BlueCross BlueShield Federal Employee Program.

FEP 2.04.29 Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening

Effective Date: April 15, 2018

Related Policies: None

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

Description

Detection of DNA abnormalities associated with colorectal cancer (CRC) in stool samples has been proposed as a screening test for CRC. This technology is another potential alternative to currently available screening approaches such as fecal occult blood testing, fecal immunochemical testing (FIT), or colonoscopy. The currently available stool DNA test combines FIT and DNA analysis and is referred to as FIT-DNA in this review.

FDA REGULATORY STATUS

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 of occult hemoglobin in human stool. A positive result may indicate the presence of 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 previously marketed test, PreGen-Plus™ (LabCorp), tests for 21 different variants in the *p53*, *APC*, and *KRAS* genes; the BAT-26 microsatellite instability marker; and incorporates the DNA Integrity Assay (DIA®). PreGen-Plus™ has not been cleared by FDA. In January 2006, FDA informed LabCorp 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. Another previously marketed test is called ColoSure™ (OncoMethylome Sciences; now MDxHealth), which detects aberrant methylation of the vimentin (*hV*) gene. This test was offered as a laboratory-developed test and is not subject to FDA regulation.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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POLICY STATEMENT

DNA analysis of stool samples can be considered **medically necessary** as a screening technique for colorectal cancer in patients at average risk of colorectal cancer.

DNA analysis of stool samples is considered **investigational** for all other indications.

POLICY GUIDELINES

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals who are asymptomatic and at average risk of CRC who receive FIT-DNA, the evidence includes a number of small studies comparing FIT-DNA (in early stages of development) with colonoscopy, 2 screening studies comparing the final version of the FIT-DNA (using colonoscopy as the reference standard), and modeling studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. The screening studies have reported that FIT-DNA 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 FIT-DNA show the potential of the test to be an effective CRC screening test, but there is uncertainty about other aspects of it. The screening interval for the test has not been firmly established nor is there evidence on 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. Clinical utility of FIT-DNA is based on modeling studies. These studies have demonstrated that the diagnostic characteristics of FIT-DNA are consistent with decreases in CRC mortality that are in the range of other accepted modalities. FIT-DNA every 3 years is less effective than most other accepted screening strategies, while FIT-DNA every year is close to the efficacy of colonoscopy every 10 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Several recommendations of specialty organizations on stool DNA testing were based on largely on the Imperiale et al (2004), which evaluated a different test and should be considered obsolete.[11] This includes 2008 guidelines from the American Cancer Society,[12] 2012 guidelines from the American College of Physicians,[13] and 2009 guidelines from the American College of Gastroenterology.[14]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.1.2017) for colorectal cancer screening state that stool DNA performs well in the average risk individual.[15] The screening interval is uncertain, but cites Berger et al (2016)[8] as recommending every 3 years. The evidence review found that there are no or limited data in high-risk individuals.

Multi-Society Task Force on Colorectal Cancer

A U.S. Multi-Society task force representing the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy provided recommendations for colorectal cancer screening in 2017.[16] The recommended first-tier tests for individuals with average risk were colonoscopy every 10 years, and for individuals who decline colonoscopy, annual fecal immunochemical testing (FIT). Recommended second-tier tests in patients who declined the first tier tests were computed tomography (CT) colonography every 5 years, FIT-DNA every 3 years, or flexible sigmoidoscopy every 5 to 10 years. Capsule colonoscopy was listed as a third tier test. The task force recommended, “CT colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low quality evidence, or flexible sigmoidoscopy every 5-10 years (strong recommendation, high quality evidence) in patients who refuse colonoscopy and FIT.”

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF) published its most recent recommendations for colorectal cancer screening in 2016.[17] Colorectal cancer screening is recommended starting at age 50 years and continuing until age 75 years (A recommendation). The recommendation statement reviewed 7 different screening strategies including FIT-DNA. Regarding comparisons or preferences between the 7 different methods mentioned: “The USPSTF found no head-to-head studies demonstrating that any of the screening strategies it considered are more effective than others, although the tests have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations…. The screening tests are not presented in any preferred or ranked order….” USPSTF noted that sensitivity of FIT-DNA is higher that with FIT, but specificity is lower “resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test.”

Medicare National Coverage

In 2014, a Centers for Medicare & Medicaid Services decision memo was issued indicating Medicare Part B will cover the Cologuard test “once every 3 years for beneficiaries who meet all of the following criteria”[18]:

- “Age 50 to 85 years,
- Asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test), and
- At average risk of developing colorectal cancer(no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn’s Disease and ulcerative

colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).

All other stool DNA tests not otherwise specified above remain nationally non-covered."

As noted in the Centers for Medicare & Medicaid Services decision memo, the optimal screening interval for Cologuard is unknown. In the interim, Centers for Medicare & Medicaid Services has indicated it will provide coverage for Cologuard every 3 years as previously specified and will reevaluate the screening interval after the Food and Drug Administration approval study is completed.

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POLICY HISTORY

Date	Action	Description
March 2015	New Policy	
December 2016	Revised Policy	Policy updated with literature review through September 1, 2016: references 5, 7-8, and 13-14. References deleted. Policy statement changed from investigational to medically necessary for average risk patients. DNA analysis of stool samples is considered investigational for all other indications. Policy only applies to FIT-DNA.
March 2018	Update Policy	Policy updated with literature review through September 11, 2017; references 9-10, and 16 added. Policy statements unchanged.