved for CRC screening for those who refuse other screening modalities. The interval for repeating testing is unknown.

**Epi proColon**

- The performance of Epi proColon has been established in cross-sectional (i.e., single point in time) studies. Programmatic performance of Epi proColon (i.e., benefits and risks with repeated testing over an established period of time) has not been studied. Performance has not been evaluated for patients who have been previously tested with Epi proColon. Non-inferiority of Epi proColon programmatic sensitivity as compared to other recommended screening methods for CRC has not been established.⁷
- Screening with Epi proColon in subsequent years following a negative test result should be offered only to patients who after counseling by their healthcare provider, again decline CRC screening methods according to appropriate guidelines. The screening interval for this follow-up has not been established.⁶
- The frequency interval that follow up Epi proColon testing should be performed has yet to be established.⁶,⁷
- A large, prospective multicenter trial (PRESEPT) evaluated men and women over the age of 50 years who were at average risk for colorectal cancer.⁸
Clinical performance of the Epi proColon test in terms of sensitivity and specificity was based on 1544 samples from subjects whose colorectal cancer status was determined by colonoscopy.

- Sensitivity was determined to be 68.2% with a specificity of 78.8%. Positive predictive value (PPV) was 2.4% with a negative predictive value (NPV) of 99.7%.

- Multiple peer reviewed publications address the analytical and clinical validity of Epi proColon. The number of well-designed prospective multicenter studies evaluating the test performance of Epi proColon in screening populations with average-risk CRC is limited. The few available studies suggest a low rate of sensitivity to detect the presence of CRC, a high rate of false positives, and a high rate of specificity to detect the absence of disease. No clinical studies were identified that reported if use of Epi proColon leads to reduction in disease-associated mortality or other meaningful health outcomes in average-risk CRC populations. Thus, the clinical utility of Epi proColon has not been established. The appropriate intervals for testing have not been established.

- Results of a meta-analysis/systematic review indicate that the area under the receiver operating curve (AUC) for the pooled diagnostic accuracy results for Epi proColon test was 0.8709. In head-to-head comparisons, the AUC of the combined results of 1) Epi proColon and mSEPT 9 tests and 2) FOBT for CRC diagnosis were 0.7857 and 0.6571, respectively.

**ColoVantage**

- The analytical validity, clinical validity, and clinical utility of the ColoVantage test for detecting CRC has not been established.

**Criteria**

- **Epi proColon and ColoVantage testing** are considered investigational and/or experimental.

  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.
References


