DNA analysis of stool samples at a frequency not to exceed once every three years may be considered **medically necessary** as a screening technique for colorectal cancer in patients at average risk of colorectal cancer.

DNA analysis of stool samples for detection of colorectal cancer is considered **not medically necessary** in patients with high risk including any of the following:

- Patients with a prior positive colorectal cancer screening test for which a colonoscopy is more appropriate
- Personal history of adenomatous polyps, colorectal cancer, inflammatory bowel disease, Crohn’s Disease, or ulcerative colitis
- Family history of colorectal cancer, adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer

### Policy Guidelines

The following CPT code is specific to the Cologuard™ test:

- **81528**: Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

### 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 will be referred to as FIT-DNA in this review.

### Related Policies

- N/A

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
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 colorectal cancer (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 mutations in the p53, APC, and K-ras genes; the BAT-26 MSI marker; and incorporates the DNA Integrity Assay (DIA®). PreGen-Plus™ has not been cleared by the FDA. In January 2006, the FDA sent correspondence to LabCorp indicating 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

Background
Several cellular genetic alterations have been associated with colorectal cancer (CRC). In the proposed multistep model of carcinogenesis, the tumor suppressor gene p53 and the proto-oncogene K-ras are most frequently altered. Mutations in APC (adenomatous polyposis coli) genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. CRC is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability [MSI]) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer) and in subgroups of patients with sporadic colon carcinoma. Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Because cancer cells are shed into stool, tests have been developed to detect these genetic alterations in the DNA from shed CRC cells isolated from stool samples.

Literature Review
The important outcome of interest in cancer screening is a reduction in the mortality and morbidity due to cancer. This is ideally determined with randomized clinical trials. However, for colon cancer screening, many of the recommended tests have not been evaluated with clinical trials. The efficacy of these tests is supported by numerous studies evaluating the diagnostic characteristics of the test for detecting cancer and cancer precursors along with a well-developed body of knowledge on the natural history of the progression of cancer precursors to cancer. Modeling studies have evaluated the robustness and quantity of health benefit of various screening tests when clinical trial evidence is lacking.

When lacking direct evidence that a screening test reduces cancer mortality, the critical parameters in the evaluation are the diagnostic performance characteristics (i.e., sensitivity, specificity, positive and negative predictive value) compared with a criterion standard, the proposed frequency of screening, and the follow-up management of test results. The diagnostic performance characteristics of the currently accepted screening options (i.e., fecal occult blood testing, fecal immunochemical testing [FIT], flexible sigmoidoscopy, double-contrast barium enema) have been established using colonoscopy as the criterion standard. Modelling studies and clinical trial evidence on some of the screening modalities have allowed some confidence on the effectiveness of several cancer screening modalities.
For patients at average risk for colorectal cancer (CRC), organizations such as the U.S. Preventive Services Task Force have recommended several options for colon cancer screening. Advocates of DNA testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations compared to imaging or direct visualization screening strategies, and tests that detect cancer-associated DNA in stool may be superior to current stool tests for the detection of cancer and cancer precursors.

Because there are no studies of stool DNA testing for screening individuals at high risk of CRC, the evidence discussed pertains only to screening of individuals at average risk of CRC. The evidence discussed herein is restricted to studies evaluating Cologuard, the only test approved by the Food and Drug Administration, which combines FIT and DNA analysis; we will call it FIT-DNA throughout.

**FIT-DNA TEST**

**Diagnostic Accuracy**

Preliminary studies of the FIT-DNA (Cologuard), which was eventually evaluated in the large-scale screening study by Imperiale et al., were conducted by Ahlquist et al. and Lidgard et al. This multigene FIT-DNA consists of quantitative measurements of molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, β-actin, and hemoglobin in a logistic-regression algorithm. Because it includes a FIT in its algorithm, it is actually a combined stool DNA and FIT. In a study of 252 patients with CRC, 133 patients with adenomas of 1 cm or larger, and 293 subjects with normal colonoscopy, the test detected 85% of cancer cases and 54% of subjects with adenomas, with 90% specificity. Another smaller study of this same test showed a sensitivity of 87% for detecting CRC and 82% sensitivity for detecting adenomas. In the study by Lidgard et al., of 1003 patients, there were 207 cases with CRC or advanced adenomas (>1 cm) and 796 control patients with no polyps or nonadvanced adenomas (<1 cm). In the case group, 93 subjects had CRC, 84 had advanced adenoma 1 cm or larger, and 30 had sessile serrated adenoma 1 cm or larger. In the control group, 155 subjects had nonadvanced adenomas and 641 had no colonic lesions. Using a logistic regression algorithm that incorporates 11 markers into a single regression score and a fixed specificity of 90%, FIT-DNA identified 84 (98% sensitivity) of 86 CRCs and 41 (56% sensitivity) of 73 advanced adenoma cases. These preliminary studies all evaluated stool DNA using preassembled samples of study subjects with and without cancer or colonic lesions. For diagnostic characteristics of tests evaluated in these types of study samples may be biased.

A large-scale evaluation of this test in a screening population was published in 2014 by Imperiale et al., who compared the FIT-DNA in 12,000 asymptomatic persons at average risk for CRC. The results of this study supported the U.S. Food and Drug Administration (FDA) approval of this fecal DNA test (Cologuard) in August 2014. All enrolled subjects were scheduled to undergo screening colonoscopy. Stool specimens were collected and tested no more than 90 days before the screening colonoscopy. Screening colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of FIT-DNA for detecting CRC and cancer precursors. In 9989 evaluable subjects, FIT-DNA sensitivity for cancer was 92.3% (95% CI, 83.0 to 97.5) and for FIT it was 73.8% (95% CI, 61.5 to 84.0). For advanced precancerous lesions, fecal DNA test sensitivity was 42.4% (95% CI, 38.9 to 46.0) and for FIT it was 23.8% (95% CI, 20.8 to 27.0). In analyses of specific types of lesions, sensitivity of the FIT-DNA did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of fecal DNA testing was higher for distal lesions than for proximal lesions. FIT-DNA sensitivity increased as lesion size increased. The specificity of the FIT-DNA was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, specificity of the FIT-DNA was 86.6% (95% CI, 85.9 to 87.2) and 94.9% (95% CI, 94.4 to 95.3) for FIT. For identification of patients only with negative colonoscopy, specificity of the FIT-DNA was 89.8% (95% CI, 88.9 to 90.7) and 96.4% (95% CI, 95.8 to 96.9) for FIT.
A second evaluation of FIT-DNA was published in 2016 by Redwood et al. Asymptomatic Alaskan natives undergoing screening or surveillance colonoscopy were enrolled in the study. Colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of the FIT-DNA and FIT for detecting CRC and cancer precursors. In 661 evaluable subjects, FIT-DNA sensitivity for cancer was 100% and for FIT it was 85%. For screening-relevant neoplasms (defined as adenoma or sessile serrated adenoma/polyp ≥1 cm, any adenoma with ≥25% villous component, or cancer), FIT-DNA sensitivity was 49% and 28% for FIT. Specificities for FIT-DNA were lower than FIT. When all patients with no screening-relevant neoplasms were considered normal, specificities were 91% for FIT-DNA and 94% for FIT. When only patients without any polyps were considered normal, specificities were 93% for FIT-DNA and 96% for FIT.

**Section Summary: Diagnostic Accuracy**

The 2 studies of FIT-DNA are consistent with each other in that both have demonstrated the higher sensitivity of FIT-DNA than for FIT for both CRC detection and cancer precursor detection, but lower specificity. The study by Imperiale is more than 10 times the size of that by Redwood and thus represents the best estimate of the diagnostic performance of FIT-DNA in a single screening.

**Clinical Utility**

There are no studies evaluating direct health outcomes of a longitudinal screening program using Cologuard. In 2014, a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Special Report evaluated FIT-DNA for CRC screening. The report found the Imperiale study to be of good quality but noted while FIT-DNA had higher sensitivity than FIT for various types of colorectal lesions, these results represented the diagnostic characteristics of the FIT-DNA in a single cross-sectional study. How these results would translate to reduced colorectal mortality in a longitudinal screening program has not been directly assessed. The optimal screening interval is unknown. However, decision modelling may help inform the effectiveness of CRC screening by indirect means.

In 2016, Knudsen et al compared different CRC screening strategies using microsimulation modeling techniques to inform the U.S. Preventive Services Task Force CRC screening recommendations (see Table 1). Diagnostic characteristics of FIT-DNA from the study by Imperiale et al were incorporated into the model and screening outcomes from various screening strategies were estimated and compared. FIT-DNA was evaluated in these models using both a yearly screening strategy and an every-3-year strategy. The modeling results suggested that stool DNA screening produces outcomes within the range of the other screening strategies. FIT-DNA every 3 years is at the lower range of effectiveness, only higher than flexible sigmoidoscopy, and testing every year is at the higher range of effectiveness, only lower than colonoscopy every 10 years. In terms of complications or lifetime burden as expressed as colonoscopies, FIT-DNA appears to be in the range of other CRC screening strategies, with every year screening having higher complication and colonoscopy rates than every 3 year screening. Both measures of harm were estimated to be lower than the screening strategy of colonoscopy every 10 years. The analysis proposed a set of screening modalities that were considered model-recommendable, based on having at least 90% of the life-year gain of colonoscopy, and having met certain efficiency criteria. FIT-DNA was not selected as a model-recommended strategy because it was not considered as efficient as other stool-based strategies.

Another modeling study, sponsored by the manufacturer of Cologuard, showed similar findings. Compared to colonoscopy every 10 years, yearly FIT-DNA was estimated to produce similar reductions in CRC incidence and mortality. Every 3-year and every 5-year testing produced less reduction in CRC incidence and mortality. Colonoscopy every 10 years was estimated to decrease CRC incidence by 65%, whereas FIT-DNA every 3 years reduced CRC incidence by 57% and FIT-DNA every 5 years reduced CRC incidence by 52%.
Table 1. Outcomes of CRC Screening Strategies Over a Lifetime, in Order of Life-Years Gained, From the U.S. Preventive Services Task Force

<table>
<thead>
<tr>
<th>Screening Method and Screening Interval</th>
<th>Life-Years Gained per 1000 Screened</th>
<th>CRC Deaths Averted per 1000 Screened</th>
<th>Complications of Screening and Follow-Up per 1000 Screened</th>
<th>Lifetime No. of Colonoscopies per 1000 Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible sigmoidoscopy, 5 y</td>
<td>221</td>
<td>20</td>
<td>10</td>
<td>1820</td>
</tr>
<tr>
<td>FIT-DNA, 3 y</td>
<td>226</td>
<td>20</td>
<td>9</td>
<td>1714</td>
</tr>
<tr>
<td>FIT, 1 y</td>
<td>244</td>
<td>22</td>
<td>10</td>
<td>1757</td>
</tr>
<tr>
<td>FOBT, 1 y</td>
<td>247</td>
<td>22</td>
<td>11</td>
<td>2253</td>
</tr>
<tr>
<td>CT colonography, 5 y</td>
<td>248</td>
<td>22</td>
<td>10</td>
<td>1743</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy, 10 y + FIT, 1 y</td>
<td>256</td>
<td>23</td>
<td>11</td>
<td>2289</td>
</tr>
<tr>
<td>FIT-DNA, 1 y</td>
<td>261</td>
<td>23</td>
<td>12</td>
<td>2662</td>
</tr>
<tr>
<td>Colonoscopy, 10 y</td>
<td>270</td>
<td>24</td>
<td>15</td>
<td>4049</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; CT: computed tomography; FIT: fecal immunochemical testing; FOBT: fecal occult blood testing.

Summary of Evidence

For individuals who are asymptomatic and at average risk of colorectal cancer (CRC) who receive fecal immunochemical testing (FIT) and DNA analysis (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 2 modelling studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. The 2 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 the test. 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. Modelling studies comparing different screening strategies have demonstrated that the diagnostic characteristics of FIT-DNA as shown in the existing studies are consistent with decreases in CRC mortality that are in the range of other accepted modalities. FIT-DNA every year is estimated to be close to but not as effective as colonoscopy every 10 years. FIT-DNA every 3 years is estimated to be less effective than most of the other accepted screening strategies. Estimates of harms and burdens are in the range of other screening strategies, but the test was considered less efficient than other methods. 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 2004 study by Imperiale et al which evaluated a different test and should be considered obsolete. This includes 2008 guidelines from the American Cancer Society, 2012 guidelines from the American College of Physicians, and 2008 guidelines from the American College of Gastroenterology.

National Comprehensive Cancer Network

The 2015 National Comprehensive Cancer Network guidelines (v.1.2016) for colorectal cancer (CRC) reviewed the study of Cologuard by Imperiale et al, and do not currently recommend FIT-DNA as a primary screening modality. However, FIT-DNA is listed in the set of stool-based screening strategies options, with the caveat that the screening interval is uncertain, but cites Berger et al as recommending 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 June 2016.14 CRC screening is recommended starting at age 50 years and continuing until age 75 years (A recommendation). The recommendation statement reviews 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....”

Medicare National Coverage
In October 2014, a Centers for Medicare & Medicaid Services (CMS) 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”15:

- “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 CRC (no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn’s Disease and ulcerative colitis; no family history of CRCs or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).”

All other stool DNA tests not otherwise specified above remain nationally noncovered.

As noted in the CMS decision memo, the optimal screening interval for Cologuard is unknown. In the interim, CMS 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Screening and Risk Factors of Colon Neoplasia</td>
<td>1600</td>
<td>Dec 2016</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Documented risk of colorectal cancer (e.g., low, average, high)
  - Documented personal or family history risk factors (as applicable)
  - Name of test
- Prior colonoscopy procedure report(s)

**Post Service**

- Laboratory report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms.
of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/NMN**
The following services may be considered medically necessary when policy criteria are met. Services may be considered not medically necessary when policy criteria are not met.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81528</td>
<td>Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2005</td>
<td>Policy Review Reviewed CTAF February 2005 technology assessment regarding PreGen-Plus testing</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2005</td>
<td>Administrative Review Re-confirmation USPTF statement; no policy modifications</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>12/07/2006</td>
<td>Policy Revision Indications updated - BCBSA MPP</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/19/2009</td>
<td>Policy Revision</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/06/2012</td>
<td>Policy title change from Stool DNA Samples for Colorectal Cancer Screening without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/22/2013</td>
<td>Coding Update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>01/30/2015</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>07/31/2015</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>10/30/2015</td>
<td>Administrative update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>01/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>04/01/2016</td>
<td>Policy title change from Fecal DNA Analysis for Colorectal Cancer Screening Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/01/2017</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance
with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.