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

Effective Date: April 1, 2019

Related Policies: None

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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), and colonoscopy. The currently available stool DNA test combines FIT and DNA analysis and is referred to as FIT-DNA in this review.

OBJECTIVE
The objective of this evidence review is to evaluate whether testing of stool DNA improves the net health outcome for asymptomatic individuals at average risk of colorectal cancer who are undergoing routine colorectal cancer screening.

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.

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).
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**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, adenomatous polyposis coli, 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.

**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 and disease-specific survival. 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.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

Several recommendations of specialty organizations on stool DNA testing were based 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 Society13 and 2009 guidelines from the American College of Gastroenterology.14

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network guidelines (v.1.2018) for colorectal cancer (CRC) screening includes use of fecal immunochemical testing DNA (FIT-DNA) to screen patients with average risk for colon cancer.15
Following a negative test, the recommendation is to rescreen with any modality after 3 years. Use of FIT-DNA tests is not described for screening of 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 CRC 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 FIT. Recommended second-tier tests in patients who declined the first tier tests were computed tomography 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, “[computed tomography] 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.”

**American Cancer Society**

In 2018, the American Cancer Society updated its guidelines for CRC screening for average-risk adults.17

Regular screening with either a structural examination (ie colonoscopy) or high-sensitivity stool-based test is recommended to start in adults who are 45 years and older (qualified recommendation) or who are 50 years and older (strong recommendation). Recommendations for screening with stool-based tests include FIT repeated every year, high-sensitivity guaiac-based fecal occult blood test repeated every year, or multitarget stool DNA test repeated every 3 years.

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force (USPSTF) published its most recent recommendations for CRC screening in 2016.18

CRC screening was 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 indicated Medicare Part B will cover the Cologuard test “once every 3 years for beneficiaries who meet all of the following criteria”19:

- “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 cover Cologuard every 3 years as previously specified and would reevaluate the screening interval after the Food and Drug Administration approval study is completed.

REFERENCES

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POLICY HISTORY

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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>March 2015</td>
<td>New Policy</td>
<td>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.</td>
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<tr>
<td>December 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review through September 11, 2017; references 9-10, and 16 added. Policy statements unchanged.</td>
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<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through September 6, 2018; reference 17 added; reference 15 updated. Policy statements unchanged.</td>
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<td>March 2019</td>
<td>Update Policy</td>
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