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FEP Medical Policy Manual

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

Effective Policy Date: **April 1, 2021**

Original Policy Date: **March 2015**

Related Policies:

None

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

Description

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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.

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

Benefit or contractual restrictions regarding preventive medicine may apply when testing is performed as part of a screening test.

FDA REGULATORY STATUS

On August 12, 2014, Cologuard (Exact Sciences Corporation) 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.[1.] A positive result may indicate the presence of CRC or advanced adenoma and should be followed by diagnostic colonoscopy.. On September 20, 2019, the FDA approved the expansion of the Cologuard label to include adults ages ≥45 years.[2.] Cologuard was previously indicated for those ≥50 years. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. On August 26, 2020, the FDA approved the post-approval study (PAS) protocol titled: "A Real-World Study of Patients Under the Age of 50 Screened for Colorectal Cancer (CRC) Using Cologuard in the U.S. (Tidal)."[3.]

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 the FDA. In January 2006, the 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 colorectal cancer (CRC) who receive fecal immunochemical testing (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.[18.] This includes 2008 guidelines from the American Cancer Society,[19.] 2012 guidelines from the American College of Physicians,[20.] and 2009 guidelines from the American College of Gastroenterology.[21.]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.2.2020) for colorectal cancer (CRC) screening includes the use of fecal immunochemical testing-DNA (FIT-DNA) to screen patients with an average risk for colon cancer.[22.] Following a negative test, the recommendation is to rescreen with any modality after 3 years. Use of FIT-DNA tests is not described for the screening of high-risk individuals. Follow-up colonoscopy is recommended within 6 to 10 months after a positive test.

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 (2017) provided recommendations for CRC screening.[23.] 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.[24.] Regular screening with either a structural examination (ie, colonoscopy) or a 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

In 2016, the U.S. Preventive Services Task Force Recommendations (USPSTF) published its most recent recommendations for CRC screening.[25.] 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 of 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:”[26.]

- "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 FDA approval study is completed.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2015	New policy	
December 2016	Replace 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	Replace policy	Policy updated with literature review through September 11, 2017; references 9-10, and 16 added. Policy statements unchanged.
March 2019	Replace policy	Policy updated with literature review through September 6, 2018; reference 17 added; reference 15 updated. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through September 9, 2019; no references added, reference on NCCN updated. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through August 20, 2020; references added. Policy statements unchanged.