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Medical Policy Manual

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

Date of Origin: October 2012

Section: Genetic Testing

Last Reviewed Date: August 2013

Policy No: 12

Effective Date: November 1, 2013

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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 deoxyribonucleic acid (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. 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.

Several types of tests have been evaluated in studies. The sole test currently available in the United States 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.

Several tests have been marketed in the past, including the PreGen-Plus™ test (LabCorp) which evaluates the presence of 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). 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.

MEDICAL POLICY CRITERIA

DNA analysis of stool samples is considered **investigational** as a screening technique for colorectal cancer in both patients with average to moderate risk, and in patients considered at high risk for colorectal cancer.

SCIENTIFIC BACKGROUND

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.

High Risk Individuals

In patients considered at high risk for colorectal cancer, due either to a family history or hereditary nonpolyposis colorectal cancer (HNPCC) mutation, colonoscopy at varying intervals is recommended by the National Comprehensive Cancer Network (NCCN).[1] 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?

Average to Moderate Risk Individuals

For patients at average to moderate risk for colorectal cancer, the NCCN also recommends 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. 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. Patient acceptance of the different options is also a relevant outcome as a technique to increase screening compliance.

Literature Appraisal

The literature on the use of the ColoSure test consists of several systematic reviews and meta-analyses, including reviews supported by the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC).

<u>High Risk Individuals</u>

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

<u>Average to Moderate Risk Individuals</u>

Systematic Reviews/Meta-Analyses

- Ned and colleagues, from the Office of Public Health Genomics at the CDC, published the results of an evidence review on the ColoSure test as proposed for use in average-risk individuals in 2012.[2] The researchers evaluated available evidence on the use of this test and reported the following conclusions:

    - Although ColoSure is proposed for the quantification of vimentin in stool sample, available literature was not sufficient to permit an understanding of how accurately the test is able to do this, indicating that the analytical validity of the ColoSure test is, at present, not known.
    - The literature on clinical validity (test accuracy) consists of case-control studies of patients with known cancer status, which is suggestive of poorer specificity when compared with fecal occult blood tests (FOBTs). However, as the ColoSure test has not been compared with any other colorectal cancer screening test, the relative test accuracy is not known in general or average-risk populations.
    - Clinical utility is also not established as test protocol (including recommended frequency of testing), diagnostic accuracy, and documented benefit of patient health outcomes are not known.

- In 2012, the AHRQ published a comparative effectiveness review of fecal DNA testing for colorectal cancer risk in average-risk adults.[3] Following an extensive review of the literature, the

researchers identified only three studies of diagnostic accuracy in screening populations (versus populations with known colorectal cancer status), which reported low sensitivities (25-56%) for the detection of colorectal cancer, and similarly low sensitivities for the detection of advanced adenomas (11 to 39%). The researchers point out that results of these publications are specific to tests no longer on the US market (such as the PreGen-Plus test) and that these results may not be applicable to the use of the ColoSure test. The review concluded:

> Despite considerable media attention and expert-based clinical recommendations that include fecal DNA testing for CRC screening, at present, fecal DNA tests have insufficient evidence about their clinical validity (diagnostic accuracy) in patients at average risk for CRC.

- Luo and colleagues published a systematic review and meta-analysis on the analytical validity of hypermethylated genes in stool samples for the diagnosis of colorectal cancer or colorectal adenomas.[4] The reviewers evaluated the use of several hypermethylated genetic tests, including APC, p16, MLH1, MGMT and vimentin. However, because they did not report estimates of diagnostic accuracy according to the test, and instead used a pooled estimate of accuracy, these results may not be applicable to the use of the ColoSure test. Interpretation of results from this analysis is therefore limited.

Non-randomized Trials

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.[5] 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, however, because it is the central piece of evidence used by some organizations to endorse such screening.

Published evidence on the currently available ColoSure test is relatively limited. 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.[6] Sensitivity was 73% 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.[7] 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 cutoff values, the sensitivity for cancer was 77% and the specificity was 83%.
- Three other studies have evaluated methylated vimentin as a method of detecting colon cancer, but used other assay methods. In these studies, the sensitivity and specificity ranged from 38 to 46%, and 90-100%, respectively.[8-10]
- Another study by Ahlquist et al. evaluated a screening test in which one component of the test was hV.[11] 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.

The published literature on additional tests were limited and reviewed below:

- A next-generation stool test has been developed by EXACT Sciences and has been evaluated in a study by Ahlquist et al.[12] 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 cancer and 82% sensitivity for detecting adenomas.[13] 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 and others described an automated stool-DNA-based (sDNA) test for general colorectal cancer (CRC) screening that was evaluated in a blinded, multi-center, case-control study from 459 asymptomatic patients and 544 referred patients.[14] Authors reported that at 90% specificity, sDNA analysis identified individuals with colorectal cancer with 98% sensitivity. A large prospective study to determine how results of this test affect clinical management of colorectal cancer is necessary.
- Authors describe the high-resolution melting assay (HRMA) stool-based DNA testing for colorectal cancer.[15] Comparing to direct DNA sequencing, the accuracy of HRMA was verified by detecting KRAS/TP53 mutations in 2 independent stages. In study stage I, the HRMA identified 14 of 17 target mutations (82.4%) in stools from cancer patients, and 4 of 5 (80.0%) target mutations in stools from advanced adenoma patients. The mutation detection rate in fecal samples (45.0%; 18/40) and referred tissue samples (55.0%; 22/40) was highly consistent ($\kappa = 0.79$). The HRMA detected 1% mutant DNA in a background of wild type DNA. In study stage II, the HRMA assay detected 58.8% (20/34) mutations in tumor samples, 41.5% (17/41) in advanced adenomas samples, and 3.33% (2/60) in age-matched normal control samples. Authors concluded that the results from HRMA and DNA sequencing revealed 100% sensitivity and specificity in both tissue and stool samples. Prospective studies on how this test effects clinical management of colorectal cancer is necessary.

None of these studies is adequate to evaluate a test that is to be used in the screening setting, as diagnostic accuracy and clinical utility are not known. Although estimates of sensitivity and specificity were calculated, interpretation of results from the above studies is limited because a larger proportion of samples used in the studies had cancer when compared with the population at large – thus, the sensitivity and specificity values calculated from these studies should not be generalized to screening populations (who may have much lower rates of cancer).

Clinical Practice Guidelines

- National Comprehensive Cancer Network (NCCN) guidelines contain the following recommendations about use of stool DNA for colorectal cancer screening:[1]

  > 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 (USPSTF) updated their guidelines for colon cancer screening in 2008.[16] Fecal DNA testing was judged to have insufficient evidence to assess the benefits and harms of testing for all populations. Clinical preventive services guidelines from the American Academy of Family Physicians, updated in 2012, have adopted these recommendations by the USPSTF.[17]

- 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.[18] 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 evidence supporting the joint guideline consisted of the study by Imperiale et al.[5] and additional older studies of diagnostic performance that did not use screening populations but used previously diagnosed or advanced cancer patients. Studies evaluating methylated vimentin were not included in the evidence review.

- The American College of Gastroenterology released evidence-based guidelines in 2008 on colorectal screening which recommend fecal DNA testing every 3 years (Grade 2 B recommendation: a weak recommendation based upon moderate quality evidence).[19] Nevertheless, the guideline does not clearly review a test matching the description of ColoSure. As such, these recommendations may not be used to support the use of this test, specifically.

Summary

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. Further, additional studies that include patients from the general population and compare to patients with a known diagnosis of colon cancer need to be conducted to evaluate the test's efficacy and impact on health outcomes. As a result, analysis of DNA in stool samples is considered investigational as a screening technique for colorectal cancer.

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CROSS REFERENCES

Genetic Testing for Inherited Susceptibility to Colon Cancer, Genetic Testing, Policy No. 06

KRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer, Genetic Testing, Policy No. 13

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

Multigene Expression Assay for Predicting Recurrence in Colon Cancer, Genetic Testing, Policy No. 22

CODES	NUMBER	DESCRIPTION
CPT	None	
HCPCS	S3890	DNA analysis, fecal, for colorectal cancer screening