**Medical Policy**

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**Fecal DNA Analysis for Colorectal Cancer Screening**

<table>
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<tr>
<th>Type:</th>
<th>Policy Specific Section:</th>
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<tbody>
<tr>
<td>Investigational / Experimental</td>
<td>Laboratory/Pathology</td>
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<table>
<thead>
<tr>
<th>Original Policy Date:</th>
<th>Effective Date:</th>
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<tbody>
<tr>
<td>March 1, 2005</td>
<td>January 30, 2015</td>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Description

Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Tests have been developed that detect these genetic alterations in the deoxyribonucleic acid (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: known or
suspected carriers of hereditary non-polyposis colorectal cancer (HNPCC) mutations (Lynch Syndrome) considered at high risk of developing colorectal cancer and in patients at average risk of colorectal cancer.

**Policy**

Deoxyribonucleic acid (DNA) analysis of stool samples is considered **investigational** as a screening technique for colorectal cancer in individuals at any level of risk whether it is average, moderate, or high risk for colorectal cancer.

**Internal Information**

There is an MD Determination Form for this Medical Policy. It can be found on the following Web page:
http://myworkpath.com/healthcareservices/MedicalOperations/PSR_Determination_Pages.htm

**Documentation Required for Clinical Review**

- No records required

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

**APPENDIX to Fecal DNA Analysis for Colorectal Cancer Screening Policy**

**Prior Authorization Requirements**

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.
Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

**Evidence Basis for the Policy**

**Rationale**

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 deoxyribonucleic acid (DNA) replication errors in microsatellite sequences (termed microsatellite instability) in patients with hereditary non-polyposis colorectal cancer (HNPCC) and in a subgroup of patients with sporadic colon carcinoma.

Testing for colorectal cancer by detecting genetic alterations in DNA from cancer cells shed into the stool has been proposed to monitor patients with known cancer who are at high risk to develop colorectal cancer. Testing over time 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. In addition, it has been proposed to test patients at average risk of colorectal cancer. 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.

Several types of tests have been evaluated for these purposes and some have been marketed. One of these is PreGen-Plus™ (EXACT Sciences Corporation, Madison, WI). This product tests for 21 different mutations in the p53, APC, and K-ras genes, the BAT-26 microsatellite instability (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 (Burlington, NC) 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. However, on January 13, 2006, the 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 studies showing better performance of other tests, this test is no longer offered. Currently the test in use is ColoSure™ (MDxHealth, Irvine, CA), which detects aberrant methylation of the vimentin (hV) gene. This test is offered as a laboratory-developed test, not subject to FDA regulation.

As with any diagnostic test, the key outcomes are the diagnostic performance 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 HNPCC mutation, colonoscopy at varying intervals is recommended in the National Clearinghouse Guidelines from the American Society of Colorectal Surgeons (ASCS), the American Gastroenterological Society (AGS), and the American Cancer Society (ACS). Therefore, for patients at high risk of colorectal cancer with suspected or known mutations of the HNPCC gene, 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.

**Published Data**

As of April 2012, 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 (2004) 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.

Published evidence on the currently available Colosure test is relatively slim. There are no studies that have evaluated the test in screening populations. Two studies allow calculation of the performance characteristics of the hV gene alone, using the same assay as the Colosure test. In a study by Itzkowitz et al. (2007), 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. (2008), 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%.

Three other studies have evaluated methylated hV as a method of detecting colon cancer, but used other assay methods. A study by Chen et al. (2005) showed a sensitivity of 46% (43/94) and a specificity of 90% (178/198) in detecting colorectal cancer. A study by Baek et al. (2009) showed a sensitivity of 38% (23/60) and a specificity of 100% (37/37). A study by Li et al. (2009) showed a sensitivity of 41% (9/22) and a specificity of 95% (36/38). Another study by Ahlquist et al. (2008) 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.

None of these studies is adequate to evaluate a test that is to be used in the screening setting. The samples used in the studies 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 screening populations. Patients with any other abnormalities such as polyps were generally excluded from these studies.

**Recommendations of Specialty Organizations**

Recommendations of specialty organizations regarding fecal DNA testing largely base their statements on the results of a large study by Imperiale et al. (2004), which used a test which is no longer marketed. Subjects underwent fecal DNA analysis using a precommercial version of the now unavailable test, fecal occult blood testing (FOBT), and colonoscopy. Of the 5,486 enrolled, 4,404 completed all aspects of the study and, from this group, 2,507 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 was the first large study of fecal DNA testing in an asymptomatic average-risk population. Since the diagnostic characteristics of the test used in that study cannot be assumed to apply to other tests, the recommendations of these organizations may not be applicable to the Colosure test.

The 2011 National Comprehensive Cancer Network (NCCN) guidelines contain the following recommendations about use of stool DNA for colorectal cancer screening:

> Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening test, but there are limited data to determine an interval between screening. At present, stool DNA is not considered a first-line screening 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 (Whitlock et al., 2008) to only one study, the study by Imperiale et al. (2004).

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 (Levin et al., 2008). 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 study by Imperiale et al. (2004) and additional older studies of diagnostic performance that did not use screening populations but used previously diagnosed or advanced cancer patients. Studies evaluating methylated hV were not included in the evidence review.

Summary

There are no large studies of the use of fecal DNA analysis for detection of colorectal cancer in a screening population using the currently available Colisure test. Only two studies have evaluated the test in relatively small samples of patients with known colon cancer and endoscopically normal controls. This evidence is insufficient to make a determination regarding the efficacy of fecal DNA testing in colon cancer screening. As a result, this technique is considered investigational for colon cancer screening.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.
## Medical Policy: Fecal DNA Analysis for Colorectal Cancer Screening

**Original Policy Date:** 3/1/2005  
**Effective Date:** 1/30/2015

### Type | Number | Description
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CPT | None |  

<table>
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<tr>
<th>Type</th>
<th>Number</th>
<th>Description</th>
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| HCPC | G0464 | Colorectal cancer screening; stool-based DNA and fecal occult hemoglobin (e.g., KRAS, NDRG4 and BMP3)  
| | S3890 | DNA analysis, fecal, for colorectal cancer screening |
| ICD9 Procedure | None |  
| ICD9 Diagnosis | All Diagnoses |  
| Place of Service | All Places of Service |  

## Tables

N/A

## Definitions

N/A

## Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- CT Colonography (Virtual Colonoscopy)
- KRAS Mutation Analysis
- Genetic Testing for Colorectal Cancer

## Key / Related Searchable Words

- ColoSure
- DNA analysis, stool samples
- PreGen-Plus
References

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/1/2005</td>
<td>Administrative Review Reconfirmation USPTF statement; no policy modifications</td>
<td>Medical Policy Committee</td>
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<tr>
<td>12/7/2006</td>
<td>Policy Revision Indications updated - BCBSA MPP</td>
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<tr>
<td>6/19/2009</td>
<td>Policy Revision</td>
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<td>7/6/2012</td>
<td>Policy title change from Stool DNA Samples for Colorectal Cancer Screening without position change</td>
<td>Medical Policy Committee</td>
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<tr>
<td>2/22/2013</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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