Name of Policy:
Immuoassay/Immunochemical Fecal Occult Blood Testing

Policy #: 192
Category: Laboratory
Latest Review Date: September 2016
Policy Grade: Effective 02/06/2013:
Active Policy but no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:
1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**

Immunochemical fecal occult blood tests (iFOBT) are proposed for colorectal cancer screening as an alternative to guaiac-based FOBT. iFOBT does not have dietary or drug restrictions prior to sample collection, and possibly simpler sampling instructions, which may lead to higher patient compliance.

Colorectal cancers and some precancerous adenomas often bleed periodically. Consequently, a small amount of blood in the stool (fecal occult blood) in the absence of other explanatory conditions is a marker for neoplasia. Immunochemical fecal occult blood tests (iFOBT) are used for the colorectal cancer screening by employing antibodies to detect the globin portion of human hemoglobin in stool. Because globin is degraded during passage through the upper gastrointestinal tract, the iFOBT is specific for bleeding that is limited to the colon and rectum.

Guaiac fecal occult blood testing (gFOBT) has been the standard test used for screening but requires complicated dietary and drug restrictions prior to testing and sampling instructions may limit patient compliance. iFOBTs offer testing without dietary or drug restrictions and may offer simpler sampling instructions.

The iFOBTs approved by the U.S. Food and Drug Administration (FDA) for marketing in the United States are InSure™ (Enterix, Inc.), Instant-View® (Alpha Scientific Designs, Inc.), immoCARE (Care Products, Inc.), and MonoHaem® (Chemicon International, Inc.). The tests require sample collection from 1 stool (Instant-View®, immoCARE), 2 stools (InSure™), or 3 stools (MonoHaem®). The test formats for several iFOBTs require minimal processing and involve developing a test strip with controls and reading a color reaction. In the case of the InSure™ iFOBT, all tests are developed by Quest Diagnostic Laboratories through an exclusive arrangement. For InSure™, a dry stool specimen is not required, and the sample may be collected by brushing the surface of the stool while in the toilet bowl water which may be more agreeable to the patient.

A number of additional iFOBTs have been cleared through the the FDA 510(k) process. Some (not the entire list) of these include Hema-Screen Specific (Immunostics), Innovacon Flipcard Fecal Occult Blood Test (Innovacon), OC Auto Micro FOB Test (Polymedco and Eiken), FlexSure OBT (SmithKline Diagnostics), Teco Rapid FOB Card Test (TECO Diagnostics), QuickVue (Quidel) and inSure II (Enterix, Inc.). In addition, the iScreen FOB is noted to be cleared by FDA and waived under Clinical Laboratory Improvement Amendments (CLIA), and thus available for point-of-care testing.

**Policy:**

*Immunoassay/Immunochemical fecal occult blood tests*, for routine physical examination and in screening for colorectal cancer or other sources of lower gastrointestinal bleeding *meet* Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.
Also refer to medical policy #447 Preventive Care Services Under Healthcare Reform for additional information. For health care reform compliant plans, mandated provision of services may apply. Please verify routine and screening benefits coverage for each contract.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
Per the American Cancer Society colorectal cancer is the third most common cancer in both men and women. Screening for colorectal cancer in persons who are at average risk for developing colorectal cancer should begin at age 50. Earlier and more frequent screening has been recommended for high risk individuals. Currently available screening methods for colorectal cancer include fecal occult blood test (FOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy, double-contrast barium enema or the “gold standard” colonoscopy.

Fecal occult blood testing (FOBT) is a noninvasive test that detects low levels of blood in the feces. FOBT as a screen for colorectal cancer continues to be the most widely used tool today. However, patient compliance with FOBT is low and this is one of the major barriers to colorectal cancer screening. Evidence from multiple well-conducted randomized trials supports the effectiveness of fecal occult blood testing (FOBT) in reducing colorectal cancer incidence and mortality rates compared with no screening for adults over age 50 who are at average risk. The U.S. Preventive Services Task Force (USPSTF) found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer and fair evidence that sigmoidoscopy alone or in combination with FOBT reduces mortality.

FOBT are generally divided into two types: immunoassay and guaiac types. Guaiac-based fecal occult blood testing (FOBT) use a peroxidase reaction to indicate presence of the heme portion of hemoglobin. As some cancerous and precancerous lesions tend to bleed spontaneously, this test can detect low levels of blood in the feces. Most FOBTs use sticks to collect stool samples and may be developed in a physician’s office or a laboratory. Disadvantages of FOBT screening include false-positive results due to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or consumption of peroxidase-rich foods such as red meat, turnips, or cabbage 3 days before the test. A false-positive result may also be related to bleeding hemorrhoid, gastrointestinal ulcer, or similar benign lesion. False negative results may occur if the patient has been taking Vitamin C.

Immunochromatographic fecal occult blood tests (e.g., Flexsure OBT, InSure FOBT, Instant-View Fecal Occult Blood Rapid Test, Clearview Ultra FOB, Hemosure One-Step Fecal Occult Blood Test)
are intended as an alternative to guaiac-based fecal occult blood testing. Immunological fecal occult blood tests (iFOBT) detect blood in fecal samples using antibodies that bind to intact human hemoglobin. An iFOBT may be less likely to give a false-positive result due to a bleeding ulcer in the upper gastrointestinal since blood from these ulcers should be at least partially degraded in the stomach and small intestine. One advantage of iFOBT is the lack of required dietary restrictions, which make it a more patient-friendly test. While most iFOBTs use spatulas to collect stool samples, some use a brush to collect toilet water surrounding the stool. Most iFOBTs require laboratory processing. Upper GI bleeding will not be detected by this method & hemoccult guaiac methodology is recommended if bleeding is suspected from UGI tract.

No randomized controlled trials of an immunochemical test have been conducted, but many case-control studies or studies comparing an immunochemical test with hemoccult have been conducted. Studies indicate that iFOBTs have either comparable or greater sensitivity than conventional guaiac-based FOBTs for detection of cancers in average-risk populations, with similar specificity, however, sensitivity for adenomas was much lower and similar for both types of tests. Immunochemical FOBT may be used as an alternative to conventional guaiac based FOBTs.

Li et al reported a multicenter study of 324 patients comparing results of guaiac-based chemical FOBT (CFOBT) to iFOBT (Hemosure IFOBT) as well as hypothetical sequential method (SFOBT), in which IFOBT was used only as a confirmatory test for CFOBT. Three consecutive stool samples were collected from each patient for simultaneous testing with each method, followed by colonoscopic examination. The sensitivity and specificity of the three methods (CFOBT, IFOBT and SFOBT) were compared in two settings, with the first two consecutive samples versus all three samples. Although the sensitivity for the detection of cancer and large (>20 mm) or multiple adenoma was similar for all three methods in the three-sample setting, in the two-sample setting IFOBT had higher sensitivity than SFOBT for detecting cancer (87.8% vs. 75.5%, respectively,) and large (>20 mm) or multiple adenomas (65.4% vs. 42.3%, respectively). The IFOBT also had a higher specificity than the CFOBT (89.2% vs. 75.5%, respectively,) in "normal" individuals defined by colonoscopy in the three-sample setting. Comparing two-sample setting to the three-sample setting, both CFOBT and SFOBT showed significant loss of sensitivity for the detection of cancer as well as adenoma, whereas the sensitivity for IFOBT did not change significantly. Overall, IFOBT with two-sample testing showed compatible sensitivity and specificity to the three-sample testing.

Tannous et al (2009) evaluated the analytical performance of 5 different FOBT methods (standard guaiac-based method and four immunochemical methods) using patient samples and spiked stool specimens. They reported the analytical sensitivity measured using spiked stool samples varied from <8 to 1500 ug hemoglobin/gram of stool. In some cases the results differed significantly from the manufacturers reported analytical sensitivity. Analysis of 71 stool samples measured by all 5 methods showed a discrepant result in 31 cases (43.7%). The rate of positive samples varied by method from 8.5% to 42.2%. The authors concluded the results demonstrate significant differences in the analytical performance among FOBT methods. Careful method validation and selection of a method with appropriate sensitivity is essential when choosing an FOBT method for colorectal cancer screening or for the assessment of gastrointestinal bleeding in the emergency department and hospital inpatients.
Graser et al (2009) compared the performance characteristics of five different screening tests in parallel for the detection of advanced colonic neoplasia: CT colonography (CTC), colonoscopy (OC), flexible sigmoidoscopy (FS), fecal immunochemical stool testing (FIT) and fecal occult blood testing (FOBT). Average risk adults provided stool specimens for FOBT and FIT, and underwent same-day low-dose 64-multidetector row CTC and OC using segmentally unblinded OC as the standard of reference. Sensitivities and specificities were calculated for each single test, and for combinations of FS and stool tests. CTC radiation exposure was measured, and patient comfort levels and preferences were assessed by questionnaire. The authors reported 221 adenomas were detected in 307 subjects who completed CTC (mean radiation dose, 4.5 mSv) and OC; 269 patients provided stool samples for both FOBT and FIT. Sensitivities of OC, CTC, FS, FIT and FOBT for advanced colonic neoplasia were 100% (95% CI 88.4% to 100%), 96.7% (82.8% to 99.9%), 83.3% (95% CI 65.3% to 94.4%), 32% (95% CI 14.9% to 53.5) and 20% (95% CI 6.8% to 40.7%), respectively. Combination of FS with FOBT or FIT led to no relevant increase in sensitivity. 12 of 45 advanced adenomas were smaller than 10 mm. 46% of patients preferred CTC and 37% preferred OC (p<0.001). The authors concluded high-resolution and low-dose CTC is feasible for colorectal cancer screening and reaches sensitivities comparable with OC for polyps >5 mm. For patients who refuse full bowel preparation and OC or CTC, FS should be preferred over stool tests. However, in cases where stool tests are performed, FIT should be recommended rather than FOBT.

Hoffman et al (2010) investigated whether colorectal cancer screening adherence is greater with fecal immunochemical tests (FIT) or guaiac-based fecal occult blood tests (gFOBT). Electronic health records were used to identify 3869 primary care patients due for screening for whom fecal blood testing was appropriate. 404 individuals were randomized to receive FIT (n=202) or gFOBT (n=202) by mail. The investigators determined the proportion of individuals completing testing within 90 days of agreeing to participate in the study. They used multivariate logistic regression to evaluate screening completion, adjusting for age, gender, race/ethnicity, clinic site, previous gFOBT testing, and co-morbidity. The authors reported screening adherence was higher with FIT than gFOBT (61.4% vs. 50.5%, P=0.03). The adjusted odds ratio for completing FIT vs. gFOBT was 1.56, 95% CI 1.04, 2.32. The authors concluded in a clinic setting of patients who were due for colorectal cancer screening, adherence was significantly higher with FIT than gFOBT.

Imperiale et al. (2014) completed the largest study of those at average risk for colon cancer. 9,989 were enrolled in an industry-sponsored cross-sectional study that compared the CologuardTM test, a noninvasive, multi-target stool DNA test with a fecal immunochemical test (FIT) in patients at average risk for colorectal cancer. The DNA test included quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay. Of the 9989 participants who could be evaluated, 65 (0.7%) had colorectal cancer and 757 (7.6%) had advanced precancerous lesions on colonoscopy. The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT (P=0.002). The sensitivity for detecting advanced precancerous 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 authors concluded that in asymptomatic individuals at average risk for colorectal cancer, multi-target stool DNA testing detected significantly more cancers than FIT but had more false positive results. In this study, one limitation was the nonrandomized study design and lack of comparison to the standard of care, colonoscopy. Letters to the editor regarding this study by Imperiale and colleagues noted several issues with the interpretation of the study’s results. Authors of the editorial letters suggested that the decreased sensitivity of FIT could have been due to the incorrect cutoff values included in the algorithm. In addition, the higher false positive rate may have contributed to the higher overall positive rate for the stool DNA test. The high number of false positives detected in this study limits the utility of the test.

Hirai et al. (2016) completed a systematic review with a meta-analysis to assess the diagnostic accuracy of fecal occult blood testing (FOBT) for relative detection of colorectal cancer (CRC) according to its anatomical location. Diagnostic studies including both symptomatic and asymptomatic cohorts assessing performance of FOBTs for CRC were searched. Primary outcome was accuracy of FOBTs according to the anatomical location of CRC. Bivariate random-effects model was used. Subgroup analyses were performed to evaluate test performance of guaiac-based FOBT (gFOBT) and immunochemical-based FOBT (iFOBT). Thirteen studies, with 17 cohorts, reporting performance of FOBT were included; a total of 26,342 patients (mean age 58.9 years; 58.1% male) underwent both colonoscopy and FOBT. Pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of FOBTs for CRC detection in the proximal colon were 71.2% (95% CI 61.3-79.4%), 93.6% (95% CI 90.7-95.7%), 11.1 (95% CI 7.8-15.8) and 0.3 (95% CI 0.2-0.4) respectively. Corresponding findings for CRC detection in distal colon were 80.1% (95% CI 70.9-87.0%), 93.6% (95% CI 90.7-95.7%), 12.6 (95% CI 8.8-18.1) and 0.2 (95% CI 0.1-0.3). The area-under-curve for FOBT detection for proximal and distal CRC were 90% vs. 94% \((P = 0.0143)\). Both gFOBT and iFOBT showed significantly lower sensitivity but comparable specificity for the detection of proximally located CRC compared with distal CRC. Faecal occult blood tests, both guaiac- and immunochemical-based, show better diagnostic performance for the relative detection of colorectal cancer in the distal colon than in the proximal bowel.

The American Cancer Society (ACS) concluded that, in comparison with conventional guaiac-based FOBTs, the immunochemical tests are more patient-friendly and are likely to be equal or better in sensitivity and specificity.

Unfortunately, both conventional and iFOBTs will give a false-negative result for a colorectal adenoma or tumor that does not bleed sufficiently. In an effort to increase the likelihood of detecting a tumor that bleeds intermittently, samples for an FOBT can be collected on two or three consecutive days. Patients with a positive test on any specimen should be followed up with colonoscopy.

**Practice Guidelines and Position Statements**
The National Comprehensive Care Network (NCCN, V2.2016) Clinical Practice Guidelines on Colorectal Cancer Screening do not mention immunochemical fecal occult blood testing.
U.S. Preventive Services Task Force Recommendations
Per the United States Preventive Services Task Force (USPSTF, updated July 2015) the summary of recommendations* for colorectal cancer screening include the following:

1. Adults, beginning at age 50 years and continuing until age 75 years
2. The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary.

Recommended screening tests and intervals are as follows:
- High-sensitivity fecal occult blood test (FOBT), every year
- Flexible sigmoidoscopy, every five years with FOBT every 3 years
- Colonoscopy, every 10 years

*Note: This recommendation was rated a Grade A by the USPSTF. This means that the USPSTF recommends this service and is high certainty that the net benefit is substantial.

Key Words:
Immunoassay fecal occult blood test, immunochemical fecal occult blood test, iFOBT, guaiac fecal occult blood test, gFOBT, FOBT, fecal occult blood test, QuickVue

Approved by Governing Bodies:
InSure™ (Enterix, Inc.), Instant-View® (Alpha Scientific Designs, Inc.), immoCARE (Care Products, Inc.), and MonoHaem® (Chemicon International, Inc.) These tests have all received FDA approval.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational and will be reviewed for medical necessity

Specific contract exclusions for screening tests/routine examinations may affect coverage eligibility for this test.
**Coding:**
CPT codes: 82274 Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations

HCPCS G0328 Colorectal cancer screening; fecal occult blood test immunoassay, 1-3 simultaneous

**References:**


Policy History:
Medical Policy Group, August 2004 (1)
Medical Policy Administration Committee, August 2004
Available for comment August 24-October 7, 2004
Medical Policy Group, August 2006 (1)
Medical Policy Group, February 2009 (4)
Medical Policy Group, March 2010 (3)
Medical Policy Group, February 2013 (3): Effective 02/06/2013: Active Policy but no longer scheduled for regular literature reviews and updates.
Medical Policy Group, September 2016 (3): Updates to Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.