



**Kaiser Foundation Health Plan of Washington**

**Clinical Review Criteria**

**Fecal DNA Testing**

- Cologuard™
- Colorectal Neoplasm Detection
- PreGen-Plus Test

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**Criteria**

**For Medicare Members**

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	See MLN Matters MM9115 - <a href="#">National Coverage Determination (NCD) for Screening for Colorectal Cancer using Cologuard™ - A Multitarget Stool DNA Test</a>
Local Coverage Article	None

**For Non-Medicare Members**

Medical necessity review no longer required.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

**Background**

Colorectal cancer is the second leading cause of death from cancer in the United States. Most colorectal cancers begin with the development of benign adenomatous polyps. It is believed that cells acquire genetic changes as adenomatous polyps develop into an adenocarcinoma, a process that can take 10-20 years.

EXACT Sciences Corporation (Marlborough, MA) has developed tests that analyze patient stool samples to see whether they contain genetic markers associated with colorectal cancer. The PreGen-Plus, the topic of the current review, is a test for the early detection of colorectal cancer in an average-risk population. It uses a multitarget assay panel that incorporates 21 point mutations in *K-ras*, adenomatous polyposis coli (APC) and *p53* genes, a microsatellite instability marker (BAT-26) and a proprietary marker, the DNA Integrity Assay (Tagore, 2003). A similar test, PreGen-26, is intended to detect colorectal cancer in high-risk patients. The BAT-26 is the basis of the PreGen-26 test (manufacturer's website).

According to a review article on emerging technologies for colorectal cancer screening (Levin, 2003), it may be possible to identify cancer at an earlier stage with DNA tests such as the PreGen-Plus than with fecal occult blood test (FOBT), the standard non-invasive test. Other potential advantages of the PreGen-Plus test may be a reduced false-positive rate because the test targets mutations specific to colorectal cancer, and the need for only a single stool sample since DNA is shed continuously from colorectal cancer and precursor polyps. A potential disadvantage is that the most appropriate markers for DNA detection of colorectal cancer are not known and clinical evaluation of the tests is limited.

The FDA has determined that approval of the PreGen-Plus test is not required.

## Medical Technology Assessment Committee (MTAC)

### Fecal DNA Testing

#### 02/11/2004: MTAC REVIEW

**Evidence Conclusion:** The Tagore study provides preliminary data on the sensitivity of the PreGen-Plus test in a population with known colorectal neoplasia (47-85% depending on the stage of disease) and specificity in normal individuals (96%). This is not an accurate assessment of how the screening test would perform in a general population sample. Studies that include a blinded comparison of PreGen-Plus to a gold standard in a screening population are needed. In addition, head-to-head comparisons with the standard noninvasive test for colorectal cancer, fecal occult blood testing, would strengthen the evidence.

**Articles:** The manufacturer’s website had an announcement dated October, 2003 stating that a study comparing the sensitivity of the PreGen-Plus test and FOBT had been conducted and would be submitted to a peer-reviewed journal when data analysis was finished.

One was on the sensitivity and specificity of a multitarget assay panel labeled as PreGen Plus using colonoscopy as the gold standard (Tagore, 2003). The second article was on a plasma DNA test, not a stool test. The broader search on DNA testing for colorectal cancer yielded 49 articles. There was an empirical study demonstrating the successful extraction of DNA from the stool of colorectal cancer patients (Dong, 2001). Another empirical study extracted DNA from stool and evaluated the sensitivity and specificity of the DNA analysis compared to colonoscopy (Ahlquist, 2000). The PreGen-Plus test was not mentioned, although analysis for the Ahlquist study was done by Exact Laboratories. The Tagore study was critically appraised because it clearly used the PreGen-Plus test and had a larger sample size than the Ahlquist study (n=292 vs. n=61). The citation is as follows: Tagore KS, Lawson MJ, Yucaitis JA. et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. *Clin Colorectal Cancer* 2003; 1: 47-53. See [Evidence Table](#)

The use of PreGen-Plus in screening of colorectal cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*

### Fecal DNA Testing

#### 10/20/2014: MTAC REVIEW

**Evidence Conclusion:** In an effort to establish the accuracy of the Cologuard™ test, Imperiale et al. compared the tests performance to the gold standard, colonoscopy. As a secondary endpoint, the investigators also compared the tests performance to the FIT. The cross-sectional study evaluated 9,989 asymptomatic averaged-risk adults between the ages of 50 and 84 years who were scheduled to undergo screening colonoscopy. All participants provided a stool specimen before routine bowel preparation for colonoscopy. Stool specimens were analyzed in three laboratories and colonoscopy results were evaluated by independent local pathologists and further confirmed and categorized by a central independent pathologist. The gold standard identified CRC in 65 participants and advanced adenomas (AA) in 757 participants. The Cologuard™ was able to accurately detect 60 cancers and 321 AA (sensitivities 92.3% and 42.4%, respectively) while the FIT identified 48 cancers and 180 AA (sensitivities 73.8% and 23.8%, respectively). The Cologuard™ had a lower specificity for detecting all nonadvanced adenomas or negative results when compared with FIT (86.6% vs. 94.9%, respectively) (Imperiale, Ransohoff et al. 2014). Risks of Diagnostic Test In terms of risk, the Cologuard™ test itself presents low risk to the patient as it is noninvasive, requires no bowel preparation or dietary restrictions and allows for collection during normal bowel movements in the toilet. The study reported four mild adverse events and one death. The death occurred prior to colonoscopy and was deemed to be unrelated to the study. Of particular concern, however, is the indirect risk as it relates to false positives and negatives. Although the Cologuard™ test yields a high sensitivity, that came at the cost of a lower specificity which could lead to additional colonoscopies as well as unnecessary stress and anxiety.

Table 1. Number Needed to Screen (NNS) to detect one CRC

	Colonoscopy	Cologuard	FIT
Any CRC (156-286)	154 (120-200)	166 (130-217)	208
Stage I to III CRC (169-313)	166 (130-217)	178 (140-238)	227
Advanced precancerous lesion (65)	13 (12-24)	31 (28-35)	55 (48-65)

Conclusions from the last review of multitarget stool DNA testing in MTAC did not live up to genetic test evaluation criteria citing the need for additional research that includes blinded comparison with the gold standard in a

screening population as well as, head-to-head comparison with the current standard noninvasive test. Since then, the Cologuard™ has undergone several evolutions reflected throughout the literature with the most current version validated by a large cross-sectional study including comparisons with the gold standard, colonoscopy, as well as the FIT. Generally speaking, the study, which was financially supported by the manufacturer Exact Sciences Inc., appears to be well-designed and well-conducted including almost 10,000 participants in 90 centers across the United States and parts of Canada. The investigators, who are also the developers of the device, fail to describe the baseline characteristics of the study population but do identify the significant differences between the participants whose results could be fully evaluated and those whose results could not. Further to this, recruitment was weighted towards the older age of the eligible age spectrum which might limit the generalizability of the results. The design of the study was the primary limiting factor. While it is typical to use a cross-sectional study design to compare diagnostic tests, the results provide only a snap shot of the situation at one given time, failing to provide adequate follow-up to demonstrate how the Cologuard™ might function in clinical practice. Further to this, the sensitivity and specificity is based on stool samples collected at one point in time limits the ability to provide an interval at which the Cologuard™ would be applied. Exact Sciences has provided the protocol for a longitudinal post-market approval study that will likely address these limitations. Conclusions: There is evidence to establish the analytic validity of the Cologuard™ test, that is, the test accurately identifies the particular gene variant.

There is evidence to establish the clinical validity of the Cologuard™ test, that is, how well the test is related to the presence, absence or risk of a disease. There is insufficient evidence to conclude that the test is not harmful to patients. There is insufficient evidence to establish the clinical utility of the Cologuard™ test, that is, the test is reasonably expected to lead to more appropriate patient management than if the test were not available.

**Articles:** The literature search for multitarget stool DNA testing for CRC screening yielded numerous publications. Among them were various editorials addressing the recent FDA approval, as well as commentary recognizing the Cologuard™ as the first product to be reviewed through the joint FDA-CMS parallel review pilot program. In addition, several publications that mirror the evolution of the device over the years were identified. The FDA's current approval relied on one clinical trial to establish the safety and effectiveness of the Cologuard™ test. This article was selected for review. See [Evidence Table](#)

The use of Stool DNA Testing for Colorectal Cancer Screening does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Date Created	Date Reviewed	Date Last Revised
02/11/2004	02/11/2004, Instituted annual review because of Medicare criteria 04/05/2011 <sup>MDCRPC</sup> , 02/07/2012 <sup>MDCRPC</sup> , 12/04/2012 <sup>MDCRPC</sup> , 04/02/2013 <sup>MDCRPC</sup> , 10/01/2013 <sup>MPC</sup> , 08/05/2014 <sup>MPC</sup> , 05/15/2015 <sup>MPC</sup> , 03/01/2016 <sup>MPC</sup> , 01/03/2017 <sup>MPC</sup> , 11/07/2017 <sup>MPC</sup> , 10/02/2018 <sup>MPC</sup>	08/05/2014

<sup>MDCRPC</sup> Medical Director Clinical Review and Policy Committee

<sup>MPC</sup> Medical Policy Committee

Revision History	Description
05/11/2017	Cologuard was added to the covered services

## Codes

CPT: 81528, S3890, G0464