

DNA Analysis of Stool for Colon Cancer Screening (Cologuard®)

Policy MP-006

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.

Description:

Colorectal cancer (CRC) is one of the most preventable cancers, yet cancer is the second leading cause of deaths in the United States. In 2021, there will be an estimated 104,270 new cases of colon cancer, 45,230 of rectal cancer and approximately 52,980 people will die from CRC. Without preventive measures, approximately 4-5% of Americans will develop colorectal cancer at some point in their lives. On August 11, 2014, Cologuard® was approved by the FDA. This is the first stool-based colorectal screening test that detects the presence of red blood cells and DNA mutations. Cologuard utilizes a multi-target approach to detect DNA and hemoglobin biomarkers associated with colorectal cancer and pre-cancer.

Eleven biomarkers are targeted and provide a stronger connection between colorectal cancer and pre-cancer. Methylation, mutation, and hemoglobin results are combined in the laboratory analysis to provide a single positive or negative reportable result.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans covers Cologuard® for stool colon cancer screening once every 3 years, for average risk members ages 45-75 years when the test is recommended by their physician and it is not within the standard interval of another screening test.

U of U Health Plans does NOT cover any other method of DNA analysis of stool testing for colon cancer screening. Use of this testing is considered investigational/experimental as current evidence is inadequate to show that stool DNA testing with any test other than Cologuard® is an effective way to screen for colon cancer and can improve health outcomes for patients.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at:

<http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

3. Medicare Plans

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at:

<http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

Clinical Rationale

As with any diagnostic test, the key outcomes are the diagnostic performance (i.e., sensitivity, specificity, positive and negative predictive value) compared to a gold standard, and consideration of how the results of the test will be used to benefit patient management. Of the various screening options (fecal occult blood testing, flexible sigmoidoscopy, double contrast barium enema, colonoscopy), colonoscopy is considered the gold standard. For example, in patients considered at high risk for colorectal cancer, due either to a family history or hereditary nonpolyposis colorectal cancer (HNPCC) mutation, colonoscopy at varying intervals is recommended by the American Society of Colorectal Surgeons, the American Gastroenterological Society, and the American Cancer Society. Therefore, patients at high risk of colorectal cancer with suspected or known mutations of the HNPCC gene, should have a colonoscopy.

For patients at average risk to moderate risk for colorectal cancer, the above organizations also recommend colonoscopy starting at age 45, with an interval of 10 years, as one screening option. In addition, other screening techniques are also considered options, and the choice of screening option may be dictated in part by patient preference. Many authors have noted the low patient acceptance of current colorectal cancer screening options, particularly flexible sigmoidoscopy and colonoscopy; at the present time only about 40% of eligible patients undergo screening for colon cancer. Advocates of genetic testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations. Therefore, for patients at average to moderate risk of colon cancer, genetic testing of stool samples will be compared to colonoscopy and also to fecal occult blood testing, the other entirely noninvasive technique. Patient acceptance of the different options is also a relevant outcome as a technique to increase screening compliance.

The available published, peer-reviewed data focus on the technical feasibility of genetic testing of stool samples. For example, Ahlquist and colleagues published a study focusing on the use of a multi-target assay panel for colorectal cancer screening. This retrospective study included 22 patients with known colorectal cancer, 11 with adenomas, and 28 patients with normal colonoscopy examinations. It was not reported whether or not these patients were considered at average, moderate, or high risk for cancer.

The panel included 15 sites on the KRAS gene, p53 and adenomatous polyposis genes, analysis of BAT-26, and highly amplifiable DNA. The panel detected 20 of the 22 cancers (91%) and 9 of the 11 adenomas (82%). The same panel assay was performed on tissue samples from 19 of the 21 cancers. The presence of point mutations was concordant in tissue and stool analysis in 12 of the 19 paired specimens. The authors attributed the high neoplasm detection rate of the stool analysis to the efficient isolation of human DNA from the stool, but also commented that cancers represented in this study were large (median 4 cm in diameter) and symptomatic, and thus may shed more aberrant DNA than smaller cancers. For the 11 patients with adenomas, the results of the stool DNA testing were compared to fecal occult blood testing. While the fecal occult blood testing was negative in all these patients, genetic mutations were detected in the stool sample of all patients with adenomas.

Dong and colleagues performed a study of stool DNA isolated from 51 colorectal cancer patients. The stool DNA and tumor tissue were evaluated for the presence of mutations in the genes p53, BAT-26, and KRAS. The 3 genetic markers together detected 71% of the 51 patients. Of interest, no genetic mutations were identified in the tumor tissue of 15 patients. Other feasibility studies using a variety of markers have also focused on patients with known cancers, and thus these studies do not duplicate the targeted populations for screening. No prospective studies were found in the published literature comparing the diagnostic performance of analysis of DNA from stool samples to either colonoscopy or fecal occult blood testing among either average to moderate risk to high risk patients. For average risk patients, the published feasibility studies focused on the use of different panels of DNA markers. No study identified focused on the use of the single marker, BAT-26, in patients with known or suspected mutations of the HNPCC gene. No studies discussed how the use of DNA analysis in stool samples might supplant or enhance current screening options.

Notably, the study by Imperiale et al., was a non-randomized, cross-sectional, multicenter trial of 9,989 patients who were included in the primary analysis. Results from a single, albeit large, study show that Cologuard has better sensitivity and worse specificity than FIT across various clinical manifestations. The other 2 included studies are 1) a model that is based on incorrect pricing information and 2) a study unique to a specific population no relevant in a broad sense. Though the test has a recommended use of once every 3 years, 1 systematic review illustrated its benefit is best if used annually. This may impact its cost effectiveness in real world settings.

A published update of the Hayes updated their Molecular Technology Assessment of Cologuard on March 29, 2021 noted 12 studies with no studies for analytical validity, 10 studies for clinical validity, and 2 studies for clinical utility. The evidence for clinical validity demonstrates strong correlation of Cologuard with neoplastic colonoscopy findings, but the evidence is largely limited to 1 test episode or follow-up of just a few years. Evidence of clinical utility is limited but suggests that Cologuard may have a positive influence on follow-up colonoscopy procedures and demonstrates high patient compliance with Cologuard, which may substantially improve compliance with CRC screening in some populations. The review concluded there is limited but consistent published evidence supporting the use of Cologuard for CRC screening in average-risk patients to detect CRC and colorectal neoplasms.

A single, small study evaluating change in patient management and 2 test preference studies do not provide sufficient evidence of clinical utility. Furthermore, these studies do not demonstrate improved outcomes. In the future, blood-based CRC screening may have a role in CRC screening, such as for patients who decline the usual recommended testing techniques; however, there is currently not enough evidence demonstrating a positive change in management or an improvement in outcomes to justify its use without additional studies.

In 2020, UpToDate reviewed updated and current literature for the screening of colorectal cancer by multitargeted stool DNA tests with fecal immunochemical testing (Cologuard). The evidence of effectiveness of mt-sDNA is based on comparison with studies of other screening strategies and modelling studies. No randomized trials of mt-sDNA for screening for CRC were found. Sensitivity for CRC appears to exceed that for FIT, no matter what stage. However, evidence for improved clinical outcomes is indirect. Also noted is that stool-based screening tests for colon cancer have a higher detection rate for CRC and less so in detecting precancerous adenoma polyps. Every positive CRC screening test other than colonoscopy should be followed immediately by a colonoscopy. A negative screening result should be re-tested for the recommended interval of every 3 years.

The American College of Gastroenterology (ACG) is currently reviewing their existing colorectal cancer screening guidelines, the current recommendations are as follows:

- Tests that prevent cancer are preferred over those that only detect cancer;
- The preferred colorectal cancer prevention test is colonoscopy every 10 years beginning at age 45;
- For patients who decline colonoscopy or another cancer prevention test, the preferred cancer test is FIT to be conducted annually (alternative cancer detection tests include annual Hemoccult Sensa® and fecal DNA testing every 3 years).

The National Comprehensive Cancer Network (NCCN) CRC screening guidelines (Version 2.2021) recommend the inclusion of mt-sDNA-based testing as a potential screening modality in average risk patients aged ≥45. However, data to help determine screening intervals and how mt-sDNA testing may fit into an overall screening program are limited. Intervals of every 3 years has been recommended by the FDA. In addition, there are no or limited data in high-risk individuals who refuse colonoscopy or have limited access to conventional screening strategies; therefore, the use of mt-sDNA-based testing should be individualized in these cases.

Applicable Coding

CPT Codes

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 (Cologuard®)

HCPCS Codes

No applicable codes

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