



## FEP Medical Policy Manual

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

**Annual Effective Policy Date: April 1, 2024**

**Original Policy Date: March 2015**

**Related Policies:**

None

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

### Description

#### 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, though other publications also use the terms stool DNA (sDNA)-FIT and multitarget stool DNA (mt-sDNA).

### 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 individuals 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 for use in average risk adults aged 50 to 84 years (P130017). Cologuard is intended for the qualitative detection of colorectal neoplasia-associated DNA markers and of occult hemoglobin in human stool.<sup>1</sup> 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 average risk adults aged  $\geq 45$  years.<sup>2</sup> 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)."<sup>3</sup>

## 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, screening studies comparing the final version of the FIT-DNA (using colonoscopy as the reference standard), 2 systematic reviews of screening studies, 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 an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2023 ) for colorectal cancer (CRC) screening includes the use of fecal immunochemical testing (FIT)-DNA to screen patients with an average risk for colon cancer.<sup>26</sup> Following a negative test, the recommendation is to rescreen with any modality in 3 years. Use of FIT-DNA 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 (AGA), and the American Society for Gastrointestinal Endoscopy (2017) provided recommendations for CRC screening.<sup>27</sup> 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." In 2022, a focused update to the 2017 CRC screening recommendations from the task force was published that addressed the age to begin and stop CRC screening in average-risk individuals.<sup>28</sup> The task force now suggests CRC screening in average-risk individuals aged 45 to 49 years. Unchanged from 2017 are the following recommendations: a) offer CRC screening to all average-risk individuals aged 50 to 75 years, b) consider starting or continuing screening for individuals aged 76 to 85 years on an individualized basis (depending on patient and disease factors), and c) screening is not recommended after age 85 years.

#### American Cancer Society

In 2018, the American Cancer Society updated its guidelines for CRC screening for average-risk adults.<sup>29</sup> Regular screening with either a structural examination (ie, colonoscopy) or a high-sensitivity stool-based test is recommended to start in adults who are age 45 years and older (qualified recommendation) or who are age 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.

#### American College of Physicians

In 2023, the American College of Physicians (ACP) released updated guidance on screening for CRC in asymptomatic, average-risk adults.<sup>30</sup> The ACP stated that "Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer". A guidance statement of approved tests is as follows: "Clinicians should select among a fecal immunochemical or high-sensitivity guaiac fecal occult blood test every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus a fecal immunochemical test every 2 years as a screening test for colorectal cancer".

#### American Gastroenterological Association

In 2022, the AGA published a clinical practice update commentary that reviewed the evidence on noninvasive CRC screening options.<sup>31</sup> Similar to the U.S. Multi-Society task force, the ACG recommends FIT-DNA every 3 years as an average-risk option for CRC screening. The commentary compares this recommendation to that of the U.S. Preventive Services Task Force (USPSTF), which recommends FIT-DNA every 1 to 3 years.

## U.S. Preventive Services Task Force Recommendations

In 2021, the U.S. Preventive Services Task Force published updated recommendations for CRC screening in asymptomatic, average risk adults (defined as no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorders that predispose them to a high lifetime risk of CRC [such as Lynch syndrome or familial adenomatous polyposis]).<sup>32</sup> The USPSTF recommended universal screening for average risk adults aged 45 to 49 years (B recommendation) and for adults aged 50 to 75 years (A recommendation). For adults aged 76 to 85 years, the USPSTF recommends selective screening due to the small magnitude of net benefit (C Recommendation). The USPSTF reviewed evidence for 6 screening strategies, including FIT-DNA. They do not recommend one screening strategy over another, and noted the lack of direct evidence on clinical outcomes when comparing screening strategies. Clinical considerations noted for FIT-DNA testing appear in Table .

**Table 1. U.S. Preventative Services Task Force Considerations for Fecal Immunochemical-DNA Testing**

Recommended screening interval	Efficacy	Other considerations
1 to 3 years	<ul style="list-style-type: none"> <li>Improved sensitivity compared with FIT per 1-time application of screening test</li> <li>Specificity is lower than that of FIT, resulting in more false-positive results, more follow-up colonoscopies, and more associated adverse events per FIT-DNA screening test compared with per FIT test</li> <li>Modeling suggests that screening every 3 years does not provide a favorable balance of benefits and harms compared with other stool-based screening options (annual FIT or FIT-DNA every 1 or 2 years)</li> <li>Insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative follow-up colonoscopy</li> <li>No direct evidence evaluating the effect of FIT-DNA on colorectal cancer mortality</li> </ul>	<ul style="list-style-type: none"> <li>Harms from screening with FIT-DNA arise from colonoscopy to follow-up abnormal FIT-DNA results</li> <li>Can be done with a single stool sample but involves collecting an entire bowel movement</li> <li>Requires good adherence over multiple rounds of testing</li> <li>Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)</li> </ul>

FIT: fecal immunochemical testing.

## 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:<sup>33</sup>

- "Age 50 to 85 years, and
- 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)."

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 post-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.
March 2022	Replace policy	Policy updated with literature review through September 26, 2021; references added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through September 22, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
March 2024	Replace policy	Policy updated with literature review through September 21, 2023; references added. Policy statements unchanged.

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