Fecal DNA testing for colorectal cancer screening and/or monitoring is unproven, investigational, and not medically necessary due to lack of U.S. Food and Drug Administration (FDA) approval.

There is insufficient evidence in the clinical literature supporting the diagnostic accuracy of fecal DNA tests to screen for colorectal cancer in asymptomatic, average-risk patients. The existing evidence has little or no applicability to currently available fecal DNA tests. Further studies are needed to determine the analytic and clinical validity of the test as compared to other screening methods.

At this time, no tests have received FDA approval. Until the FDA completes its review of fecal DNA tests, they are investigational. The FDA has classified DNA testing as a device; therefore, it is subject to FDA review.
The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

### CPT® Code

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### HCPCS Code

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<th>Code</th>
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### DESCRIPTION OF SERVICES

Despite recent declines in both incidence and mortality, colorectal cancer (CRC) remains the third leading cause of cancer in the United States (American Cancer Society, 2013). Many deaths from colorectal cancer might be prevented with the use of widespread screening, since prognosis improves dramatically with early detection and treatment. A number of diagnostic and screening tests for CRC are available, such as the fecal occult blood test (FOBT), flexible sigmoidoscopy, barium enema and colonoscopy. However, these tests have limited sensitivity or are invasive and cause discomfort, thereby leading to poor patient acceptance. Some tests identify a precancer state, e.g. colonoscopy, and others identify cancer after it has already developed, e.g. fecal occult blood testing.

Fecal deoxyribonucleic acid (DNA) testing detects CRC based on the presence of specific, cancer-associated mutations in DNA extracted from stool samples. The potential advantage of this test over widely used FOBT is that all cancers have DNA alterations but not all cancers bleed. Fecal DNA testing is intended as a first-line screening test for colorectal cancer in asymptomatic individuals or as a monitoring tool in patients with known or suspected hereditary nonpolyposis colorectal cancer (HNPCC). A positive test result indicates the need for definitive diagnosis via colonoscopy and biopsy. Researchers are investigating next-generation tests that include additional biomarkers, as well as the use of fecal DNA testing as a potential screening tool for other types of gastrointestinal cancers.

### CLINICAL EVIDENCE

The clinical evidence was reviewed on January 17, 2014 with no additional information identified that would change the unproven and not medical necessary conclusion.

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of the evidence on fecal DNA testing to screen for colorectal cancer. The report concluded that there is insufficient evidence about the diagnostic accuracy of fecal DNA tests to screen for colorectal cancer in asymptomatic, average-risk patients. There is also insufficient evidence for the harms, analytic validity and acceptability of testing in comparison to other screening modalities. Existing evidence has little or no applicability to currently available fecal DNA testing (Lin et al., 2012).

Ahlquist et al. (2012) assessed colorectal neoplasm detection by a next-generation stool DNA (sDNA) test. The authors performed a blinded, multicenter, case-control study using archived stool samples from 252 patients with colorectal cancer (CRC), 133 with adenomas ≥1 cm and 293 individuals with normal colonoscopy results (controls). The sDNA test identified 85% of...
patients with CRC and 54% of patients with adenomas ≥1 cm with 90% specificity. The test had a high rate of detection for all nonmetastatic stages of CRC. Detection rates increased with adenoma size: 54% ≥1 cm, 63% >1 cm, 77% >2 cm, 86% >3 cm, and 92% >4 cm. The authors concluded that early-stage CRC and large adenomas can be detected throughout the colorectum and with high levels of accuracy by the sDNA test. Neoplasm size, but not anatomical site, affected detection rates. Further studies are needed to validate the findings in a larger population and optimize the sDNA test.

Ned et al. (2011) examined the published literature on the analytic validity, clinical validity and clinical utility of ColoSure™. The authors concluded that in order to consider integrating fecal DNA testing into current colorectal cancer (CRC) screening strategies, additional research is needed to establish analytic validity, clinical validity and clinical utility within the general (average-risk) population. The estimates of DNA marker sensitivity and specificity found from small case-control studies should not be extrapolated to make any estimates of the performance of methylated vimentin or ColoSure in the general population. In addition, the ongoing development and refinement of stool DNA tests presents some difficulty for the integration of these tests as a CRC screening approach.

Zou et al. (2009) conducted a validation study using stool DNA testing with a novel digital melt curve (DMC) assay. The DMC assay was found to have a high level of sensitivity in detecting individuals with colon neoplasms and was better than current stool screening methods in detecting those with advanced adenomas. Specificities did not differ significantly. Further studies are indicated.

Itzkowitz et al. (2008) conducted a validation study on an improved stool DNA assay utilizing only two markers, hypermethylated vimentin gene (hv) and a two site DNA integrity assay (DY). Using stool samples from forty-two patients with CRC and 241 subjects with normal colonoscopy, the authors reported high sensitivity (83%) and specificity (82%) for CRC.

In a National Cancer Institute (NCI) funded randomized, multicenter trial, Ahlquist et al. (2008) compared fecal occult blood testing and multitarget DNA-based testing, followed by colonoscopy, for detecting CRC. Of the 4482 average-risk adults enrolled in the trial, 3764 were evaluated. The study was designed to evaluate two outcomes: to compare an older DNA test (STD-1) with two occult blood tests (Hemoccult and HemoccultSensa) and to determine how well a novel stool DNA test (SDT-2) detected colon cancer, compared with STD-1 and the two occult blood tests. SDT-1 was a precommercial 23-marker assay, and SDT-2 targeted 3 broadly informative markers. The authors reported that the newer DNA test was twice as effective at detecting cancer and serious precancerous polyps than either current blood stool sample tests or an older version of DNA testing. While STD-2 detected significantly more neoplasms than either of the occult blood tests, it is unclear whether this increased sensitivity is offset by a loss of specificity. A limitation of the study was that STD-2 was not performed on all subsets of patients.

Itzkowitz et al. (2007) conducted a study to determine the sensitivity and specificity of a second-generation assay (version 2) that uses improved DNA stabilization/isolation techniques and a new promoter methylation marker. Forty patients with CRC and 122 subjects with normal colonoscopy provided stool samples to which DNA preservation buffer was added immediately. DNA was purified using gel-based capture, and analyzed for the original panel of 22 mutations, DIA, and 2 new promoter methylation markers. By using DNA that was optimally preserved and purified from stool, the sensitivity of the prototype version 1 assay increased to 72.5% because of enhanced performance of DIA. Vimentin gene methylation alone provided sensitivity and specificity of 72.5% and 86.9%, respectively. The optimal combination of vimentin methylation plus DIA resulted in 87.5% sensitivity and 82% specificity; cancers were detected regardless of stage or location. False-positive vimentin methylation was associated with older age. An improved fecal DNA test that incorporates only 2 markers shows much higher sensitivity for CRC. The new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening.
In a multicenter, prospective trial, fecal DNA analysis detected significantly more colorectal cancers than the fecal occult blood test (FOBT), but neither screening method was as accurate as the gold standard, colonoscopy, which identified nearly twice as many cases. This study enrolled 5486 asymptomatic adults at average risk of colorectal cancer who were over 50 years of age, of which 4404 underwent complete evaluation, including fecal DNA analysis, FOBT, and colonoscopy. Following colonoscopy, patients were stratified according to the most advanced finding, and 2507 patients (mean age, 69.5 years) were selected for analysis. This subgroup included 33 patients with adenocarcinoma, rectal carcinoid tumor, or cloacogenic cancer; all 403 patients diagnosed with advanced adenomas, plus a randomly selected group of 648 patients with minor polyps and 1423 patients with negative colonoscopy findings. All patients included in the analysis were screened with a fecal DNA panel designed to detect 21 mutations associated with colorectal cancer and the Hemoccult II (Beckman Coulter) FOBT. Of the 31 TNM stage I, II, or III invasive adenocarcinomas diagnosed with colonoscopy, the fecal DNA panel detected 16 of the invasive cancers compared with 4 detected by FOBT, corresponding to sensitivities of 51.6% and 12.9%, respectively. The specificity of fecal DNA analysis compared with FOBT was 94.4% versus 95.2%, respectively. This study suggests that fecal DNA analysis, compared with the Hemoccult II FOBT, is significantly more sensitive for diagnosing invasive cancers without significantly compromising specificity (Imperiale et al., 2004).

The National Cancer Institute (NCI) states that stool DNA testing looks promising but would be improved by increased sensitivity (perhaps by increasing the number of DNA markers) and reduced cost (NCI, 2012).

The National Comprehensive Cancer Network (NCCN) states that emerging technologies such as stool DNA have shown increasing evidence as a reasonable accurate screening test, but there is limited data to determine the optimal testing interval. At present, stool DNA is not considered a first line screening test (NCCN, 2012).

The U.S. Preventive Services Task Force (USPSTF) recommendation on screening for colorectal cancer concludes that there is insufficient evidence to assess the benefits and harm for fecal DNA testing as a screening modality for colorectal cancer (USPSTF, 2008).

Exact Sciences is conducting a trial of the company’s multi-marker molecular diagnostic screening test for the early detection of colorectal cancer. The multi-center DeeP-C study (NCT01397747) will generate data to support Exact Sciences’ planned PMA submission to the FDA. Additional information available at: http://clinicaltrials.gov/ct2/show/NCT01397747?term=Exact+Sciences&rank=1. Accessed January 14, 2014.

Professional Societies
American Cancer Society (ACS)/American College of Radiology/U.S. Multi-Society Task Force on Colorectal Cancer (comprised of the American College of Gastroenterology, the American Gastroenterological Association Institute and the American Society for Gastrointestinal Endoscopy)
In a joint guideline, a multi-society panel, emphasized that the primary goal of CRC screening should be colon cancer prevention. Based on historic and recent evidence, the panel of experts concluded that stool DNA tests, with high sensitivity for cancer, are an acceptable option for the early detection of colorectal cancer. The panel deemed the following tests acceptable options for the early detection of CRC and adenomatous polyps for asymptomatic, average-risk adults, aged 50 years and older:

Tests That Detect Adenomatous Polyps and Cancer
- Flexible sigmoidoscopy every 5 years, or
- Colonoscopy every 10 years, or
• Double contrast barium enema (DCBE) every 5 years, or
• Computed tomographic colonography (CTC) every 5 years

Tests That Primarily Detect Cancer

• Annual guaiac-based fecal occult blood test (gFOBT) with high test sensitivity for cancer, or
• Annual fecal immunochemical test (FIT) with high test sensitivity for cancer, or
• Stool DNA test (sDNA), with high sensitivity for cancer; the panel concluded that there is insufficient evidence to recommend an appropriate testing interval (Levin et al., 2008).

**American College of Gastroenterology (ACG)**

ACG guidelines for colorectal cancer screening state that annual Hemoccult Sensa and fecal DNA testing every 3 years are alternative cancer detection tests. However, because of more extensive data (compared with Hemoccult Sensa), and the high cost of fecal DNA testing, the ACG recommends the fecal immunochemical testing (FIT) as the preferred cancer detection test (Grade 1B – strong recommendation, moderate-quality evidence) (Rex et al., 2009).

**American College of Physicians (ACP)**

The ACP guidance statement on screening for colorectal cancer is based on current guidelines developed by other organizations. The ACP recommends using a stool-based test, flexible sigmoidoscopy or optical colonoscopy as a screening test in patients who are at average risk. Stool-based tests include guaiac-based fecal occult blood test (gFOBT), immunochemical-based fecal occult blood test (iFOBT) and stool DNA panel (sDNA). Of the available screening methods, only gFOBT and flexible sigmoidoscopy have been evaluated in randomized, controlled trials that showed that they are associated with decreased colorectal cancer–related mortality (Qaseem et al., 2012).

**American Society of Colon and Rectal Surgeons**

In a 2006 practice parameter, the organization acknowledged that screening tests searching for altered DNA in the stool may be a promising approach. Trials measuring the performance of the test in large numbers of average-risk people are needed (Ko et al., 2006).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Currently, there are no fecal DNA tests approved by the FDA for screening or for diagnosing colorectal cancer. The FDA classifies a test for DNA detection in stool intended to replace fecal occult blood detection to be a class II device (moderate risk), which would require a Premarket Notification (510(k)) to the FDA prior to marketing. Such a test intended to replace colonoscopy would represent a device with a new intended use and would be considered a class III device (high risk) by the FDA. Class III devices require premarket approval by the FDA prior to marketing.

**Additional Products**

ColoSure™ is a non-invasive test that detects an epigenetic marker (methylated vimentin) associated with colorectal cancer and pre-cancerous adenomas. Colosure has not obtained FDA clearance or approval.

PreGen-Plus was commercially available in the United States from 2003 until its withdrawal from the market in 2008. Originally classified as a home brew assay, the early version of the test was discontinued due to FDA reclassification. A second version of the test (Version 2) is in phase III trials.
Medicare does not have a National Coverage Determination (NCD) for fecal DNA testing used for colorectal cancer screening and/or monitoring. However, stool DNA testing is mentioned as not covered in the NCD for Colorectal Cancer Screening Tests (210.3).

Local Coverage determinations (LCDs) do not exist at this time. Accessed January 14, 2014.

REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

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<td>• Reorganized policy content&lt;br&gt;• Updated coverage rationale; added language to indicate the unproven services are &quot;not medically necessary&quot;&lt;br&gt;• Updated supporting information to reflect the most current clinical evidence and references&lt;br&gt;• Archived previous policy version 2013T0383J</td>
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