Colorectal Cancer Screening

Number: 0516

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Routine Screening

Aetna considers any of the following colorectal cancer screening tests medically necessary preventive services for average-risk members aged 50 years and older when these tests are recommended by their physician:

- Colonoscopy (considered medically necessary every 10 years for persons at average risk); or
- CT Colonography (virtual colonoscopy) (considered medically necessary every 5 years) (see CPB 535 - Virtual Gastrointestinal Endoscopy); or
- Double contrast barium enema (DCBE) (considered medically necessary every 5 years for persons at average risk); or
- Sigmoidoscopy (considered medically necessary every 5 years for persons at average risk)
- Sigmoidoscopy (every five years) with annual immunohistochemical or guaiac-based fecal occult blood testing (FOBT); or
- Annual immunohistochemical or guaiac-based FOBT; or
■ Stool DNA (FIT-DNA, Cologuard) (considered medically necessary every 3 years).

Performance of multiple screening strategies simultaneously (for example, virtual colonoscopy screening every 5 years plus stool DNA testing every 3 years) in the same individual has no proven value. Colorectal cancer screening beginning at age 45 is considered a medically necessary preventive service for African Americans because of the high incidence of colorectal cancer and a greater prevalence of proximal or right-sided polyps and cancerous lesions in this population. There is insufficient evidence to support earlier screening of members at increased risk from smoking or obesity.

Aetna considers screening upper endoscopy experimental and investigational. No current guidelines of leading medical professional organizations or Federal public health agencies recommend routine upper endoscopy screening of asymptomatic persons.

Aetna considers colorectal cancer screening of stool using molecular genetic techniques other than Cologuard (e.g., ColoSure, PreGen-Plus) experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Aetna considers colorectal cancer screening using methylated Septin 9 (ColoVantage, Epi proColon) experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Aetna considers colorectal cancer screening using microRNA experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Aetna considers colorectal cancer screening using chromoendoscopy or narrow-band imaging optical colonoscopy experimental and investigational because of insufficient evidence in the peer-reviewed literature.
Aetna considers plasma/serum biomarkers (C-reactive protein, complement C3a anaphylatoxin, plasma GATA5 and SFRP2 methylation, serum CD26 (sCD26), serum matrix metalloproteinase-7 (MMP-7), and tissue inhibitor of metalloproteinases (TIMP-1)) experimental and investigational for colorectal cancer screening because of insufficient evidence in the peer-reviewed literature.

Aetna considers PolypDx (Atlantic DiagnosticLaboratories, LLC, Metabolomic Technologies Inc.) experimental and investigational for colorectal cancer screening and for all other indications.

For the ColonSentry test for colorectal cancer screening, see CPB 0352 - Tumor Markers (../300_399/0352.html).

II. High-Risk Testing:

Aetna considers colorectal cancer testing with sigmoidoscopy, DCBE, or colonoscopy as frequently as every 2 years medically necessary for members with any of the following risk factors for colorectal cancer:

- A first-degree relative (sibling, parent, child) who has had colorectal cancer or adenomatous polyps (screening is considered medically necessary beginning at age 40 years, or 10 years younger than the earliest diagnosis in their family, whichever comes first); or
- Family history of familial adenomatous polyposis (screening is considered medically necessary beginning at puberty); or
- Family history of hereditary non-polyposis colorectal cancer (HNPCC) (screening is considered medically necessary beginning at age 20 years); or
- Family history of MYH-associated polyposis in siblings (screening is considered medically necessary beginning at age 25 years); or
- Diagnosis of Cowden syndrome (screening is considered medically necessary beginning at age 35 years).
Aetna considers annual FOBT, alone or in conjunction with sigmoidoscopy, medically necessary for testing of members with any of the above risk factors for colorectal cancer.

III. Surveillance:

Aetna considers colorectal cancer surveillance with colonoscopy, flexible sigmoidoscopy or DCBE medically necessary as frequently as every year for members who meet any of the following criteria:

- Member has inflammatory bowel disease (including ulcerative colitis or Crohn's disease) (colorectal cancer surveillance is considered medically necessary as frequently as every year); or
- Personal history of adenomatous polyps (surveillance is considered medically necessary as frequently as every 2 years); or
- Personal history of colorectal cancer (surveillance is considered medically necessary as frequently as every year).

Aetna considers annual FOBT, alone or in conjunction with sigmoidoscopy, medically necessary for surveillance of colorectal cancer.

IV. Diagnostic Testing:

Aetna considers diagnostic testing with FOBT, colonoscopy, sigmoidoscopy and/or DCBE medically necessary for evaluation of members with signs or symptoms of colorectal cancer or other gastrointestinal diseases. Diagnostic upper endoscopy is considered medically necessary for evaluation of persons with signs and symptoms of upper gastrointestinal disease.

V. Anal Pap Smear:

Aetna considers screening for anal cytological abnormalities
(anal Pap smear) or for anal HPV infection experimental and investigational because of the lack of evidence that such screening improves clinical outcomes.

**Note:** The USPSTF guidelines apply to routine screening. The USPSTF have no A or B recommendations for high-risk screening. The USPSTF guidelines explain: “This recommendation applies to asymptomatic adults 50 years and older who are at average risk of colorectal cancer and who do not have a family history of known genetic disorders that predispose them to a high lifetime risk of colorectal cancer (such as Lynch syndrome or familial adenomatous polyposis), a personal history of inflammatory bowel disease, a previous adenomatous polyp, or previous colorectal cancer. When screening results in the diagnosis of colorectal adenomas or cancer, patients are followed up with a surveillance regimen, and recommendations for screening no longer apply. The USPSTF did not review or consider the evidence on the effectiveness of any particular surveillance regimen after diagnosis and removal of adenomatous polyps or colorectal cancer” (USPSTF, 2016).

See also CPB 0140 - Genetic Testing (../100_199/0140.html), CPB 0352 - Tumor Markers (../300_399/0352.html), CPB 0535 - Virtual Gastrointestinal Endoscopy (0535.html), and CPB 0783 - In Vivo Analysis of Colorectal Polyps and Crohn's Disease (../700_799/0783.html).

**Background**

Colorectal cancer (CRC) is a term used to describe cancer that develops in the colon or rectum. Colorectal cancer (CRC) is the third most commonly diagnosed cancer among persons in the United States. The 5-year survival rate of CRC detected in early stages is 90%, but the 5-year survival rate is only 8% for those diagnosed after the cancer has metastasized. Almost 90% of CRC cases are found in persons age 50 and older.

CRC screening refers to the process of looking for cancer in people who have no symptoms of the disease. Screening tests may identify cancers at an early and potentially more treatable...
stage. Testing may also detect precancerous abnormal growths (eg, polyps) which can be removed before becoming malignant.

The American Cancer Society (Levin et al, 2008) recommends the following testing options for the early detection of adenomatous polyps and cancer for asymptomatic adults aged 50 years and older:

**Tests that detect adenomatous polyps and cancer:**

- Colonoscopy every 10 years; or
- Computed tomographic (CT) colonography every 5 years; or
- Double-contrast barium enema (DCBE) every 5 years; or
- Flexible sigmoidoscopy every 5 years.

**Tests that primarily detect cancer:**

- Annual fecal immunochemical test with high test sensitivity for cancer; or
- Annual guaiac-based fecal occult blood test with high sensitivity for cancer; or
- Stool DNA test with high sensitivity for cancer, interval uncertain.

The U.S. Preventive Services Task Force (USPSTF, 2016) recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary. The USPSTF stated that the decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient’s overall health and prior screening history. Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. The USPSTF stated that screening 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 (2016) found convincing evidence that screening for colorectal cancer in adults aged 50 to 75 years reduces colorectal cancer mortality. The USPSTF found no head-to-head studies demonstrating that any of the screening strategies it considered are more effective than others, although the tests
have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations:

- Colonoscopy every 10 years
- CT colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years plus fecal immunochemical test (FIT) every year
- Guaiac-based fecal occult blood test (gFOBT) every year
- FIT test every year
- Stool DNA (FIT-DNA) every one or three years.

A guidance statement from the American College of Physicians on "Screening for colorectal cancer" (Qaseem et al, 2012) stated that “The screening interval for average-risk adults older than 50 years is 10 years for colonoscopy; 5 years for flexible sigmoidoscopy, double-contrast barium enema (DCBE), and computed tomography colonography (CTC); annually for guaiac-based fecal occult blood test (gFOBT) and immunochemical-based fecal occult blood test (iFOBT); and uncertain for stool DNA (sDNA)”.

More frequent screening has been recommended for persons with a first-degree relative (parent, sibling or child) with a history of CRC. The increased risk of developing cancer at younger ages may justify beginning screening before the age of 50 in persons with a positive family history, especially when affected relatives developed CRC at younger ages. The American Society of Colon and Rectal Surgeons (2010) recommends that people with a first-degree relative with colon cancer or adenomatous polyps diagnosed at age less than 60 years of age or 2 first degree relatives diagnosed at any age should be advised to have screening colonoscopy starting at age 40 years or 10 years younger than the earliest diagnosis in their family, whichever comes first, and repeated every 5 years. The American Society for Gastrointestinal Endoscopy (2006) has a similar position.

Regular colonoscopic screening is part of the routine diagnosis and management of individuals at high-risk of developing CRC, including those with a family history of hereditary syndromes (familial polyposis, hereditary non-polyposis colon cancer (HNPCC)); individuals with long-standing ulcerative colitis or...
Crohn's disease; or high-risk adenomatous polyps or colon cancer. Referral to specialists is appropriate. It has been recommended that persons with a family history of adenomatous polyposis begin screening at puberty, and persons with a family history of HNPCC begin screening at 20 to 30 years of age.

Fecal occult blood test (FOBT) is a noninvasive test that detects hidden (occult) blood in the stool. Such blood may come from anywhere along the digestive tract and for that reason additional types of tests may be ordered. Blood in the stool may be the only symptom of early cancer. There are two main types of FOBT tests: guaiac and immunochemical. Fecal immunochemical testing (FIT) differs from guaiac based FOBT in that there are no dietary or drug restrictions prior to this form of testing. Colonoscopy will be needed if the test is positive. Randomized controlled trials (RCTs) have proven that the fecal occult blood test can detect CRC significantly lowers the rate of death from the disease.

Guaiac FOBTs have been recognized among various CRC screening methods as having the highest quality supporting evidence. Immunochemical tests (e.g., Flexsure OBT, InSure FOBT) may be used as an alternative to standard guaiac-based tests of fecal occult blood, and have several potential advantages that make them more convenient than guaiac tests: (i) unlike guaiac tests, a fecal smear is not required for immunochemical tests -- samples may be obtained from a brush sample of toilet bowl water; (ii) unlike guaiac tests, immunochemical tests are not affected by diet or medications, so that dietary and medicinal restrictions are not necessary prior to testing.

The USPSTF (2016) found that multiple randomized clinical trials (RCTs) have shown that screening with the guaiac-based fecal occult blood test (gFOBT) reduces colorectal cancer deaths. Fecal immunochemical tests (FITs), which identify intact human hemoglobin in stool, have improved sensitivity compared with gFOBT for detecting colorectal cancer. Among the FITs that are cleared by the US Food and Drug Administration (FDA) and available for use in the United States, the OC FIT-CHEK family of FITs (Polymedco)—which include the
OC-Light and the OC-Auto—have the best test performance characteristics (ie, highest sensitivity and specificity) (USPSTF, 2016).

Flexible sigmoidoscopy enables the physician to look at the inside of the large intestine from the rectum through the last part of the colon, called the sigmoid or descending colon. Using this short, flexible fiberoptic tube that is inserted through the anus, the physician can see abnormal growths, bleeding, inflammation and ulcers in the lower part of the large intestine (colon) and the rectum. If polyps or cancer are found, then a colonoscopy will be necessary to screen for polyps or cancer in the rest of the colon. Although there are no RCTs proving that sigmoidoscopy reduces the mortality rate from CRC, a number of case-control studies have suggested that sigmoidoscopy is effective in reducing CRC mortality. The literature indicates that sigmoidoscopy can detect 70 to 80% of CRC. However, sigmoidoscopy is unable to detect the substantial number of cancers that arise solely in the proximal colon. The literature indicates that some of the additional neoplasms that it misses can be detected by combining sigmoidoscopy with fecal occult blood testing.

The USPSTF (2016) identified several RCTs that show that flexible sigmoidoscopy alone reduces deaths from colorectal cancer. Flexible sigmoidoscopy combined with FIT has been studied in a single trial and was found to reduce the colorectal cancer-specific mortality rate more than flexible sigmoidoscopy alone (citing Holme, et al, 2014). The USPSTF noted that modeling studies also consistently estimate that combined testing yields more life-years gained and colorectal cancer deaths averted compared with flexible sigmoidoscopy alone (citing Zauber, et al., 2015). Flexible sigmoidoscopy can result in direct harms, such as colonic perforations and bleeding, although the associated event rates are much lower than those observed with colonoscopy. Harms can also occur as a result of follow-up colonoscopy.

Some have advocated whole-bowel screening with colonoscopy or DCBE because it is able to detect proximal colon lesions. One study found that approximately 30% of cancers detected by colonoscopy would not have been detected by sigmoidoscopy. However, no direct evidence proves that...
whole-bowel screening, either by colonoscopy or DCBE, reduces mortality, although clinical trials are now underway to investigate this.

Double contrast barium enema (DCBE), also called a lower gastrointestinal (GI) exam, is an x-ray examination of the large intestine (colon and rectum). In a DCBE study, the colon is filled with barium, which helps to see the outline of the colon on an x-ray. The barium is then removed, leaving only a thin layer on the wall of the colon, which is then filled with air. This helps to provide a detailed view of the inner surface of the colon, making it easier to see colon polyps and/or other abnormalities (eg, inflammation, strictures). If the test is positive, a colonoscopy will be needed for further evaluation. A study comparing the use of colonoscopy to DCBE for patients with previously identified polyps found that colonoscopy detected more polyps than DCBE. Double contrast barium enema found only 20% of adenomatous polyps found by colonoscopy.

Colonoscopy allows the physician to examine the lining of the entire large intestine by using a flexible, fiberoptic instrument (colonoscope) that is inserted through the anus. This test may reveal inflamed tissue, abnormal growths, ulcers or early signs of cancer in the colon or rectum. Special instruments can be passed through the colonoscope to remove polyps if needed. Although the rate of complications from colonoscopy has been shown to be low, complications from colonoscopy are more common than from other screening procedures. Perforation of the colon and complications from anesthesia have been reported to occur in 0.1 to 0.3% of colonoscopies performed by gastroenterologists, and death occurs in 0.01% of colonoscopies.

The USPSTF (2017) found that completed trials of flexible sigmoidoscopy provide indirect evidence that colonoscopy -- a similar endoscopic screening method -- reduces colorectal cancer mortality. A prospective cohort study also found an association between patients who self-reported being screened with colonoscopy and a lower colorectal cancer mortality rate. Colonoscopy has both indirect and direct harms. Harms may be caused by bowel preparation prior to the procedure (eg, dehydration and electrolyte imbalances), the sedation used during the procedure (eg, cardiovascular events), or the
Genetic testing of stool samples is also a possible way to screen asymptomatic high-risk individuals for CRC. Colorectal cancer cells are shed into the stool, providing a potential means for the early detection of the disease by detecting specific tumor-associated genetic mutations in stool samples. Fecal/stool DNA testing (sDNA) is performed on stool samples that are submitted to a laboratory after being collected by individuals at home. This test detects CRC based on the presence of specific, cancer-associated mutations in DNA extracted from the stool sample. Individuals with a positive sDNA test result must then undergo a definitive test for colon cancer, such as a colonoscopy. sDNA testing is intended as a first line screening test for colon cancer in asymptomatic individuals. An example of an sDNA test is Cologuard, which may detect colorectal neoplasia associated with DNA markers and the presence of occult hemoglobin.
The U.S. Preventive Services Task Force (2017) stated that multitargeted stool DNA testing (FIT-DNA) is an emerging screening strategy that combines a FIT with testing for altered DNA biomarkers in cells shed into the stool. The USPSTF found that multitargeted stool DNA testing has increased single-test sensitivity for detecting colorectal cancer compared with FIT alone. The harms of stool-based testing primarily result from adverse events associated with follow-up colonoscopy of positive findings. The specificity of FIT-DNA is lower than that of FIT alone, which means it has a higher number of false-positive results and higher likelihood of follow-up colonoscopy and experiencing an associated adverse event per screening test. The USPSTF found no empirical data on the appropriate longitudinal follow-up for an abnormal FIT-DNA test result followed by a negative colonoscopy; there is potential for overly intensive surveillance due to clinician and patient concerns about the implications of the genetic component of the test.

Computed tomographic colonography (CTC), also known as virtual colonoscopy, was developed as a minimally invasive method to examine the colon. This test has been used in screening and to detect abnormalities in the colon and rectum (eg, colorectal cancer [CRC] and polyps). It involves the use of helical computed tomography (CT) and computer generated images to produce high-resolution two- and three-dimensional (3D) images of the colon and rectum. Prior to virtual colonoscopy, standard bowel cleansing preparations are needed to evacuate any stool and fluid from the colon. During the procedure, a rectal tube is inserted and the colon is distended using room air or carbon dioxide and images are then taken by a helical CT scanner. The results are interpreted by a radiologist. If suspicious lesions are detected, the individual generally must undergo further testing via conventional colonoscopy.

The USPSTF (2017) found that evidence for assessing the effectiveness of computed tomography (CT) colonography is limited to studies of its test characteristics. The USPSTF stated that computed tomography colonography can result in unnecessary diagnostic testing or treatment of incidental
extracolonic findings that are of no importance or would never have threatened the patient’s health or become apparent without screening (ie, overdiagnosis and overtreatment). The USPSTF stated that extracolonic findings are common, occurring in about 40% to 70% of screening examinations. Between 5% and 37% of these findings result in diagnostic follow-up, and about 3% require definitive treatment. As with other screening strategies, indirect harms from CT colonography can also occur from follow-up colonoscopy for positive findings.

The American Cancer Society's guidelines on CRC screening recommend several methods of screening, including virtual colonoscopy, based in part upon the presumption that the availability of multiple methods of screening will improve compliance (Levin et al, 2008). Colorectal cancer screening guidelines from the American Cancer Society recommend CT colonography (virtual colonoscopy) performed every 5 years as an acceptable alternative to optical colonoscopy performed every 10 years for screening of average-risk persons. Virtual colonoscopy is similar to optical colonoscopy in that it requires completion of a pre-procedure cathartic regimen. If a lesion is found on virtual colonoscopy, the patient must return another day and complete another cathartic regimen for an optical colonoscopy to remove the lesion. By contrast, optical colonoscopy allows for identification and removal of a lesion in one procedure.

An assessment of CT colonography prepared for the Washington State Health Care Authority (Scherer et al, 2008) found that, in direct comparison to optical colonoscopy, CT colonography every 10 years is substantially more expensive and marginally less effective in preventing cases of cancer (47 versus 52 in a lifetime cohort of 1,000 individuals) and cancer deaths (24 versus 26). The investigators reported that only one CT colonography screening strategy is as effective as optical colonoscopy every 10 years, and that strategy is to perform CT colonography every 5 years with colonoscopy referral for polyps greater than 6 mm. For this strategy, the cost per life-year gained for CT colonography versus optical colonoscopy was $630,700.
The ACG (Agrawal et al, 2005) issued recommendations to healthcare providers to begin CRC screening in African Americans at age 45 rather than 50 years. Colonoscopy is the preferred method of screening for CRC and data support the recommendation that African-Americans begin screening at a younger age because of the high incidence of CRC and a greater prevalence of proximal or right-sided polyps and cancerous lesions in this population.

In a meta-analysis of surveillance colonoscopy in individuals at risk for HNPCC, Johnson et al (2006) concluded that the best available evidence supports surveillance with complete colonoscopy to the cecum every 3 years in patients with HNPCC (B recommendation). There is no evidence to support or refute more frequent screening. Further research is needed to examine the potential harms and benefits of more frequent screening. However, given the potential for rapid progression from adenoma to carcinoma and missing lesions at colonoscopy, there is consensus that screening more frequently than every 3 years is required.

MYH is a DNA repair gene that corrects DNA base pair mismatch errors in the genetic code before replication. Mutation of the MYH gene may result in colon cancer. In this regard, the MYH gene has been found to be significantly involved in colon cancer, both in cases where there is a clear family history of the disease, as well as in cases without any sign of a hereditary cause.

The NCCN practice guidelines on CRC screening (2006) recommends colonoscopy surveillance of asymptomatic individuals with known MYH mutations and colonoscopy screening of siblings of affected patients. Surveillance and screening is recommended beginning at age 25 to 30 years of age at 3 to 5 year intervals (the shorter intervals with advancing age). The NCCN guidelines recommend that patients with MYH-associated colorectal adenomas be managed similarly to patients with attenuated FAP. Those with small adenoma burden are surveilled with colonoscopy and complete polypectomies of all polyps. Those with dense polyposis not manageable by polypectomy are recommended surgery.
Guidelines from the NCCN (2011) recommend that persons with Cowden syndrome should consider colonoscopy, starting at age 35 years, then every 5 to 10 years or more frequently if the person is symptomatic or if polyps are found.

No current guidelines of leading medical professional organizations or Federal public health agencies recommend routine upper endoscopy screening of asymptomatic persons. Although screening upper endoscopy has been performed in conjunction with screening colonoscopy, there is no evidence-based support for this practice.

Currently, no leading medical professional organizations or Federal public health agencies recommend anal dysplasia screening. Recommendations from the Centers for Disease Control and Prevention state (Workowski and Berman, 2006): "Routine testing for anal cytological abnormalities or anal HPV infection is not recommended until more data are available on the reliability of screening methods, the safety of and response to treatment, and programmatic considerations." The Ontario Health Technology Advisory Committee (OHTAC, 2007) recently systematically reviewed the evidence for anal dysplasia screening. OHTAC "does not recommend screening of high risk individuals at this time based on the low specificity for cytological screening, inadequate evidence of effectiveness for current treatment of precancerous lesions, high recurrence rates, and no evidence that cytological screening reduces the risk of developing anal cancer."

Regarding risk factors (smoking and obesity) under consideration for more intense screening, the 2009 ACG guidelines for CRC screening (Rex et al, 2009) did not recommend that screening be initiated earlier in these groups (smokers and obese patients) at this time. The ACG recommended additional study to characterize the potential benefits, harms, and cost-effectiveness of earlier screening in these groups.

MicroRNAs (miRNAs) are short non-coding RNA sequences that play an important role in the regulation of gene expression. They have significant regulatory functions in basic cellular processes (e.g., cell differentiation, proliferation, and
apoptosis). Available evidence suggests that miRNAs may function as both tumor suppressors as well as oncogenes. The main mechanism for changes in the function of miRNAs in cancer cells is due to aberrant gene expression.

Dong and colleagues (2011) noted that recent researches have shed light on the biological importance of miRNAs in CRC genesis, progression and response to treatments. The potential utility of miRNAs in the pre-clinical stage have been explored and investigated. These researchers explored the literature and reviewed the cutting edge progress in the discovery of non-invasive plasma and fecal miRNAs for CRC early diagnosis, as well as their measurability and predictability. They also discussed the utility of miRNAs as novel prognostic and predictive markers, and their association with CRC clinical phenotypes including recurrence, metastasis and therapeutic outcomes. These investigators summarized miRNA-related single-nucleotide polymorphisms and their potential influence on sporadic CRC susceptibility and therapeutic response. The authors concluded that the use of miRNAs as biomarker for CRC is still in its infancy and need further characterization and evaluation.

Sandhu and Garzon (2011) stated that early studies have established that miRNAs are widely de-regulated in cancer and play a critical role in cancer pathogenesis. Recent research efforts are directed now towards translating these basic discoveries into novel tests or treatments that could improve the diagnosis and outcome of cancer patients. These researchers summarized the potential applications of miRNAs for cancer diagnosis, prognosis, as well as treatment; and discussed current pitfalls and future directions. The authors noted that there are still hurdles to overcome such as the development of reliable and reproducible miRNA expression assays and improvements in oligonucleotide delivery to specific tissues or cell types.

Ma et al (2012) carried out a comprehensive systematic review of published studies that compared the miRNA expression profiles between CRC tissue and paired neighboring non-cancerous colorectal tissue to determine candidate miRNA biomarkers for CRC. A miRNA ranking system that takes the number of comparisons in agreement, total study sizes and
direction of differential expression into consideration was devised and used. One of the most up-regulated miRNAs, miRNA-106a, was consistently reported to be differentially expressed in 6 studies and the 5 most down-regulated miRNAs, miR-30a-3p, miR-139, miR-145, miR-125a and miR-133a, were consistently reported to be differentially expressed in 4 studies. Moreover, these investigators further validated 5 miRNAs in a clinical setting using quantitative reverse transcription polymerase chain reaction (qRT-PCR), which demonstrated that miR-106a expression was increased, whereas the expression of miR-30a-3p, miR-145, miR-125a and miR-133a was decreased in the CRC tissues. The authors concluded that these miRNAs may be the candidates to develop a panel of biomarkers with sufficient sensitivity and specificity for the diagnosis of CRC in a clinical setting.

Wang et al (2012) stated that the recently identified class of miRNAs provided a new insight in cancer research. As members of miRNAs family, miR-34a, miR-155 and miR-200c abnormalities have been found in various types of cancer. However, the relationship between these 3 miRNAs (miR-34a, miR-155 and miR-200c) and CRC is unclear. These researchers applied stem-loop real-time PCR to quantitatively detect miR-34a, miR-155 and miR-200c expression in 109 pair-matched human CRC and the corresponding normal mucosa. MiR-34a (2.2-fold), miR-155 (2.3-fold) and miR-200c (3.1-fold) were all expressed at higher levels in CRC (p = 0.001, 0.005 and 0.001, respectively). In the rectum, miR-34a and miR-200c were significantly up-regulated (p = 0.006 and 0.007), while the miR-155 over-expression was not statistically significant (p = 0.083). In the colon, the higher expression of 3 miRNAs was seen, however, without significant difference (p > 0.05). The investigators also found that the miR-34a expression was higher in rectal cancer having more advanced TNM stage (III + IV, p = 0.03). Then miR-200c expression was positively correlated with and sera CEA level of rectal cancer patients (p = 0.04). The authors concluded that these findings suggested that the over-expression of miR-34a, miR-155 and miR-200c may be associated with the development of CRC, meanwhile miR-34a may be involved in the development and progression of rectal cancer. They stated that more deeply and larger scale research are required to prove the correlation.
Peacock et al (2012) noted that accurate discrimination of miRNA profiles between tumor and normal mucosa in CRC allows definition of specific expression patterns of miRNAs, giving good potential as diagnostic and therapeutic targets. MicroRNAs expressed in CRC are also abundantly present and stable in stool and plasma samples; their extraction from these sources is feasible and reproducible. The ease and reliability of determining miRNA profiles in plasma or stool makes them potential molecular markers for CRC screening.

Kannan et al (2013) examined the potential use of circulating miRNAs as biomarkers of CR adenomas. These investigators screened for 380 plasma-miRNAs using microfluidic array technology (Applied BioSystems) in a screening cohort of 12 healthy controls, 9 patients with CR adenomas, and 20 patients with CRC. A panel of the most dysregulated miRNAs (p < 0.05, False Discovery Rate: 5 %) was then validated in a blinded cohort of 26 healthy controls, 16 patients with large adenomas, and 45 patients with CRC. A panel of 8 plasma miRNAs (miR-532-3p, miR-331, miR-195, miR-17, miR-142-3p, miR-15b, miR-532, and miR-652) distinguished polyps from controls with high accuracy [area under curve (AUC) = 0.868 (95 % confidence interval [CI]: 0.76 to 0.98)]. In addition, a panel of 3 plasma miRNAs (miR-431, miR-15b, and miR-139-3p) distinguished stage IV CRC from controls with an [AUC = 0.896 (95 % CI: 0.78 to 1.0)]. Receiver-operating-characteristic curves of miRNA panels for all CRC versus controls and polyps versus all CRC showed AUC values of 0.829 (95 % CI: 0.73 to 0.93) and 0.856 (95 % CI: 0.75 to 0.97), respectively. The authors concluded that plasma miRNAs are reliable, non-invasive, and inexpensive markers for CR adenomas. They stated that this miRNA panel warrants study in larger cohorts to confirm and then increase its sensitivity and specificity. Plasma-based assays could provide better screening compliance compared to fecal occult blood or endoscopic screening.

Furthermore, a guidance statement from the American College of Physicians on "Screening for colorectal cancer" (Qaseem et al, 2012) does not list miRNA as one of the tests for CRC.
In vivo analysis can be described as real time additional imaging that has been suggested for use as an adjunct to endoscopic procedures. The methods include, but may not be limited to, chromoendoscopy, confocal microscopy, fiberoptic analysis and narrow band imaging. These techniques are utilized during the endoscopic procedures and purportedly improve analysis of the lesions in the colon. An example of a confocal microscopy device is the Cellvizio system.

Chung et al (2014) stated that virtual chromoendoscopy (CE) is expected to enhance adenoma yield and reduce variation in performance between colonoscopists. These researchers compared the efficacy of narrow-band imaging (NBI), flexible spectral imaging CE (FICE) and white light (WL) colonoscopy and their impact for less experienced endoscopists. They performed a randomized tandem colonoscopy trial controlling for withdrawal time and bowel preparation. Average-risk adults undergoing screening colonoscopy were enrolled and randomly assigned to first withdrawal with one of the three imaging modalities (NBI (NBI-WL group), FICE (FICE-WL group) and WL (WL-WL group)). Eight colonoscopists were categorized into expert and non-expert subgroups. A total of 1,650 subjects (mean age of 51.4 years, 63.9% men) were included (550 in each group). Compared with WL, neither NBI nor FICE increased the mean number of adenomas detected per patient (0.37 versus 0.35 and 0.36; p = 0.591) or the percentage of patients with adenoma (25.3% versus 24.5% and 23.6%; p = 0.753). For all 3 modalities, expert subgroups had higher yields of adenomas than non-expert subgroups. Learning curves were observed only for non-expert subgroups with all 3 modalities. The percentage of missed adenomas did not differ between the 3 groups (20.8% by WL versus 22.9% by NBI and 26.0% by FICE, p = 0.300) and was not affected by endoscopists' expertise. The authors concluded that neither NBI nor FICE improved adenoma detection or miss rates, with no difference in diagnostic efficacy between the 2 systems; virtual CE had no additional benefits over WL for non-experts.

Jang et al (2014) noted that distinguishing deep submucosa (SM) from superficial SM cancer in large sessile and flat colorectal polyps (greater than 2 cm) is crucial in making the
most appropriate therapeutic decision. These researchers evaluated the additional role of magnifying NBI and magnifying CE (MCE) in assessing the depth of invasion in large sessile and flat polyps in comparison to morphological evaluation performed by experienced endoscopists. From May 2011 to December 2011, a total of 85 large sessile and flat polyps were analyzed. Endoscopic features of the polyps were independently evaluated by experienced endoscopists. Subsequently, the polyps were observed using magnifying NBI and MCE. A total of 58 intra-mucosal lesions and 27 SM cancers (5 superficial and 22 deep) were identified. The diagnostic accuracy of the experienced endoscopists, NBI, and MCE were 92.9, 90.6, and 89.4 %, respectively, for deep SM cancer. In combination with NBI or MCE, the diagnostic accuracy of the experienced endoscopists did not change significantly for deep SM cancer, with an accuracy of 95.3 % for both NBI and MCE. The authors concluded that conventional colonoscopy can differentiate superficial from deep SM cancers with an accuracy of as high as 92.9 % in large sessile and flat polyps.

In a meta-analysis, Xing and colleagues (2014) identified the value of serum matrix metalloproteinase-7 (MMP-7) levels for the diagnosis of CRC. Through searching the following electronic databases: Cochrane Library (Issue 12, 2014), Web of Science (1945 to 2014), PubMed (1966 to 2014), CINAHL (1982 to 2014), EMBASE (1980 to 2014), and CBM (1982 to 2014), related articles were determined without any language restrictions. Stata statistical software (Version 12.0, Stata Corporation, College Station, TX) was chosen to deal with statistical data. Standard mean difference (SMD) and its corresponding 95 % CI were calculated to clarify the correlation between serum MMP-7 levels and CRC. A total of 7 clinical case-control studies that recruited 430 CRC patients and 357 healthy subjects were selected for statistical analysis. The main findings of the meta-analysis showed that the serum MMP-7 level in CRC patients was significantly higher than that in control subjects (SMD = 2.15, 95 % CI: 1.46 to 2.84, p < 0.001). Ethnicity-stratified analysis indicated a higher serum MMP-7 level in CRC patients than that of control subjects among the Asians and the Caucasians (Asians: SMD = 2.83, 95 % CI: 1.76 - 3.91, p < 0.001; Caucasians: SMD = 1.06, 95 % CI: 0.46 to 1.66, p = 0.001; respectively). The authors concluded that the
present meta-analysis indicated that the increased serum level of MMP-7 may be connected with the development of CRC; thus, serum levels of MMP-7 could be an independent biomarker for CRC patients.

Shah et al (2014) stated that there is growing interest in early detection of CRC as current screening modalities lack compliance and specificity. These researchers reviewed the literature to identify biomarkers for early detection of CRC and polyps. Literature searches were conducted for relevant papers since 2007. Human studies reporting on early detection of CRC and polyps using biomarkers were included. Methodologic quality was evaluated, and sensitivity, specificity, and the positive predictive value (PPV) were reported. The search strategy identified 3,348 abstracts. A total of 44 papers, examining 67 different tumor markers, were included. Overall sensitivities for CRC detection by fecal DNA markers ranged from 53 % to 87 %. Combining fecal DNA markers increased the sensitivity of CRC and adenoma detection. Canine scent detection had a sensitivity of detecting CRC of 99 % and specificity of 97 %. The PPV of iFOBT was 1.26 %, compared with 0.31 % for the current screening method of gFOBT. A panel of serum protein biomarkers provided a sensitivity and specificity above 85 % for all stages of CRC, and a PPV of 0.72 %. Combinations of fecal and serum biomarkers produced higher sensitivities, specificities, and PPVs for early detection of CRC and adenomas. The authors concluded that further research is needed to validate these biomarkers in a well-structured population-based study.

An UpToDate review on “Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy” (Fletcher, 2015) states that “Serum markers -- Current serum markers are not sufficiently sensitive or specific to be used for screening. The potential to utilize a combination of six serum markers to improve the test has been reported in a feasibility study, but validation studies in screening populations are needed before clinical relevance can be determined.

One blood test that detects Septin 9 hypermethylation in DNA from plasma (ColoVantage™) has been approved in 2011 by the New York State Health Department for colon cancer. In one study of an assay for Septin 9 (SEPT9), the sensitivities for
adenomas (1 to 5 cm), for stage I to III CRC, and for stage IV CRC were 14, 50, and 88 %, respectively. The false-positive rate was 27 %. These test characteristics suggest that a serum Septin 9 assay is not sufficiently sensitive for identifying cancer or cancer precursors at a treatable stage, but would lead to many false-positive findings.

Blood-based biomarker panels are tests to assess the expression of genes to purportedly calculate a relative risk of having CRC. An example of this type of test is ColonSentry, which is supposedly believed to increase individual compliance with colonoscopy. The seven genes that are measured in this test include: ANXA3, CLEC4D, IL2RB, LMNB1, PRRG4, TNFAIP6, and VNN139.

The New York State Department of Health also approved a 7-gene test (ColonSentry) in February 2012 to be used to identify patients at increased risk of colorectal cancer in order to target such patients for monitoring to assure compliance with regular colonoscopy. However, it has not been shown that the test can detect early-stage cancers, for which screening would be most effective, and test sensitivity (61 to 82 %) and specificity (64 to 77 %) were only fair for CRC at any stage when tested in populations that included a substantial proportion of patients with known CRC.

In a study that compared the performance of serum markers (C-reactive protein, serum CD26 [sCD26], complement C3a anaphylatoxin, and tissue inhibitor of metalloproteinases [TIMP-1]) with stool fecal occult blood tests for the detection of colon cancer and advanced adenomas among patients with known and no known colon disease, at a specificity of 97.7 %, the sensitivity of the 4 serum markers was less than 20 % compared with 40 % for gFOBT and 66 % for iFOBT.

Thus, until further evidence is available, we do not recommend serum tests for colorectal cancer screening”.

The UpToDate review (Fletcher, 2015) also states that “Several other technologies have been used in various clinical settings, but their value in screening for colorectal cancer has yet to be established.
• Chromoendoscopy involves the application of stains or pigment to improve the identification of abnormal mucosal tissue.

• Magnification endoscopy, with or without staining, allows the endoscopist to better visualize mucosal details with 80- to 100-fold image enhancement.

• Narrow band imaging optical colonoscopy modifies the bandwidth and wavelength of the light used in colonoscopy, allowing better visualization of vascular changes in superficial lesions”.

Retrograde imaging/illumination (eg, Third Eye Retroscope, Third Eye Panoramic Auxiliary Endoscopy System) are imaging devices that have been suggested to provide illumination and continuous retrograde views of the colon. Examples of these devices include, but may not be limited to, are the Third Eye Retroscope, which involves the use of a J-shaped catheter that contains an imaging device that can be inserted into endoscopic working channel. It is intended for single use and is disposable. Another example of these devices is the Third Eye Panoramic device, which can be attached to the distal end of the colonoscope with a flexible clip and provides continuous left side and right-side views of the colon and are displayed simultaneously on three monitors.

Cologuard:

Redwood and colleagues (2016) evaluated the accuracy of a multi-target stool DNA test (MT-sDNA) compared with FIT for hemoglobin for detection of screening-relevant colorectal neoplasia (SRN) in Alaska Native people, who have among the world’s highest rates of CRC and limited access to conventional screening approaches. These researchers performed a prospective, cross-sectional study of asymptomatic Alaska Native adults aged 40 to 85 years and older undergoing screening or surveillance colonoscopy between February 6, 2012, and August 7, 2014. Among 868 enrolled participants, 661 completed the study (403 [61 %] women). Overall, SRN detection by MT-sDNA (49 %) was superior to that by FIT (28 %; p < 0.001); in the screening group, SRN detection rates were 50 % and 31 %, respectively (p = 0.01). Multi-target stool DNA testing detected 62 % of adenomas 2 cm or larger versus 29 %
by FIT \( (p = 0.05) \). Sensitivity by MT-sDNA increased with adenoma size (to 80% for lesions greater than or equal to 3 cm; \( p = 0.01 \) for trend) and substantially exceeded FIT sensitivity at all adenoma sizes. For sessile serrated polyps larger than 1 cm \( (n = 9) \), detection was 67% by MT-sDNA versus 11% by FIT \( (p = 0.07) \). For CRC \( (n = 10) \), detection was 100% by MT-sDNA versus 80% by FIT \( (p = 0.48) \). Specificities were 93% and 96%, respectively \( (p = 0.03) \). The authors concluded that the sensitivity of MT-sDNA for cancer and larger polyps was high and significantly greater than that of FIT for polyps of any size, while specificity was slightly higher with FIT. They stated that these findings could translate into high cumulative neoplasm detection rates on serial testing within a screening program; the MT-sDNA represents a potential strategy to expand CRC screening and reduce CRC incidence and mortality, especially where access to endoscopy is limited. These investigators stated that further consideration and evaluation of the optimal test frequency, physician and patient acceptance, cost-effectiveness, and logistic algorithms for use and distribution within the Alaska Tribal Health System are needed.

Imperiale et al (2014) compared a non-invasive, multi-target stool DNA test with a fecal immunochemical test (FIT) in persons at average risk for CRC. The DNA test includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and \( \beta \)-actin, plus a hemoglobin immunoassay. Results were generated with the use of a logistic-regression algorithm, with values of 183 or more considered to be positive. Fecal immunochemical test values of more than 100 ng of hemoglobin per milliliter of buffer were considered to be positive. Tests were processed independently of colonoscopic findings. Of the 9,989 participants who could be evaluated, 65 (0.7%) had CRC and 757 (7.6%) had advanced pre-cancerous lesions (advanced adenomas or sessile serrated polyps measuring greater than or equal to 1 cm in the greatest dimension) on colonoscopy. The sensitivity for detecting CRC was 92.3% with DNA testing and 73.8% with FIT \( (p = 0.002) \). The sensitivity for detecting advanced pre-cancerous lesions was 42.4% with DNA testing and 23.8% with FIT \( (p < 0.001) \). The rate of detection of polyps with high-grade dysplasia was 69.2% with DNA testing and 46.2% with FIT \( (p = 0.004) \); the rates of detection of serrated sessile polyps measuring 1 cm or more were 42.4% and 5.1%, respectively \( (p < 0.001) \).
Specificities with DNA testing and FIT were 86.6 % and 94.9 %, respectively, among participants with non-advanced or negative findings ($p < 0.001$) and 89.8 % and 96.4 %, respectively, among those with negative results on colonoscopy ($p < 0.001$). The numbers of persons who would need to be screened to detect 1 cancer were 154 with colonoscopy, 166 with DNA testing, and 208 with FIT. The authors concluded that in asymptomatic persons at average risk for CRC, multi-target stool DNA testing detected significantly more cancers than did FIT but had more false-positive results.

In an editorial that accompanied the afore-mentioned study, Robertson and Dominitz (2014) stated that “The new multitarget stool DNA test is clearly an improvement over its predecessors, and the results of this study will help to inform the current effort of the U.S. Preventive Services Task Force to reevaluate screening tests. Comparative-effectiveness studies are now needed to clarify the role of stool DNA testing with respect to programmatic screening with other test options. Only through a better understanding of other key factors, such as the screening interval, adherence, cost, and diagnostic evaluation of positive results, can we determine the appropriate place for stool DNA testing on the screening menu”.

Onieva-Garcia and colleagues (2015) evaluated the available evidence on the validity, diagnostic accuracy and clinical utility of the multi-target DNA test in feces (Cologuard™) for screening for colorectal cancer (CRC). A systematic review was performed by consulting MedLine, EMBASE and Web of Science to July 2014. Studies on diagnostic tests were selected that evaluated the test in asymptomatic adults who underwent CRC screening. The quality and risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool. The level of evidence was defined according to the National Institute for Health and Clinical Excellence. A qualitative synthesis was conducted. A total of 299 literature references were identified, including 1 synthesis report and 5 diagnostic test studies; 3 of the 5 studies had a case-control design in Sackett phase II and were of moderate quality, and 2 had a prospective design in Sackett phase III and were of high quality. The sensitivity for
detecting CRC was greater than 90%, but only 40% for detecting advanced adenomas. The test provided conclusive diagnostic evidence to rule out CRC (negative likelihood ratio, LR-: 0.02 to 0.09), although it was not useful for ruling out advanced adenoma (LR-: 0.5 to 0.7). The authors concluded that Cologuard™ test is a valid screening test for ruling out cancerous lesions but is suboptimal for ruling out precancerous lesions. They stated that there is no evidence in terms of mortality, survival or cost-effectiveness.

An UpToDate review on “Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy” (Doubeni, 2016) states that “Cologuard has been approved by the US Food and Drug Administration (FDA) in August 2014, as a screening test for colorectal carcinoma to be followed, when abnormal, by diagnostic colonoscopy. The implications of "false positives," abnormal DNA testing in patients who are not found to have colonic lesions on colonoscopy, is uncertain. In a study of screening with 3 modalities (stool DNA, colonoscopy, and fecal immunochemical tests) in average-risk patients, nearly 10% of those with an entirely negative colonoscopy had a positive stool DNA test. It is not known whether these positive tests are clinically important, for example, by representing carcinomas elsewhere in the gastrointestinal tract or mucosal predisposition to cancer. The appropriate interval between screening fecal DNA tests is unknown. As of October 2014 the Centers for Medicare and Medicaid Services (CMS) include coverage for this test once every 3 years for asymptomatic Medicare beneficiaries age 50 to 84 years at average risk for CRC. Stool DNA testing is not currently incorporated into screening guidelines from the US Preventive Services Task Force (USPSTF), which were prepared before evidence regarding the current generation fecal test was available”.

**Septin9:**
Septin9 (Sept9) DNA methylated assay for the early detection of colorectal cancer (eg, Epi proColon, ColoVantage) is a plasma based test that detects methylated Septin9 DNA, which is purportedly a marker of the presence of colorectal cancer. It is designed for those who have avoided established CRC screening methods such as colonoscopy, FOBT or fecal immunochemical test (FIT). This test is not intended to replace established CRC tests.

ColoVantage is a plasma-based test that detects circulating methylated DNA from the SEPT9 gene which is involved in cytokinesis and cell cycle control. According to the manufacturer, case-control studies show that presence of methylated SEPT9 DNA in plasma is 58 % to 69 % sensitive for CRC detection at a specificity of 86 % to 90 % (citing Lofton-Day et al, 2008; Grützmann et al, 2008; de Vos et al, 2009). The test is non-invasive and requires no patient preparation. The manufacturer suggests that a physician may order the test for screen-eligible patients who have previously avoided established CRC screening methods such as colonoscopy, FOBT, and fecal immunochemical tests. A patient whose ColoVantage test result is positive may be at increased risk for CRC and further evaluation should be considered. The manufacturer notes, however, that the ColoVantage test has yet to be clinically validated as a screening test. There are no evidence-based guidelines from leading medical professional organizations or public health agencies that recommend measurement of methylated Septin 9 in plasma for CRC screening.

Molnar and colleagues (2015) noted that many countries have implemented various CRC screening programs, but have not achieved the desired compliance. Colonoscopy -- considered the gold standard for CRC screening -- has its limitations as well as the other techniques used, such as irrigoscopy, sigmoidoscopy, fecal blood and hemoglobin tests. The biomarker septin 9 has been found to be hyper-methylated in nearly 100 % of tissue neoplasia specimens and detected in circulating DNA fractions of CRC patients. A commercially
available assay for septin 9 has been developed with moderate sensitivity (approximately 70%) and specificity (approximately 90%) and a 2nd generation assay, Epi proColon 2.0 (Epigenomics AG), shows increased sensitivity (approximately 92%). The performance of the assay proved to be independent of tumor site and reaches a high sensitivity of 77%, even in early cancer stages (I and II). Furthermore, septin 9 was recently used in follow-up studies for detection of early recurrence of CRC. The authors evaluated the opportunities, known limitations and future perspectives of the recently introduced Epi proColon® 2.0 test, which is based on the detection of aberrantly methylated DNA of the v2 region of the septin 9 gene in plasma.

Jin and associates (2015) evaluated the performance of the Epi proColon 2.0 test for the detection of CRC, and compared it with FIT. A total of 135 patients with CRC, 169 with adenomatous polyps, 81 with hyperplastic polyps, and 91 healthy controls were included. In all patients, peripheral blood samples were taken for SEPT9 testing using Epi proColon 2.0 test. For 177 patients, both SEPT9 and FIT were performed. The sensitivity and specificity of SEPT9 for CRC were 74.8% (95% CI: 67.0 to 81.6%) and 87.4% (versus non-CRC, 95% CI: 83.5 to 90.6%), respectively. SEPT9 was positive in 66.7% of stage I, 82.6% of stage II, 84.1% of stage III, and 100% of stage IV CRCs. The sensitivity of SEPT9 for advanced adenomas was 27.4% (95% CI: 18.7 to 37.6%). The sensitivity and specificity of FIT for CRC was 58.0% (95% CI: 46.1 to 69.2%) and 82.4% (95% CI: 74.4 to 88.7%), respectively. SEPT9 showed better performance in CRC detection than FIT, but similar among advanced adenomas. The authors concluded that with improved performance characteristics in detecting CRC, the 2nd-generation SEPT9 assay could play an important role in CRC screening and early detection.

Ørntoft et al (2015) stated that the Sept9 DNA-methylation assay is among the most well-studied blood-based screening markers. However, earlier reported performances may be misleading: The Sept9 test was recently examined in 2
screening based cohorts and yielded performances lower than expected. These investigators hypothesized that co-morbidities and/or demographic characteristics affect the results of the Sept9 test. Using a retrospective nested case-control study design, these researchers studied plasma from 150 cancer and 150 controls selected from a well-characterized cohort of 4,698 subjects referred for diagnostic colonoscopy due to CRC-related symptoms. The cases and controls were matched on age and gender. Moreover, cases were stratified on tumor-site and tumor-stage. The selected cohort included a wide range of co-morbidities. Plasma Sept9 levels were assessed using a commercially available PCR-based assay (Epi-proColon). Clinical sensitivity for CRC stages I-IV was 37 %, 91 %, 77 %, and 89 %, and the overall sensitivity 73 % (95 % CI: 64 to 80 %) and specificity 82 % (95 % CI: 75 to 88 %), respectively. Age greater than 65 was associated with both increased false positive and false negative results (p < 0.05). Arthritis was associated with a higher false negative rate (p = 0.005) whereas arterio-sclerosis was associated with a higher false positive rate (p = 0.007). Diabetes was associated with Sept9 positivity with an odds ratio (OR) of 5.2 (95 % CI: 1.4 to 19.1). When the performance of Sept9 was adjusted for these parameters in a final multivariate regression model, the OR for a positive Sept9 test to be associated with CRC increased from 8.25 (95 % CI: 4.83 to 14.09) to 29.46 (95 % CI: 12.58 to 69.02). The authors concluded that the findings of this study indicated that the performance of the Sept9 assay is negatively affected by several factors commonly associated with CRC screening populations: early-stage disease, age greater than 65 years, diabetes, arthritis, and arterio-sclerosis. This should be taken into account if the Sept9 assay is used as a single marker for CRC screening, but may also have a wider impact, as it is likely that such factors may affect other blood based DNA markers as well.

On April 14, 2016, the FDA cleared Epi proColon (Epigenomics AG) as the first blood-based screening test for CRC in average-risk patients who choose not to be screened by colonoscopy or a stool-based FIT.
An UpToDate review on “Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy” (Doubeni, 2016) lists “Septin 9 hypermethylation in DNA from plasma (ColoVantage)” as an investigational test. It states that “Current serum markers are not sufficiently sensitive or specific to be used for screening. The potential to utilize a combination of 6 serum markers to improve the test has been reported in a feasibility study, but validation studies in screening populations are needed before clinical relevance can be determined”.

The USPSTF (2016) stated that the FDA approved a blood test, Epi proColon (Epigenomics) to detect circulating methylated SEPT9 DNA in April 2016. A single test characteristic study met the inclusion criteria for the systematic evidence review supporting this recommendation statement; it found the SEPT9 DNA test to have low sensitivity (48%) for detecting colorectal cancer.

Measurements of Plasma GATA5 and SFRP2 Methylation as Biomarkers for Colorectal Cancer:

Zhang and colleagues (2015) examined GATA5, SFRP2, and ITGA4 methylation in plasma DNA as non-invasive biomarkers for CRC or adenomas. There were 57 CRC patients, 30 adenomas patients, and 47 control patients enrolled in this study. Methylation-specific PCR was used to determine the promoter methylation status of GATA5, SFRP2, and ITGA4 genes in plasma DNA, and their association with clinical outcome in CRC. The predictive ability of GATA5, SFRP2, and ITGA4 methylation, individually or in combination, to detect CRC or adenomas was further analyzed. Hyper-methylated GATA5 was detected in plasma in 61.4 % (35/57) of CRC cases, 43.33 % (13/30) of adenoma cases, and 21.28 % (10/47) of control cases. The hyper-methylation of SFRP2 was detected in 54.39 % (31/57), 40.00 % (12/30), and 27.66 % (13/47) in plasma.
samples from CRC, adenomas, and controls, respectively. ITGA4 methylation was detected in 36.84% (21/57) of plasma samples of CRC patients and in 30.00% (9/30) of plasma samples from patients with colorectal adenomas, and the specificity of this individual biomarker was 80.85% (9/47). Moreover, GATA5 methylation in the plasma was significantly correlated with larger tumor size (p = 0.019), differentiation status (p = 0.038), TNM stage (p = 0.008), and lymph node metastasis (p = 0.008). SFRP2 and ITGA4 methylation in plasma significantly correlated with differentiation status (SFRP2, p = 0.012; ITGA4, p = 0.007), TNM stage (SFRP2, p = 0.034; ITGA4, p = 0.021), and lymph node metastasis (SFRP2, p = 0.034; ITGA4, p = 0.021). From the perspective of predictive power and cost-performance, using GATA5 and SFRP2 together as methylation markers seemed the most favorable predictor for CRC (OR = 8.06; 95% CI: 2.54 to 25.5; p < 0.01) and adenomas (OR = 3.35; 95% CI: 1.29 to 8.71; p = 0.012). The authors concluded that a combination of GATA5 and SFRP2 methylation could be promising as a marker for the detection and diagnosis of CRC and adenomas.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>CPT codes covered if selection criteria are met:</th>
</tr>
</thead>
<tbody>
<tr>
<td>44401 ‐ 44408 Colonoscopy through stoma</td>
</tr>
<tr>
<td>45330 ‐ 45350 Sigmoidoscopy, flexible</td>
</tr>
<tr>
<td>45378 ‐ 45398 Colonoscopy, flexible</td>
</tr>
<tr>
<td>74270                                            Radiologic examination, colon; contrast (eg, barium) enema, with or without KUB</td>
</tr>
<tr>
<td>74280                                            Air contrast with specific high density barium, with or without glucagon</td>
</tr>
<tr>
<td>Code</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>82270</td>
</tr>
<tr>
<td>82272</td>
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<td>82274</td>
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</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81528</td>
<td>Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result</td>
</tr>
<tr>
<td>86140 - 86141</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>87623</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (eg, 6, 11, 42, 43, 44)</td>
</tr>
<tr>
<td>87624</td>
<td>Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)</td>
</tr>
<tr>
<td>87625</td>
<td>Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81201 - 81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis</td>
</tr>
<tr>
<td>81292 - 81294</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis</td>
</tr>
<tr>
<td>Code Range</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>81295 - 81300</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis</td>
</tr>
<tr>
<td>81301 - 81317</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis</td>
</tr>
<tr>
<td>81318 - 81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis</td>
</tr>
<tr>
<td>88271 - 88275</td>
<td>Molecular cytogenetics</td>
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</table>

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0104</td>
<td>Colorectal cancer screening; flexible sigmoidoscopy</td>
</tr>
<tr>
<td>G0105</td>
<td>Colorectal cancer screening; colonoscopy on individual at high risk</td>
</tr>
<tr>
<td>G0106</td>
<td>Colorectal cancer screening; alternative to G0104, screening sigmoidoscopy, barium enema</td>
</tr>
<tr>
<td>G0120</td>
<td>Colorectal cancer screening; alternative to G0105, screening colonoscopy, barium enema</td>
</tr>
<tr>
<td>G0121</td>
<td>Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk</td>
</tr>
<tr>
<td>G0122</td>
<td>Colorectal cancer screening; barium enema</td>
</tr>
<tr>
<td>S0285</td>
<td>Colonoscopy consultation performed prior to a screening colonoscopy procedure</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0464</td>
<td>Colorectal cancer screening; stool-based DNA and fecal occult hemoglobin (e.g., KRAS, NDRG4 and BMP3)</td>
</tr>
<tr>
<td>G0476</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); human papillomavirus HPV), high-risk types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) for cervical cancer screening, must be performed in addition to pap test</td>
</tr>
</tbody>
</table>

**Other HCPCS codes related to the CPB:**
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3833</td>
<td>Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP</td>
</tr>
<tr>
<td>S3834</td>
<td>Single-mutation analysis (in individual with a known APC mutation in the family) for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP</td>
</tr>
<tr>
<td><strong>ICD-10 codes covered if selection criteria are met:</strong></td>
<td></td>
</tr>
<tr>
<td>C18.0 - C21.8</td>
<td>Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal</td>
</tr>
<tr>
<td>C7a.020 - C7a.026</td>
<td>Malignant carcinoid tumors of the appendix, large intestine, and rectum</td>
</tr>
<tr>
<td>D12.0 - D12.9</td>
<td>Benign neoplasm of colon, rectum, anus and anal canal</td>
</tr>
<tr>
<td>D3a.020 - D3a.029</td>
<td>Benign carcinoid tumors of the appendix, large intestine, and rectum</td>
</tr>
<tr>
<td>D50.0</td>
<td>Iron deficiency anemia secondary to blood loss (chronic)</td>
</tr>
<tr>
<td>D50.9</td>
<td>Iron deficiency anemia, unspecified</td>
</tr>
<tr>
<td>D62</td>
<td>Acute posthemorrhagic anemia</td>
</tr>
<tr>
<td>K51.00 - K55.9</td>
<td>Noninfective enteritis and colitis</td>
</tr>
<tr>
<td>K57.20 - K57.93</td>
<td>Diverticular disease of intestine</td>
</tr>
<tr>
<td>K59.00 - K59.09</td>
<td>Constipation</td>
</tr>
<tr>
<td>K62.0 - K62.1</td>
<td>Anal and rectal polyp</td>
</tr>
<tr>
<td>K62.5</td>
<td>Hemorrhage of anus and rectum</td>
</tr>
<tr>
<td>K63.5</td>
<td>Polyp of colon</td>
</tr>
<tr>
<td>K92.1</td>
<td>Melena</td>
</tr>
<tr>
<td>Q85.8</td>
<td>Other phakomatoses, not elsewhere classified [Cowden syndrome]</td>
</tr>
<tr>
<td>R19.5</td>
<td>Other fecal abnormalities</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Z12.10 - Z12.12</td>
<td>Encounter for screening for malignant neoplasm of intestinal tract, colon and rectum</td>
</tr>
<tr>
<td>Z15.09</td>
<td>Genetic susceptibility to other malignant neoplasm</td>
</tr>
<tr>
<td>Z80.0</td>
<td>Family history of malignant neoplasm of digestive organs</td>
</tr>
<tr>
<td>Z83.71</td>
<td>Family history of colonic polyps</td>
</tr>
<tr>
<td>Z85.038, Z85.048</td>
<td>Personal history of other malignant neoplasm of large intestine, rectum, rectosigmoid junction, and anus</td>
</tr>
<tr>
<td>Z86.010</td>
<td>Personal history of colonic polyps</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B97.7</td>
<td>Papillomavirus as the cause of diseases classified elsewhere</td>
</tr>
<tr>
<td>R85.610 - R85.619</td>
<td>Abnormal cytologic smear of anus</td>
</tr>
<tr>
<td>R85.81 - R85.82</td>
<td>Other abnormal findings in specimens from anus</td>
</tr>
<tr>
<td>Z11.51</td>
<td>Encounter for screening for human papillomavirus (HPV)</td>
</tr>
</tbody>
</table>

**The above policy is based on the following references:**

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Amendment to
Aetna Clinical Policy Bulletin Number CPB 0516
Colorectal Cancer Screening

There are no amendments for Medicaid.