Name of Policy:
Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening

Policy #: 099       Latest Review Date: November 2015
Category: Laboratory  Policy Grade: B

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:**
Detection of genetic abnormalities associated with colorectal cancer in stool samples has been proposed as a screening test for colorectal cancer. This technology is another potential alternative to currently available screening approaches such as fecal occult blood testing, fecal immunochemical testing (FIT), or colonoscopy.

Several cellular genetic alterations have been associated with colorectal cancer (CRC). In the proposed multistep model of carcinogenesis, the tumor suppressor gene p53 and the proto-oncogene K-ras are most frequently altered. Mutations in APC (adenomatous polyposis coli) genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. Colorectal cancer is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer) and in subgroups of patients with sporadic colon carcinoma. Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Because cancer cells are shed into stool, tests have been developed that detect these genetic alterations in the DNA from shed colorectal cancer cells isolated from stool samples.

**Policy:**
DNA analysis of stool samples to screen for colorectal cancer does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in all patients and is considered investigational.

*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:**
This policy is regularly updated with searches of the MEDLINE database. The most recent literature search was performed through October 1, 2015.

*The important outcome of interest in cancer screening is a reduction in the mortality and morbidity due to cancer. This is ideally determined with randomized clinical trials. However, for colon cancer screening, many of the recommended tests have not been evaluated with clinical trials. The efficacy of these tests is supported by numerous studies evaluating the diagnostic characteristics of the test for detecting cancer and cancer precursors along with a well-developed body of knowledge regarding the natural history of the progression of cancer precursors to cancer. Modelling studies have evaluated the robustness and quantity of health benefit of various screening tests when clinical trial evidence is lacking.*
Lacking direct evidence of screening in reducing cancer mortality, the critical parameters in the evaluation of a screening test are the diagnostic performance characteristics (i.e., sensitivity, specificity, positive and negative predictive value) compared with a criterion standard, the proposed frequency of screening, and the follow-up management of test results. The diagnostic performance characteristics of the currently accepted screening options (i.e., fecal occult blood testing [FOBT], fecal immunochemical testing [FIT], flexible sigmoidoscopy, double contrast barium enema) have been established using colonoscopy as the criterion standard. Modelling studies and clinical trial evidence on some of the screening modalities have allowed some confidence on the effectiveness of currently recommended cancer screening modalities.

For patients at average to moderate risk for colorectal cancer, organizations such as the U.S. Preventive Services Task Force recommend several options for colon cancer screening. Advocates of DNA testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations, and the detection of cancer-associated DNA may be superior to current stool tests for the detection of cancer and cancer precursors.

There are no studies of stool DNA testing for screening of individuals at high risk of colorectal cancer.

**Literature Review of FDA-Approved Cologuard**

**Diagnostic Accuracy**

Preliminary studies of the test which was eventually evaluated in the large scale screening study by Imperiale et al were conducted by Ahlquist et al and Lidgard et al. This multtarget stool DNA test consists of quantitative measurements of molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, β-actin, and hemoglobin in a logistic-regression algorithm. Since it includes a fecal immunochemical test (FIT) in its algorithm, it is actually a combined fecal DNA and FIT test. In a study of 252 patients with CRC, 133 patients with adenomas of 1 cm or larger, and 293 subjects with normal colonoscopy, the test detected 85% of colon cancer cases and 54% of subjects with adenomas, with 90% specificity. Another smaller study of this same test showed a sensitivity of 87% for detecting CRC and 82% sensitivity for detecting adenomas. In the study by Lidgard et al of 1003 patients, there were 207 cases with CRC or advanced adenomas (>1 cm), and 796 control patients with no polyps or nonadvanced adenomas (<1 cm). In the case group, 93 subjects had CRC, 84 had advanced adenoma 1 cm or larger and 30 had sessile serrated adenoma 1 cm or larger. In the control group, 155 subjects had nonadvanced adenomas and 641 did not have any colonic lesions. Using a logistic regression algorithm that incorporates 11 markers into 1 regression score and a fixed specificity of 90%, the fecal DNA test identified 84 of 86 (98% sensitivity) CRCs and 41 of 73 (56% sensitivity) advanced adenoma cases. These preliminary studies all evaluated fecal DNA using pre-assembled samples of study subjects with and without cancer or colonic lesions. Diagnostic characteristics of tests evaluated in these types of study samples may be biased.

A large-scale evaluation of this test in a screening population was published in 2014 by Imperiale et al and compared the fecal DNA test with FIT in 12,000 asymptomatic persons at average risk for CRC. The results of this study supported the U.S. Food and Drug Administration...
(FDA) approval of this fecal DNA test (Cologuard™) in August 2014. All enrolled subjects were scheduled to undergo screening colonoscopy. Stool specimens were collected and tested no more than 90 days before the screening colonoscopy. Screening colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of the fecal DNA test and FIT for detecting CRC and cancer precursors. In 9989 evaluable subjects, fecal DNA test sensitivity for cancer was 92.3% and 73.8% for FIT. For advanced precancerous lesion, fecal DNA test sensitivity was 42.4% and 23.8% for FIT. In analyses of specific types of lesions, sensitivity of the fecal DNA test did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of fecal DNA testing was higher for distal lesions than for proximal lesions. Fecal DNA test sensitivity increased as lesion size increased. The specificity of the fecal DNA test was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, specificity of the fecal DNA test was 86.6% versus 94.9% for FIT. For identification of patients with negative colonoscopy, specificity of the fecal DNA test was 89.8% versus 96.4% for FIT.

Impact on Health Outcomes
There are no studies evaluating direct health outcomes of a screening program using Cologuard. In 2014, the Blue Cross Blue Shield Association Technology Evaluation Center evaluated fecal DNA analysis for CRC screening in a special report. The report found the Imperiale study to be of good quality but noted while fecal DNA testing had higher sensitivity than FIT for various types of colorectal lesions, these results represent the diagnostic characteristics of the fecal DNA test in a one-time cross sectional study. How these study results may translate to reduced colorectal mortality in a screening program are uncertain. The study of the diagnostic characteristics of a test for detecting cancer and cancer precursors does not establish efficacy for prevention of CRC. Effective screening for CRC requires a screening program with established screening intervals and appropriate follow-up for positive tests. Given what is known about relative efficacy of different screening strategies from the results of modelling studies, the fecal DNA test would produce equivalent or better outcomes than FIT if both were used annually. However, the fecal DNA test has a considerably higher false-positive rate and would therefore consume greater health care resources than FIT at this screening frequency. Formal modelling studies of the fecal DNA test are needed to estimate the efficacy of the test in preventing CRC and help determine the optimal strategy for its use.

Literature Review of Previously Marketed Tests
Diagnostic Accuracy
A 2004 study by Imperiale et al evaluated a test marketed as the PreGen-Plus™. This study was a prospective trial of 5486 enrolled subjects. The results of this study were the principal evidence used to support prior practice recommendations regarding fecal DNA cancer screening.

Subjects underwent fecal occult blood testing (FOBT), fecal DNA analysis using a precommercial version of the test, and colonoscopy, considered the criterion standard for this trial. Of the 5486 enrolled, 4404 completed all aspects of the study and, from this group, 2507 underwent comparative analysis. The subgroup was chosen by including all subjects who were found to have adenocarcinoma (n=31) and a random selection of subjects with adenomas, polyps, or normal findings. The sensitivity of fecal DNA analysis and FOBT for all cancers and
adenomas with high-grade dysplasia was 40.8% versus 14.1%, respectively. Specificity in subjects with a negative finding on colonoscopy was 94.4% for fecal DNA and 95.3% for FOBT. This study is the first large study of fecal DNA testing in an asymptomatic average-risk population.

However, several problematic issues regarding the study were addressed in an editorial by Woolf, who urges caution in interpreting the results of the Imperiale et al study. For example, Woolf notes the wide confidence intervals around the sensitivity of fecal DNA, ranging from 35% to 68%, which preclude any firm estimates of the magnitude of benefit associated with fecal DNA testing.

Another previously marketed test, ColoSure™, has not been evaluated in a large screening study. Two studies allow calculation of the performance characteristics of the hypermethylated vimentin (hV) gene alone. In a study by Itzkowitz et al, separately assembled groups of patients with colorectal cancer (n=40) and patients with normal colonoscopy (n=122) were tested with hV. Sensitivity was 72% and specificity was 87%. In a second study by Itzkowitz et al, separately assembled groups of patients with colorectal cancer (n=82) and patients with normal colonoscopy (n=363) were tested with hV and a two-site DNA integrity assay. The purpose of the study was to calculate diagnostic performance characteristics of this combined test, but the results are also presented for hV alone. Using data-derived cut-off values, the sensitivity for cancer was 77% and the specificity was 83%. Other studies of hypermethylated vimentin using different assays have shown sensitivities of 38% and 41% for detecting colorectal cancer.

None of these studies is adequate to evaluate a screening test. The study samples are enriched with cancer cases that may not represent the prevalence or spectrum of disease present in a screening situation. The sensitivity and specificity values calculated from these studies should not be generalized to actual clinical populations. Patients with any other clinically relevant abnormalities such as polyps have been excluded from many of the studies. The cutoff values have been determined post hoc by examining the data.

**Impact on Health Outcomes**
There were no studies directly assessing the health outcomes of these previously marketed fecal DNA tests, and no modelling studies estimating health outcomes based on their test characteristics.

**Summary of Evidence**
The evidence for use of stool DNA in patients being screened for colorectal cancer includes a number of studies comparing stool DNA analysis (in early stages of development) with colonoscopy, and one large population screening study comparing the final version of the stool DNA testing and fecal immunochemical testing (FIT), using colonoscopy as the reference standard. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. The population screening study reported that stool DNA analysis has higher sensitivity and lower specificity than FIT. There are no studies directly assessing health outcomes such as overall survival or disease-specific survival. The test characteristics of stool DNA testing show the potential of the test to be an effective colorectal cancer screening test, but there is uncertainty regarding other aspects of the test. The screening interval for the test has not been firmly...
established, nor is there evidence regarding the adherence of the test at a recommended screening interval. Effective screening for CRC requires a screening program with established screening intervals and appropriate follow-up for positive tests. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**
Several recommendations of specialty organizations regarding fecal DNA testing were based largely on the 2004 study by Imperiale et al summarized previously, and should be considered obsolete. This includes 2008 guidelines from the American Cancer Society, 2012 guidelines from the American College of Physicians, and 2008 guidelines from the American College of Gastroenterology.

**National Comprehensive Cancer Network**
The 2015 National Comprehensive Cancer Network guidelines for CRC reviewed the study of Cologuard by Imperiale et al, and do not currently recommend stool DNA testing as a primary screening modality.

**U.S. Preventive Services Task Force Recommendations**
The U.S. Preventive Services Task Force (USPSTF) published recommendations for CRC screening with fecal DNA testing in October 2008. USPSTF concluded evidence is insufficient to assess the benefits and harms of fecal DNA testing as screening modalities for CRC (grade I statement). They limited their evidence review to only one study, the previously summarized study by Imperiale et al.

Draft recommendations released by the USPTF in 2015 refer to fecal DNA testing as a “FIT-DNA” test and categorize the test as an alternative test, which may be useful in certain clinical situations, but has a less mature evidence base to evaluate the test. Their recommendation is based solely on the study of Cologuard by Imperiale et al.

**Key Words:**
Colorectal cancer (CRC), DNA analysis, stool samples, chromosomal instability (CIN) pathway, mutator pathway, microsatellite instability (MSI), Mismatch repair (MMR) system, K-RAS gene, APC gene, p53 gene, BAT-26, L-DNA, PreGen™, stool-based DNA test, and Hereditary Nonpolyposis Colon Cancer (HNPPC), ColoSure™, vimentin methylation, vimentin (hV) gene, ColoGuard, ColoVantage, methylated septin 9

**Approved by Governing Bodies:**
On August 12, 2014, Cologuard™ (Exact Sciences) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as an automated fecal DNA testing product (P130017). Cologuard™ is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma and should be followed by diagnostic colonoscopy. Cologuard™ is indicated to screen adults of
either sex, 50 years or older, who are at average risk for CRC. Cologuard™ is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Over the past several years, different stool DNA tests have been evaluated in studies and some have been marketed. One of these previously marketed tests, PreGen-Plus™, tests for 21 different mutations in the \( p53 \), \( APC \), and \( K-ras \) genes; the BAT-26 MSI marker; and incorporates the DNA Integrity Assay (DIA®). PreGen-Plus™ has not been cleared by the U.S. Food and Drug Administration (FDA). On January 13, 2006, FDA sent correspondence to LabCorp indicating that PreGen-Plus™ may be subject to FDA regulation as a medical device. As a consequence, and as a result of the studies showing better performance of other tests, this test is no longer offered. Another previously marketed test is called ColoSure™ developed by OncoMethylome, which detects aberrant methylation of the vimentin (hV) gene. This test is offered as a laboratory-developed test, not subject to FDA regulation.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

- **ITS:** Covered if covered by the Participating Home Plan
- **FEP contracts:** FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
- **CPT coding:**
  - **81528** 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 *(Effective 01/01/2016)*

- **HCPCS:**
  - **G0464** Colorectal cancer screening; stool-based dna and fecal occult hemoglobin (e.g., kras, ndrg4 and bmp3) *(Effective 01/01/15)*

**Previous Coding:**
- **CPT coding:**
  - There are no specific codes for this laboratory procedure. A series of molecular diagnostic codes *(83890-83914)* would likely be used. *(Deleted 01/01/13)*
    - **81479** Unlisted molecular pathology procedure *(Effective 1/1/13)*

- **HCPCS:**
  - **S3713** KRAS mutation analysis testing *(Deleted 4/1/12)*
S3890 DNA analysis, fecal, for colorectal cancer screening (Deleted effective 01/01/2016)

References:

Policy History:
Medical Policy Group, April 2003 (3)
Medical Policy Administration Committee, April 2003
Available for comment May 7-June 20, 2003
Medical Policy Group, March 2005 (1)
Medical Policy Group, September 2006 (1)
Medical Policy Group, September 2008 (1)
Medical Policy Group, September 2010 (1): Key Points updated, no policy statement change
Coding update, effective January 1, 2011(1): Added code 88363, December 2010
Medical Policy Group, December 2010 (1): No additional information to be added to Key Points, recently updated in September.

Medical Policy Group, November 2011 (1): Update to Description, Key Points and References; no change in policy statement

Medical Policy Group, December 2011 (3): Coding update effective January 2012-added code 81275

Medical Policy Group, January 2012 (1): Update to Key Words with addition of vimentin methylation and vimentin (hV) gene

Medical Policy Group, February 2012 (1): Deleted HCPCS S3713 effective 4/1/12

Medical Policy Group, December 2012 (3): 2013 Coding Update: Deleted 83890-83914, addition of 81403, 81405, 81479 and 81599

Medical Policy Panel, November 2012

Medical Policy Group, January 2013 (1): Updates to Description, Key Points and References; no change to policy statement

Medical Policy Panel, November 2013

Medical Policy Group, January 2014 (1): Update to Key Points and References; no change to policy statement

Medical Policy Group, March 2014 (1): Added new Key Words, cologuard, colovantage and methylated septin 9; added code 81401 to policy


Medical Policy Panel, November 2014

Medical Policy Group, February 2015 (3): Updates to Description, Key Points, Current Coding – removed incorrect codes, and References; no change to policy statement.

Medical Policy Group, November 2015: 2016 Annual Coding Update. Added new CPT code 81528 to current coding and moved CPT S3890 from current coding to previous coding.

Medical Policy Panel, November 2015

Medical Policy Group, November 2015 (3): Updates to Key Points, Approved by Governing Bodies and References; no change to 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.