Medical Policy

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

Professional
Original Effective Date: August 8, 2016
Revision Date(s): August 8, 2016; January 1, 2017
Current Effective Date: January 1, 2017

Institutional
Original Effective Date: August 8, 2016
Revision Date(s): August 8, 2016; January 1, 2017
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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
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<td>• Who are asymptomatic and at average or high risk of colorectal cancer</td>
<td>• Stool DNA testing</td>
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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), or colonoscopy. The currently available stool DNA
test combines FIT and DNA analysis and will be referred to as FIT-DNA in this medical policy.

**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 (eg, hypermethylation of specific genes) have also been detected. CRC is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability) 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 that detect these genetic alterations in the DNA from shed CRC cells isolated from stool samples.

**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 for the presence 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 of previously marketed tests, PreGen-Plus™, 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 FDA. On January 13, 2006, 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™, developed by OncoMethylome Sciences, which detects aberrant methylation of the vimentin (\( hV \)) gene. This test was offered as a laboratory-developed test, not subject to FDA regulation.
POLICY
A. DNA analysis of stool samples using Cologuard™ may be considered **medically necessary** as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 50 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval:

1. Guaiac-based fecal occult blood test in the past year, or
2. Fecal immunochemical test in the past year, or
3. Multitargeted stool DNA test in the past 3 years, or
4. Colonoscopy in the past 10 years, or
5. CT colonography in the past 5 years, or
6. Flexible sigmoidoscopy in the past 5 years.

B. In individuals who are considered candidates for Cologuard™ screening, repeat testing at intervals of every 3 years may be considered **medically necessary**.

C. DNA analysis of stool samples is considered **experimental / investigational** when the criteria above are not met and for all other indications including post colorectal cancer diagnosis surveillance.

D. All other screening stool DNA tests are considered **experimental / investigational**.

Policy Guidelines
1. Average risk of developing colorectal cancer include those individuals who have 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.

2. Asymptomatic individuals include those who have 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.

RATIONALE
This evidence review was regularly updated with searches of the MEDLINE database. The most recent literature review was performed for the period through September 1, 2016.

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 regarding 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.

Lacking direct evidence of screening in reducing cancer mortality, the critical parameters in the evaluation of a screening test are the diagnostic performance characteristics (ie, 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 (ie, fecal occult blood testing [FOBT], 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 currently recommended cancer screening modalities.

For patients at average to moderate risk for CRC, organizations such as the U.S Preventive Services Task Force recommend 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, and the detection of cancer-associated DNA 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 called 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 multitarget 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 colon 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 lesion, 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 Alaska 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 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 1-time cross-sectional study. How these study 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 modeling 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>
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<tr>
<td>FIT, 1 y</td>
<td>244</td>
<td>22</td>
<td>10</td>
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<tr>
<td>FOBT, 1 y</td>
<td>247</td>
<td>22</td>
<td>11</td>
<td>2253</td>
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<tr>
<td>CT colonography, 5 y</td>
<td>248</td>
<td>22</td>
<td>10</td>
<td>1743</td>
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<tr>
<td>Flexible sigmoidoscopy, 10 y + FIT, 1 y</td>
<td>256</td>
<td>23</td>
<td>11</td>
<td>2289</td>
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<tr>
<td>FIT-DNA, 1 y</td>
<td>261</td>
<td>23</td>
<td>12</td>
<td>2662</td>
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<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 modeling 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. Modeling 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.

Practice Guidelines and Position Statements
Several recommendations of specialty organizations regarding fecal DNA testing were based on largely on the 2004 study by Imperiale et al summarized previously, and should be considered obsolete.9 This includes 2008 guidelines from the American Cancer Society,10 2012 guidelines from the American College of Physicians,11 and 2008 guidelines from the American College of Gastroenterology.12

National Comprehensive Cancer Network
The 2015 National Comprehensive Cancer Network guidelines for CRC reviewed the study of Coloregard by Imperiale et al,1 and do not currently recommend stool DNA testing as a primary screening modality.13 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 al14 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...”

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>
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<tbody>
<tr>
<td>Ongoing</td>
<td>Screening and Risk Factors of Colon Neoplasia</td>
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<td>Dec 2016</td>
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NCT: national clinical trial.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

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

ICD-10 Diagnoses

Z12.10 Encounter for screening for malignant neoplasm of intestinal tract, unspecified
Z12.11 Encounter for screening for malignant neoplasm of colon
Z12.12 Encounter for screening for malignant neoplasm of rectum

REVISIONS

<table>
<thead>
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<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>08-08-2016</td>
<td>Policy added to the bcbsks.com web site on 07-07-2016 with an effective date of 08-08-2016.</td>
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<tr>
<td>01-01-2017</td>
<td>Updated Description section.</td>
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<td>In Policy section:</td>
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<td>▪ Removed entire previous policy statement, &quot;DNA analysis of stool samples is considered experimental / investigational as a screening technique for colorectal cancer in patients at average-to-high risk of colorectal cancer.&quot;</td>
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<td></td>
<td>▪ Added &quot; A. DNA analysis of stool samples using Cologuard™ may be considered medically necessary as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 50 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval: 1. Guaiac-based fecal occult blood test in the past year, or 2. Fecal immunochemical test in the past year, or 3. Multitargeted stool DNA test in the past 3 years, or Colonoscopy in the past 10 years, or 4. CT colonography in the past 5 years, or 5. Flexible sigmoidoscopy in the past 5 years. B. In individuals who are considered candidates for Cologuard™ screening, repeat testing at intervals of every 3 years may be considered medically necessary. C. DNA analysis of stool samples is considered experimental / investigational when the criteria above are not met and for all other indications including post colorectal diagnosis surveillance. D. All other screening stool DNA tests are considered experimental / investigational.&quot;</td>
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<td>▪ Added &quot;Policy Guidelines 1. Average risk of developing colorectal cancer include those individuals who have 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. 2. Asymptomatic individuals include those who have 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.&quot;</td>
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<td>Updated Rationale section.</td>
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Contains Public Information
REFERENCES


Other References
1. Blue Cross and Blue Shield of Kansas Family Medicine Liaison Committee, August 2016.