POLICY STATEMENT:

I. Based upon our criteria and review of peer-reviewed literature, DNA analysis of stool samples using the Cologuard® multi-targeted stool DNA test is considered medically appropriate for colorectal cancer screening for average risk, asymptomatic individuals between the ages of 50 and 85 years.

II. Based upon our criteria and review of peer-reviewed literature, all other screening stool DNA tests are considered investigational.

Refer to Corporate Medical Policy #2.02.11 regarding Genetic Testing for Inherited Susceptibility to Colorectal Cancer: Familial Adenomatous Polyposis and Hereditary Nonpolyposis Colorectal Cancer.

Refer to Corporate Medical Policy #11.01.03 Experimental and Investigational Services.

Refer to Corporate Medical Policy #11.01.12 regarding Screening Tests.

POLICY GUIDELINES:

I. The Cologuard® test is repeated at intervals of every 3 years.

II. 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.

III. Asymptomatic individuals include those individuals 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.

IV. It is important to note that because the FDA does not regulate diagnostic tests unless they are sold as kits, companies can market these so-called “home-brew” tests without FDA approval. Laboratories involved in fecal DNA testing are regulated by the Clinical Laboratory Improvement Act (CLIA) regulations of the FDA.

DESCRIPTION:

Colorectal cancer is the third most frequently diagnosed cancer in the USA. Screening for colorectal cancer lowers both the mortality and incidence of the disease and is recommended for people age 50 or older. Interest in screening has increased in recent years but compliance remains low. Colonoscopy, sigmoidoscopy, and double-contrast barium enema are standard tests for neoplasia but are limited by their invasive nature, requirements for trained personnel, cost and acceptance by patients. Tests for fecal occult blood are noninvasive and useful however, the relatively high false-positivity rates and other problems have led to a search for more specific non-invasive tests. In this regard, assays for mutations in fecal DNA are seen as promising. Gene mutations that characterize colorectal neoplasia are detectable in exfoliated epithelial cells in the stool. Whereas neoplastic bleeding is intermittent, epithelial shedding is continual, potentially making fecal DNA testing more sensitive than other methods for screening.
Several genetic alterations have been associated with colorectal cancer. 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. Colorectal cancer is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability or MSI) in patients with hereditary nonpolyposis colorectal cancer (HNPC) and in a subgroup of patients with sporadic colon carcinoma. Since cancer cells are shed into stool, tests have been developed that detect these genetic alterations in the DNA from shed colorectal cancer cells isolated from stool samples. This has been proposed for use in screening two populations of patients for colon cancer:

I. **Known or suspected carriers of HNPCC mutations, considered at high risk of developing colorectal cancer.** In this setting, testing of fecal samples could be used to monitor patients over time for development of colorectal cancer. The test may be used either in lieu of routinely scheduled surveillance colonoscopies or during intervals between scheduled colonoscopies. Those patients testing positive for cancer-related genetic alterations could be further evaluated with colonoscopy.

II. **In patients at average risk of colorectal cancer.** In this setting, testing of fecal samples could be offered in lieu of, or as an adjunct to, other recommended colorectal cancer screening tests, including fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema.

In addition, investigators are beginning to study changes in this assay following surgery for colon cancer.

**RATIONALE:**

The Cologuard® (Exact Sciences, Madison, WI) was approved by the FDA on August 11, 2014. The test includes molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, and β-actin and an immunochromat test assay for human hemoglobin.

The BCBS Association TEC Special Report (2014) evaluated fecal DNA analysis for CRC screening. The report found the Imperiale2 study to be of good quality but noted while fecal DNA testing had higher sensitivity than FIT for various types of colorectal lesions, these results represent the diagnostic characteristics of the fecal DNA test in a 1-time cross sectional study. How these study results may translate to reduced colorectal mortality in a screening program are uncertain. The study of the diagnostic characteristics of a test for detecting cancer and cancer precursors does not establish efficacy for prevention of CRC. Effective screening for CRC requires a screening program with established screening intervals and appropriate follow-up for positive tests. Given what is known about relative efficacy of different screening strategies from the results of modeling studies, the fecal DNA test would produce equivalent or better outcomes than FIT if both were used annually. However, the fecal DNA test has a considerably higher false-positive rate and would therefore consume greater health care resources than FIT at this screening frequency. Formal modeling studies of the fecal DNA test are needed to estimate the efficacy of the test in preventing CRC and help determine the optimal strategy for its use.

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 (Levin et al.) have noted the benefits of fecal analysis of DNA for colorectal cancer screening and surveillance include the fact that the test is noninvasive, causes no physical harm to the patient, appears to be accepted by both patients and providers, is not dependent upon the detection of occult bleeding and requires only a single stool sample. The limitations of the test include, but are not limited to the following: (1) Test sensitivity is based on a panel of markers that appear to identify some, but not all colorectal cancers; (2) The cost of the test is significantly higher than the cost of other stool tests; (3) The interval at which the test should be performed is unclear; and (4) The uncertainty around how positive results without evidence of cancer or advanced lesions on follow-up should be interpreted and whether or not these patients require an alternate plan for ongoing surveillance.

Draft recommendations released by the US Preventative Services Task Force (USPSTF) in 2015 refer to fecal DNA testing as a “FIT-DNA” test and categorize the test as an alternative test. Multitargeted stool DNA testing can be viewed simply as a more sensitive but less specific stool-based test than FIT. However, the theoretical advantage of the test is
the stool DNA component. At present, there is only one fair-quality study that compares the sensitivity and specificity of a single FIT-DNA test with FIT. While modeling can be used to understand the impact of the test’s reduced specificity and increased false-positive rate, empiric evidence is lacking on appropriate follow-up of abnormal results, making it difficult to accurately bound the potential net benefit of this screening test.

The National Cancer Institute (NCI) (11/12/14) report that while most expert groups generally recommend high-sensitivity FOBT, sigmoidoscopy, and colonoscopy as standard colorectal cancer screening tests, there are several other types of tests. Cologuard® is an example of one of these tests which is able to detect tiny amounts of blood in stool (with an immunochemical test similar to FIT) as well as nine DNA biomarkers in three genes that have been found in colorectal cancer and precancerous advanced adenomas. The DNA comes from cells from the lining of the colon and rectum that collect in stool as it passes through the large intestine and rectum. As with both types of FOBT, the stool sample for the Cologuard® test is collected by the patient using a kit; the sample is mailed to a laboratory for testing. A computer program analyzes the results of the two tests (blood and DNA biomarkers) and provides a finding of negative or positive. People who have a positive finding with this test are advised to undergo a colonoscopy. In August 2014, the FDA approved the Cologuard® test. At the same time, in a pilot program known as parallel review, the Centers for Medicare & Medicaid Services proposed national coverage for this test. This test is still being evaluated to see where it fits in screening guidelines. To date, it has not been incorporated into clinical practice guidelines or recommended by the U.S. Preventive Services Task Force as a method to screen for colorectal cancer. The Task Force is currently updating its guideline and is examining recent evidence on the Cologuard® test.

**CODES:**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<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>
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**REFERENCES:**


KEY WORDS:
Colorectal cancer screening, DNA Analysis, Fecal DNA, Pre-Gen tests.
There is currently a National Coverage Determination (NCD) for Colorectal Cancer Screening Tests. Please refer to the following NCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=281&ncdver=5&bc=AgAAgAAAAQAAAA%3d%3d&

There is currently a Decision Memo for Screening for Colorectal Cancer – Stool DNA Testing. Please refer to the following CMS website for Medicare Members: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=277