BlueCross BlueShield of Alabama

Name of Policy:

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

Policy #: 099
Category: Laboratory

Latest Review Date: January 2014
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 or colonoscopy.

Several genetic alterations have been associated with colorectal cancer. In the proposed multistep model of carcinogenesis, the tumor suppressor gene *p53* and the proto-oncogene K-*ras* are most frequently altered. Mutations in adenomatous polyposis coli *(APC*) 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 or MSI) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) and in a subgroup of patients with sporadic colon carcinoma. Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Since 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. This has been proposed for use in screening two populations of patients for colon cancer:

1. Known or suspected carriers of Lynch syndrome mutations, considered at high risk of developing colorectal cancer.
In this setting, testing of fecal samples could be used to monitor patients over time for development of colorectal cancer. The test could be used either in lieu of routinely scheduled surveillance colonoscopies or during intervals between scheduled colonoscopies. Those patients testing positive for cancer-related genetic alterations could be further evaluated with colonoscopy.

2. In patients at average risk of colorectal cancer
In this setting, testing of fecal samples could be offered in lieu of, or as an adjunct to, other recommended colorectal cancer screening tests, including fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema.

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:

As with any diagnostic test, the key outcomes are the diagnostic performance (i.e., sensitivity, specificity, positive and negative predictive value) compared to a gold standard and consideration of how the results of the test will be used to benefit patient management. Of the various screening options (fecal occult blood testing, flexible sigmoidoscopy, double contrast barium enema, colonoscopy), colonoscopy is considered the gold standard. For example, in patients considered at high risk for colorectal cancer, due either to a family history or Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) mutation, colonoscopy at varying intervals is recommended by the American Society of Colorectal Surgeons, the American Gastroenterological Society, and the American Cancer Society. Therefore, for patients at high risk of colorectal cancer with suspected or known Lynch syndrome mutations, the diagnostic performance of DNA analysis of stool samples should be compared with colonoscopy. In addition, the role of DNA analysis in the context of the recommended colonoscopic screening must be explored. Will this test be offered in lieu of colonoscopy, such that patients with a negative test can defer a scheduled colonoscopy, or will this test be offered as an adjunct to colonoscopy screening, for example during the intervals between colonoscopies?

For patients at average to moderate risk for colorectal cancer, these organizations also recommend colonoscopy starting at age 50 years, with an interval of 10 years, as one screening option. In addition, other screening techniques are also considered options, and the choice of screening option may be dictated in part by patient preference. Many authors have noted the low patient acceptance of current colorectal cancer screening options, particularly flexible sigmoidoscopy and colonoscopy; at the present time, only approximately 40% of eligible patients undergo screening for colon cancer. Advocates of genetic testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations. Therefore, for patients at average to moderate risk of colon cancer, genetic testing of stool samples will be compared to colonoscopy and also to fecal occult blood testing, the other entirely noninvasive technique.

Literature Review

No clinical trials have been published that evaluate use of DNA stool tests in those at high risk for colon cancer.

The largest study of those at average risk for colon cancer is that of Imperiale and colleagues who reported on the results of a prospective trial of 5,486 enrolled subjects. However, this study evaluated a test that is no longer available and that used completely different DNA markers than the ColoSure™ test. Thus, the results do not represent the performance of the currently marketed ColoSure™ test. It is worth reviewing here because it is the central piece of evidence used by some organizations to endorse such screening.

Subjects underwent fecal occult blood testing (FOBT), fecal DNA analysis using a precommercial version of the test, and colonoscopy, considered the gold 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. The following limitations are noted:

- The Imperiale et al study is not an intention-to-treat analysis. Approximately 20% of subjects were not evaluated (12% did not provide an adequate stool sample for DNA testing; 8% did not complete FOBT cards; 14% did not complete colonoscopy). Missing data were not imputed.
- The observed sensitivity for cancer of the Hemoccult II FOBT in this study was lower at 13% than reported in other studies. Imperiale et al also note in their discussion section that "the difference between our results (on Hemoccult sensitivity) and those of other reports is potentially important and deserves further study."
- The Hemoccult II FOBT tests were performed at each of the 81 study sites (including private-practice and university-based settings); quality control procedures were not described. In contrast, the DNA test was conducted in a single laboratory. Screening would require dissemination of the DNA test to more laboratories, which, as the authors note, could introduce greater variability in results.

However, the results of this study suggest that fecal DNA analysis offers an improved sensitivity, and thus the question arises as to whether fecal DNA should be considered an alternative to FOBT for patients who are unwilling to undergo, or do not have access to colonoscopy. The authors comment on the large percentage of patients who forego recommended screening for colorectal cancer, particularly the gold standard of colonoscopy, and propose that a simple noninvasive screening test with an improved sensitivity compared to FOBT would be a viable alternative.

These issues are addressed in an accompanying 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. Fecal DNA testing does provide some advantages in that, unlike FOBT, the patient does not have to undergo a specialized diet prior to the test. However, the patient must collect, refrigerate, and mail an entire bowel movement, which may be unacceptable to some patients. Woolf suggests that increasing screening rates is an important outcome but one that may be achieved by improving the accessibility and delivery of current screening methods.

Subsequently, Schroy and Heeren conducted a study of patient perceptions of stool-based DNA testing of those participating in the Imperiale et al study. A total of 4042 subjects completed the survey, an 84% response rate. The survey consisted of 25 questions using a five-point ordinal scale or a yes/no format. Stool-based testing received the same or higher mean ratings as fecal occult blood, and higher ratings than colonoscopy, except for perceived accuracy.

Published evidence on the currently available ColoSure™ test is relatively slim. 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 test that is to be used in the screening setting. 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.

Another study by Ahlquist et al, evaluated a screening test in which one component of the test was *hV*. However, *hV* was only one of three different types of markers used in this multicomponent test. Data were not analyzed separately for *hV,* thus the results of this study do not represent the performance of *hV* alone. In addition, normal patients were not tested, meaning that specificity could not be calculated. Without knowing what the corresponding specificity is, the sensitivity of a test is uninformative because it can be manipulated by simply changing the cut-off value for a positive test.

A next-generation stool test has been developed by Exact Sciences and has been evaluated in a study by Ahlquist et al This test detects four methylated genes, a mutant form of *K-ras*, and the alpha-actin gene. In a study of 252 patients with colorectal cancer, 133 patients with adenomas ≥1 cm, 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 colorectal cancer and 82% sensitivity for detecting adenomas.

Lidgard et al reported on another study by Exact Sciences in 2013. In this multicenter, blinded, case-control study of 1,003 patients, there were 207 cases with colorectal cancer or advanced adenomas (>1cm), and 796 control patients with no polyps or nonadvanced adenomas (<1cm). In the case group, 93 subjects had colorectal cancer, 84 had advanced adenoma ≥1 cm and 30 had sessile serrated adenoma ≥1cm. In the control group, 155 subjects had nonadvanced adenomas and 641 did not have any colonic lesions. Stool samples were drawn from 544 patients prior to bowel prep for colonoscopy, and from 459 patients one week after colonoscopy but before any treatment had been given. An automated fecal DNA assay measured β-actin, mutant *K-ras*, aberrantly methylated BMP3 and NDRG4, along with fecal hemoglobin. Using a logistic regression algorithm that incorporates 11 markers into one regression score and a fixed specificity of 90%, the fecal DNA test identified 84 of 86 (98% sensitivity) colorectal cancers and 41 of 73 (56% sensitivity) advanced adenoma cases.

These automated fecal DNA tests are not yet commercially available. The test characteristics need to be evaluated in a prospective manner in general population samples, rather than in case-controlled, predefined cancer cases and normal controls.

Summary
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 or colonoscopy.

The evidence on the accuracy of stool DNA as a screening test for colorectal cancer consists of a number of studies that have compared stool DNA analysis to colonoscopy. The largest study was done with a test that is no longer commercially available, and the evidence on the commercially available test is limited to smaller studies. These studies report a low to moderate sensitivity and a high specificity for the test. The sensitivity varies widely in the available studies and the evidence is not sufficient to determine the true sensitivity of the test. A new test that uses next generation sequencing technology has reported a higher sensitivity, but prospective studies are lacking and this test is not yet commercially available. In addition to uncertainty about the diagnostic accuracy of the test, clinical utility of this test has not yet been demonstrated, since there is no evidence that this test improves outcomes. As a result, analysis of DNA in stool samples is considered investigational as a screening technique for colorectal cancer.

Practice Guidelines and Position Statements
Recommendations of specialty organizations regarding fecal DNA testing largely base their statements on the study by Imperiale et al summarized previously, which used a different test than the currently offered ColoSure™ test.

The U.S. Preventive Services Task Force updated their guidelines for colon cancer screening in 2008. Fecal DNA testing was judged to have insufficient evidence to assess the benefits and harms of testing for all populations. They limited their evidence review to only 1 study, the previously summarized study by Imperiale et al.

Updated guidelines for colon cancer screening were also issued in 2008 by a group consisting of the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. This guideline endorses the use of fecal DNA testing as an acceptable means of colon cancer screening. However, unlike all the other recommendations in this guideline that recommended specific time intervals between tests, the recommended interval for fecal DNA testing is “uncertain.” The document notes that the manufacturer of the one commercially available test recommends a five-year interval after an examination with normal results. Such an interval was judged by the committee to be only suitable for a test that has high sensitivity for both cancer and adenomatous polyps—a standard that has not been documented for fecal DNA to date. The evidence supporting the joint guideline consisted of the previously summarized study by Imperiale et al, and additional older studies of diagnostic performance that did not use screening populations but used previously diagnosed or advanced cancer patients.

The National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer screening note fecal DNA testing is not considered a first-line screening test but may be an option for those unwilling or unable to undergo screening colonoscopy. The NCCN guidelines also indicate more research is needed to determine the optimal interval for fecal DNA testing.

In 2012, the American College of Physicians issued a guidance statement on colorectal cancer screening. Fecal DNA testing is listed as an option for screening in the guidance statement. However, the screening interval is noted to be uncertain.

The 2008 American College of Gastroenterology guidelines on colorectal cancer screening also indicate fecal DNA testing is an alternative option for screening every 3 years. This is based on a Grade 2B weak recommendation from moderate quality evidence.

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 (HNPCC), ColoSure™, vimentin methylation, vimentin (hV) gene, ColoGuard, ColoVantage, methylated septin 9

Approved by Governing Bodies:

On January 13, 2006, the FDA sent correspondence to Lab Corp indicating that PreGen-Plus may be subject to FDA regulation as a medical device. As a consequence, and as a result of studies showing better performance of other tests, this test is no longer offered. Exact Sciences is currently seeking FDA premarket approval for its latest automated fecal DNA testing product, Cologuard™.

Several types of tests have been evaluated in studies and some have been marketed. One of these, 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). Although the scientific studies that are the basis of the PreGen-Plus™ test were conducted or funded by Exact Sciences, LabCorp is identified as the test developer. LabCorp is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 and is certified as qualified to perform high-complexity testing. As a result, LabCorp may develop tests in-house and offer them as laboratory services (i.e., laboratory-developed tests). Historically, the FDA has not regulated laboratory-developed tests.

The currently available 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:

81275	KRAS (v-Ki-RAS2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis, variants in codons 12 and 13 **(Effective 1/1/12)**
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) – includes *SEPT9 (septin 9)* (eg, colon cancer), methylation analysis **(Effective 1/1/13)**
81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) – includes *KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene)*(e.g. carcinoma) gene analysis, variants on exon 3 (e.g. codon 61) **(Effective 1/1/13)**
81405	Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) – includes *KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene)* (e.g., Noonan syndrome), full gene sequence added range to include 83890-83914 **(Effective 1/1/13)**
81479	Unlisted molecular pathology procedure **(Effective 1/1/13)**
81599	Unlisted multianalyte assay with algorithmic analysis **(Effective 1/1/13)**

HCPCS:

S3890	DNA analysis, fecal, for colorectal cancer screening

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 1/1/13)**

HCPCS:

S3713	KRAS mutation analysis testing (**Deleted 4/1/12**)

References:

1. Agency for Healthcare Research and Quality (AHRQ). Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American college of Radiology. National Guideline Clearinghouse. www.ahrq.gov.
2. Ahlquist, David A., et al. Colorectal cancer screening by detection of altered human DNA in stool: Feasibility of a multitarget assay panel, Gastroenterology 2000; 119: 1219-1227.
3. Ahlquist, David A., et al. Stool screening for colorectal cancer: Evolution from occult blood to molecular markers, Review Article, Clinica Chimica Act 315 (2002); 157-168.
4. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008; 149: 441-450.
5. Ahlquist DA, Taylor WR, Manoney DW et al. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Clin Gastroenterol Hepatol 2012; 10(3): 272-7.
6. Ahlquist DA, Zou H, Domanico M et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012; 142(2): 248-56.
7. Baek YH, Chang E, Kim YJ et al. Stool methylation-specific polymerase chain reaction assay for the detection of colorectal neoplasia in Korean patients. Dis Colon Rectum 2009; 52(8):1452-9.
8. Blue Cross Blue Shield Association. Special report: Fecal DNA analysis for colon cancer screening. Technical Evaluation Criteria (TEC) Assessment Program, August 2006, Vol. 21, No. 6.
9. Chen WD, Han ZJ, Skoletsky J et al. Detection in fecal DNA of colon cancer-specific methylation of the nonexpressed vimentin gene. J Natl Cancer Inst 2005; 97:1124-32.
10. Dong, S.M., et al. Detecting colorectal cancer in stool with the use of multiple genetic targets, Journal of the National Cancer Institute, June 6, 2001, Vol. 93, No. 11, pp. 858-865.
11. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population, N Engl J Med, December 2004; 351(26): 2704-14.
12. Itzkowitz SH, Jandorf L, Brand R, et al. Improved fecal DNA test for colorectal cancer screening. Clin Gastroenterol Hepatol, January 2007; 5(1) 111-117.
13. Itzkowitz S, Brand R, Jandorf L, et al. A simplified, noninvasive stool DNA test for colorectal cancer detection. Am J Gastroenterol, November 2008; 103(11): 2862-2870.
14. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society task force on colorectal cancer, and the American College of Radiology. CA Cancer J Clin 2008; 58(3):130-160.
15. Li M, Chen WD, Papadopoulos N et al. Sensitive digital quantification of DNA methylation in clinical samples. Nat Biotechnol 2009; 27(9):858-63.
16. Lidgard GP, Domanico MJ, Bruinsma JJ et al. Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia. Clin Gastroenterol Hepatol 2013; 11(10):1313-8.
17. National Cancer Institute. Colorectal Cancer Screening (PDQ®). www.cancer.gov/cancertopics/pdq/screening/colorectal/healthprofessional.
18. National Guideline Clearinghouse: www.guidelines.gov.

19. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening, v 2:2013 Available online at: www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Last accessed October 2013.
20. Qaseem A, Denberg TD, Hopkins RH, Jr. et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med 2012; 156(5):378-86.
21. Rex DK, Johnson DA, Anderson JC et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009; 104(3):739-50.
22. Schroy PC III and Heeren TC. Patient perceptions of stool-based DNA testing for colorectal cancer screening. Am J Prev Med, February 2005; 28(2): 208-214.
23. Song K. Fecal DNA testing compared with conventional colorectal cancer screening methods: A decision analysis. Gastroenterology 2004; 126(5): 1270-1279.
24. Traverso, G., et al. Detection of APC Mutation for colorectal cancer (CRC) screening, New England Journal of Medicine 2002; 346; 311-20.
25. Traverso, G., et al. Detection of proximal colorectal cancers through analysis of fecal DNA, Lancet 2002; 359; 403-4.
26. U.S. Preventive Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2008; 149: 627-637.
27. Whitlock EP, Lin JS, et al. Screening for colorectal cancer: A targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149: 638-658.
28. Woolf SH. Editorial: A smarter strategy? Reflections on fecal DNA screening for colorectal cancer. NEJM 2004; 351(26): 2755-2758.

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

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