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

Policy # 00003

Original Effective Date: 08/25/2003
Current Effective Date: 03/19/2014

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers deoxyribonucleic acid (DNA) analysis of stool samples as a screening technique for colorectal cancer to be **investigational.***

Background/Overview

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 (FOBT) 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 *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 or MSI) in patients with hereditary nonpolyposis colorectal cancer (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 HNPCC 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. *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 FOBT, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema.



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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 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. 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.

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.

Rationale/Source

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 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 mutations of the HNPCC gene, the diagnostic performance of DNA analysis of stool samples will 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



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blood testing, the other entirely noninvasive technique. Patient acceptance of the different options is also a relevant outcome as a technique to increase screening compliance.

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 evaluates a test that is no longer available and that uses completely different DNA markers than the Colosure test. Thus, the results do not represent the performance of the 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 FOBT, fecal DNA analysis using a precommercial version of the test, and colonoscopy, considered the gold standard for this trial. 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 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

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sensitivity of fecal DNA, ranging from 35–68%, 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 4,042 subjects completed the survey, an 84% response rate. The survey consisted of 25 questions using a 5-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 hV using different assays have shown sensitivities of 38% and 41% for detecting colorectal cancer (Baek et al., 2009, Li et al., 2009).

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 cut off 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 1 of 3 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 4 methylated genes, a mutant form of KRAS, 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

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cancer and 82% sensitivity for detecting adenomas. This test is not yet commercially available. The test characteristics need to be evaluated in a prospective manner in general population samples, rather than predefined cancer cases and normal controls.

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 (> 1 cm), and 796 control patients with no polyps or nonadvanced adenomas (< 1 cm). In the case group, 93 subjects had colorectal cancer, 84 had advanced adenoma ≥ 1 cm and 30 had sessile serrated adenoma ≥ 1 cm. 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.

Thesis 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.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov on October 24, 2013 identified 5 open studies on fecal DNA for detection of colorectal cancer. The largest study will evaluate fecal DNA testing prior to colonoscopy in 1600 patients to evaluate the test's efficacy in detecting advanced adenoma (NCT01647776). This study has an estimated completion date of November 2015.

The automated fecal DNA assay is currently being evaluated in the Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer (DeeP-C) study (NCT01397747). The DeeP-C study is evaluating the sensitivity and specificity of the Exact Sciences colorectal screening test in 12,776 subjects compared to colonoscopy. This study was completed in 2013, but results have not yet been published.

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 FOBT 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

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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.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No code
HCPSCS	S3890
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

Policy History

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08/19/2003 Medical Policy Committee review
08/25/2003 Managed Care Advisory Council approval
08/03/2005 Medical Director review
08/16/2005 Medical Policy Committee review. No change to coverage eligibility.
08/24/2005 Managed Care Advisory Council approval
07/07/2006 Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
05/02/2007 Medical Director review
05/23/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
05/07/2009 Medical Director review
05/20/2009 Medical Policy Committee approval. Coverage eligibility unchanged.
05/06/2010 Medical Director review
06/16/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2011 Coding review
05/05/2011 Medical Director review
05/18/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2012 Medical Policy Committee review
05/16/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2013 Coding updated
05/02/2013 Medical Director review
05/22/2013 Medical Policy Implementation Committee approval. No change to coverage.
03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 03/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

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