Medical Policy

BlueCross BlueShield of Kansas
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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; December 20, 2017; January 4, 2019
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Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic and at average risk of colorectal cancer	Interventions of interest are: • FIT-DNA testing	Comparators of interest are: • Established tests for colorectal cancer screening	Relevant outcomes include: • Overall survival • Disease-specific survival

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 is referred to as FIT-DNA in this medical policy.

OBJECTIVE

The objective of this policy 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.

BACKGROUND

Colorectal Cancer

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 *KRAS* are most frequently altered. Variants in adenomatous polyposis coli (*APC*) 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 CRC) and in subgroups of patients with sporadic colon carcinoma. Tumor-associated gene variants 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.

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 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 variants in the *p53*, *APC*, and *KRAS* genes; the BAT-26 microsatellite instability marker; and incorporates the DNA Integrity Assay (DIA®). PreGen-Plus™ has not been cleared by FDA. In January 2006, 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.

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.
3. Individuals with an estimated life expectancy of less than 10 years should not be screened for colorectal cancer.

RATIONALE

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through September 6, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Fecal Immunochemical Testing–DNA Testing

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 with 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.

The diagnostic performance characteristics of the currently accepted screening options (ie, fecal occult blood testing, fecal immunochemical testing (FIT), flexible sigmoidoscopy, double-contrast barium enema) have been established using colonoscopy as the criterion standard. Modeling studies and clinical trial evidence on some of the screening modalities have allowed some confidence in the effectiveness of several cancer screening modalities. 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.

Clinical Context and Test Purpose

The purpose of stool DNA testing in patients who are at average risk of CRC is to inform a decision whether to proceed to colonoscopy.

The question addressed in this evidence review is this: Does testing of stool DNA improve the net health outcome for asymptomatic individuals at average risk of CRC who are undergoing routine CRC screening?

The following PICOTS were used to select literature to inform this review.

Patients

The evidence discussed pertains only to screening individuals at average risk of CRC. There are no studies of stool DNA testing for screening individuals at high risk of CRC.

Interventions

The evidence discussed is restricted to studies evaluating Cologuard, the only test approved by the Food and Drug Administration, which combines FIT and DNA analysis (FIT-DNA).

Comparators
The criterion standard for CRC screening is colonoscopy every 10 years.

Outcomes
The important outcome of interest in cancer screening is a reduction in the mortality and morbidity due to cancer. This is ideally determined by randomized controlled trials. However, for colon cancer screening, many of the recommended tests have not been evaluated with clinical trials. When lacking direct evidence that a screening test reduces cancer mortality, the critical parameters in the evaluation 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. Modeling studies have evaluated the robustness and quantity of health benefit of various screening tests when clinical trial evidence is lacking.

Timing
The time of interest is during standard-interval screening. For patients of average risk undergoing colonoscopy, this is every 10 years beginning at age 50. CRC screening with Cologuard may be needed more frequently.

Setting
A stool sample is collected at home, prepared in a collection kit, and shipped to the manufacturer for analysis.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Preliminary studies of the FIT-DNA (Cologuard), which was eventually evaluated in the large-scale screening study by Imperiale et al (2014),[1] were conducted by Ahlquist et al (2012)[2,3] and Lidgard et al (2013).[4] 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.[2] Another smaller study of this same test showed a sensitivity of 87% for detecting CRC and 82% sensitivity for detecting adenomas.[3] In the Lidgard study, 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.[4] 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 might have been biased.

A large-scale evaluation of this test in a screening population was published by Imperiale et al (2014), who compared the FIT-DNA in 12,000 asymptomatic persons at average risk for CRC.[1] The results of this study supported the U.S. Food and Drug Administration 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% confidence interval [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, the 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, the 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 by Redwood et al (2016).[5] 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 or 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: Clinically Valid

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 Imperiale study 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There are no studies evaluating direct health outcomes of a longitudinal screening program using Cologuard.

A comparative effectiveness modeling study by Barzi et al (2017) found that colonoscopy was the most effective screening strategy with the highest life years gained (0.022 life years) and CRCs prevented (n=1068), and the lowest total cost.[6] Modeling for FIT-DNA every year or every other year found 0.011 life years gained, 647 CRCs prevented, and a higher total cost. The main reason for the difference in CRCs prevented was due to the detection of precancerous polyps. The study found that if the sensitivity of FIT-DNA for adenomas increased, it could surpass the sensitivity of colonoscopy. An unexpected consequence of a positive FIT-DNA test may be to improve the quality of the subsequent colonoscopy.[7]

Knudsen et al (2016) compared different CRC screening strategies using microsimulation modeling techniques to inform the U.S. Preventive Services Task Force CRC screening recommendations (see Table 1).[8] Diagnostic characteristics of FIT-DNA from the Imperiale study 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.

Table 1. Outcomes of CRC Screening Strategies Over a Lifetime, in Order of Life-Years Gained

Screening Method and Screening Interval	Life-Years Gained per 1000 Screened	CRC Deaths Averted per 1000 Screened	Complications of Screening and Follow-Up per 1000 Screened	Lifetime No. of Colonoscopies per 1000 Screened
Flexible sigmoidoscopy, 5 y	221	20	10	1820
FIT-DNA, 3 y	226	20	9	1714
FIT, 1 y	244	22	10	1757
FOBT, 1 y	247	22	11	2253

Screening Method and Screening Interval	Life-Years Gained per 1000 Screened	CRC Deaths Averted per 1000 Screened	Complications of Screening and Follow-Up per 1000 Screened	Lifetime No. of Colonoscopies per 1000 Screened
CT colonography, 5 y	248	22	10	1743
Flexible sigmoidoscopy, 10 y + FIT, 1 y	256	23	11	2289
FIT-DNA, 1 y	261	23	12	2662
Colonoscopy, 10 y	270	24	15	4049

Adapted from Knudsen et al (2016).[8]
CRC: colorectal cancer; CT: computed tomography; FIT: fecal immunochemical testing; FOBT: fecal occult blood testing.

Another modeling study, by Berger et al (2016), sponsored by the manufacturer of Cologuard, showed similar findings.[9] Compared with 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%.

A TEC Special Report (2014) evaluated FIT-DNA for CRC screening.[10] The report found the Imperiale study[1] 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 one-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.

Section Summary: Clinically Useful
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.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic and at average risk of CRC who receive 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.

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.[11] This includes 2008 guidelines from the American Cancer Society,[12] 2012 guidelines from the American College of Physicians,[13] and 2009 guidelines from the American College of Gastroenterology.[14]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.1.2018) for colorectal cancer (CRC) screening includes use of fecal immunochemical testing–DNA (FIT-DNA) to screen patients with average risk for colon cancer.[15] Following a negative test, the recommendation is to rescreen with any modality after 3 years. Use of FIT-DNA tests is not described for screening of high-risk individuals.

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 provided recommendations for CRC screening in 2017.[16] 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.[17] Regular screening with either a structural examination (ie colonoscopy) or 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

The U.S. Preventive Services Task Force (USPSTF) published its most recent recommendations for colorectal cancer screening in 2016.[18] Colorectal cancer screening is 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 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….” 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.”

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01647776	Screening and Risk Factors of Colon Neoplasia	1600	Mar 2019
NCT02419716[a]	A Longitudinal Study of Cologuard™ in an Average Risk Population Assessing a Three Year Test Interval	2404	Jul 2020

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored 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

08-08-2016	Policy added to the bcbsks.com web site on 07-07-2016 with an effective date of 08-08-2016.
01-01-2017	Updated Description section.
	In Policy section: ▪ Removed entire previous policy statement, "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."

	▪ Added " 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." ▪ Added "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."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes: Z12.10, Z12.11, Z12.12.
	Updated References section.
12-20-2017	Updated Description section.
	In Policy section: ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
01-04-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.

REFERENCES

1. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* Apr 3 2014;370(14):1287-1297. PMID 24645800
2. Ahlquist DA, Zou H, Domanico M, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. *Gastroenterology.* Feb 2012;142(2):248-256; quiz e225-246. PMID 22062357
3. Ahlquist DA, Taylor WR, Mahoney DW, et al. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. *Clin Gastroenterol Hepatol.* Mar 2012;10(3):272-277 e271. PMID 22019796
4. Lidgard GP, Domanico MJ, Bruinsma JJ, et al. Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia. *Clin Gastroenterol Hepatol.* Oct 2013;11(10):1313-1318. PMID 23639600
5. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for screening detection of colorectal neoplasia in Alaska Native people. *Mayo Clin Proc.* Jan 2016;91(1):61-70. PMID 26520415
6. Barzi A, Lenz HJ, Quinn DI, et al. Comparative effectiveness of screening strategies for colorectal cancer. *Cancer.* May 01 2017;123(9):1516-1527. PMID 28117881

7. Johnson DH, Kisiel JB, Burger KN, et al. Multitarget stool DNA test: clinical performance and impact on yield and quality of colonoscopy for colorectal cancer screening. *Gastrointest Endosc.* Mar 2017;85(3):657-665.e651. PMID 27884518
8. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. *JAMA.* Jun 21 2016;315(23):2595-2609. PMID 27305518
9. Berger BM, Schroy PC, 3rd, Dinh TA. Screening for colorectal cancer using a multitarget stool DNA test: modeling the effect of the intertest interval on clinical effectiveness. *Clin Colorectal Cancer.* Sep 2016;15(3):e65-74. PMID 26792032
10. Blue Cross Blue Shield Association Technology Evaluation Center. Special Report: Fecal DNA Analysis for Colorectal Cancer Screening. *TEC Assessment.* 2014;Volume 29:Tab 8.
11. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med.* Dec 23 2004;351(26):2704-2714. PMID 15616205
12. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin.* May-Jun 2008;58(3):130-160. PMID 18322143
13. Qaseem A, Denberg TD, Hopkins RH, Jr., et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. *Ann Intern Med.* Mar 6 2012;156(5):378-386. PMID 22393133
14. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol.* Mar 2009;104(3):739-750. PMID 19240699
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Accessed October 17, 2018.
16. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* Jul 2017;153(1):307-323. PMID 28600072
17. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin.* Jul 2018;68(4):250-281. PMID 29846947
18. U. S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA.* Jun 21 2016;315(23):2564-2575. PMID 27304597
19. Centers for Medicare & Medicaid Services (CMS). Decision Memo for Screening for Colorectal Cancer - Stool DNA Testing (CAG-00440N). 2014; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=277 Accessed October 18, 2018.

Other References

1. Blue Cross and Blue Shield of Kansas Family Medicine Liaison Committee, August 2016; February 2017.
2. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, June 2017.