Cologuard® colorectal cancer screening test is a registered trademark of Exact Sciences Corporation.

Cologuard® Physician Brochure

Indications for Use

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 (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.

Contraindications

Cologuard is intended for use with patients, age 50 years and older, at average risk who are typical candidates for CRC screening. Cologuard was not clinically evaluated for the following types of patients:

- Patients with a history of colorectal cancer, adenomas, or other related cancers.
- Patients who have had a positive result from another colorectal cancer screening method within the last 6 months.
- Patients who have been diagnosed with a condition that is associated with high risk for colorectal cancer. These include but are not limited to:
  - Inflammatory Bowel Disease (IBD)
  - Chronic ulcerative colitis (CUC)
  - Crohn's disease
  - Familial adenomatous polyposis (FAP)
  - Family history of colorectal cancer
- Patients who have been diagnosed with a relevant familial (hereditary) cancer syndrome, such as Hereditary non-polyposis colorectal cancer syndrome (HNPCCC or Lynch Syndrome), Peutz-Jeghers Syndrome, MYH-Associated Polyposis (MAP), Gardner's syndrome, Turcot's (or Crail's) syndrome, Cowden's syndrome, Juvenile Polyposis, Cronkhite-Canada syndrome, Neurofibromatosis, or Familial Hyperplastic Polyposis.

Warnings and Precautions

- The performance of Cologuard has been established in a cross sectional study (i.e., single point in time). Programmatic performance of Cologuard (i.e., benefits and risks with repeated testing over an established period of time) has not been studied. Performance has not been evaluated in adults who have been previously tested with Cologuard. Non-inferiority or superiority of Cologuard programmatic sensitivity as compared to other recommended screening methods for CRC and AA has not been established.
- CRC screening guideline recommendations vary for persons over the age of 75. The decision to screen persons over the age of 75 should be made on an individualized basis in consultation with a healthcare provider. Cologuard test results should be interpreted with caution in older patients as the rate of false positive results increases with age.
- A negative Cologuard test result does not guarantee absence of cancer or advanced adenoma. Patients with a negative Cologuard test result should be advised to continue participating in a colorectal cancer screening program with another recommended screening method. The screening interval for this follow-up has not been established.
- Cologuard may produce false negative or false positive results. A false positive result occurs when Cologuard produces a positive result, even though a colonoscopy will not find cancer or precancerous

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polyps. A false negative result occurs when Cologuard does not detect a precancerous polyp or colorectal cancer even when a colonoscopy identifies the positive result.

- Patients should not provide a sample for Cologuard if they have diarrhea or if they have blood in their urine or stool (e.g., from bleeding hemorrhoids, bleeding cuts or wounds on their hands, rectal bleeding, or menstruation).
- To ensure the integrity of the sample, the laboratory must receive the patient specimens within 72 hours of collection. Patients should send stool samples to the laboratory according to the instructions stated in the Cologuard Patient Guide.
- Patients should be advised of the caution listed in the Cologuard Patient Guide. Patients should NOT drink the preservative liquid.
- The risks related to using the Cologuard Collection Kit are low, with no serious adverse events reported among people in a clinical trial. Patients should be careful when opening and closing the lids to avoid the risk of hand strain.

RX Only

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Cologuard Overview

Cologuard uses advanced multiple-marker, stool DNA technology to detect colorectal cancer (CRC) and advanced adenomas (AA). Cologuard is 92% sensitive for detection of CRC. Cologuard is a statistically superior noninvasive stool test for detecting CRC and AA, as shown in a head-to-head, cross-sectional clinical study of Cologuard and a commercially available fecal immunochemical test (OC FIT-CHEK, Polymedco, Inc.) ("FIT"). In the study, Cologuard specificity was 87% (the specificity calculation excluded both CRC and AA), which is lower than that of FIT.

Cologuard is designed to analyze patients' stool for the presence of 11 molecular markers, including hemoglobin and DNA markers, which may indicate the presence of colorectal cancer or advanced adenomas. Because cellular exfoliation of DNA into stool occurs continuously, Cologuard can detect pre-malignant neoplasia at early onset of abnormality.

Based on combined results of all of the DNA markers and hemoglobin, a single Cologuard result is determined. Cologuard results are qualitative, positive or negative. A patient with a positive result should be referred to a diagnostic colonoscopy. A patient with a negative result should continue with a regular screening schedule. If no result is obtained, a second stool collection may be requested.

Patient Samples for Cologuard

Patients are not required to undergo bowel preparation or follow dietary or medication restrictions in order to complete the test. Patients follow the detailed instructions in the Cologuard Patient Guide received with the collection kit, consisting of a container for collection of stool for DNA testing and a separate sampler for collection of stool for hemoglobin testing. Both of these stool samples are required to obtain a Cologuard result. Samples are sent to a qualified laboratory for processing and testing.

Cologuard Compliance Program

Cologuard includes a compliance program to handle collection kit shipment to the patient's home in addition to live representatives for patient support, patient reminders, and billing and reimbursement questions. The compliance program also provides compliance tracking for physicians to measure and improve patient compliance.

Colorectal Cancer Overview

Colorectal cancer (CRC) is the second leading cause of death from cancers affecting both men and women in the United States. One in 17 Americans will suffer from CRC during their lifetime; the lifetime risk is 35% higher for men than for women.[1] Early detection by screening has been shown to reduce CRC mortality.[2,3,4] Current guidelines for CRC screening in the average-risk population recommend initiation of screening at age 50 (age 45 for African Americans), as the incidence of both CRC and premalignant lesions increases sharply after this age.[5]

Detection of potentially pre-malignant lesions, also known as advanced adenomas (AA), is essential for CRC prevention. Advanced adenomas include any size adenomas with carcinomas in situ or high grade dysplasia (HGD), adenomas with villous growth patterns (>25%), or adenoma ≥1.0 cm in size.[6,7,8,9] Serrated lesions (polyps and sessile serrated adenoma) are typically found in the proximal colon, occur more frequently in the elderly, are often flat and inconspicuous endoscopically, and may have a more aggressive natural history than classic colorectal adenomas.[9]

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Device Description

Cologuard utilizes a multi-target approach to detect DNA and hemoglobin markers associated with CRC, as well as pre-malignant colorectal neoplasia (i.e., AA). Three independent categories of biomarkers are targeted and provide an additive association with CRC and pre-malignant colorectal neoplasia

The first category of biomarkers involves epigenetic DNA changes characterized by aberrant gene promoter region methylation. The specific methylated gene targets include N-Myc Downstream-Regulated Gene 4 (NDRG4) and the Bone Morphogenetic Protein 3 (BMP3).[10,11] NDRG4 and BMP3 have been shown to be hypermethylated in colorectal cancer.[1,10] The Cologuard procedure incorporates bisulfite conversion of non-methylated cytosine residues to uracil in the DNA sequence to enable sensitive detection of hypermethylated NDRG4 and BMP3.

The second category targets specific DNA point mutations in the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, which encodes a small GTPase that is activated transiently as a response to extracellular stimuli or signals.[12,13,14] KRAS mutations have been detected in up to 35% of colorectal cancers and the 7 mutations in Exon 2 detected by Cologuard account for 98% of KRAS mutations.[16] KRAS mutations, along with NDRG4 and BMP3 methylation markers, have been shown to be detected in the stool of subjects with colorectal neoplasia, including subjects with colorectal cancer and pre-malignant lesions.[15,16]

The third category of biomarker is non-DNA based and detects hemoglobin, which can be associated with colonic bleeding. Results from the methylation, mutation, and hemoglobin assays are combined in the laboratory analysis to determine a positive or negative reportable result or no result.

Assay Technology

The patient stool samples are processed at the laboratory to isolate the DNA for testing. Amplification and detection of methylated target DNA (NDRG4, BMP3), KRAS point mutations, and ACTB (a reference gene for quantitative estimation of the total amount of human DNA in each sample) is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTS™) technology. Multi-plexed QuARTS reactions are processed using a real-time cycler with each marker (NDRG4, BMP3, KRAS, and ACTB) monitored separately through independent fluorescent detection channels. The hemoglobin stool sample is prepared and analyzed in a quantitative Enzyme-Linked Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.

Run control samples for both the QuARTS assays and hemoglobin assay are tested along with patient samples to show that the process has been performed appropriately. Results from the methylation, mutation, and hemoglobin assays are combined during analysis to determine a positive result, negative result, or no result.

Clinical Study: Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer (DeeP-C)

Overview

Cologuard was the subject of a prospective, multi-centered, pivotal trial ("Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer: DeeP-C Study"). A total of 12,776 patients were enrolled from 90 sites, including both colonoscopy centers and primary care sites. The results of the study demonstrated the safety and effectiveness of Cologuard as a screening test for the detection of markers associated with the presence of CRC and colorectal neoplasia. Cologuard demonstrated 92.3% CRC sensitivity and 86.6% specificity (specificity in this study excludes CRC and AA), using

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colonoscopy with histopathological confirmation as the reference method. These results met the protocol-specified criteria for primary performance measures and study success. The study results exceeded the prospectively specified sensitivity threshold by nearly 20%. The study further compared CRC and AA detection by Cologuard to a commercially available fecal immunochemical test (OC FIT-CHEK, Polymedco, Inc.) ("FIT"), successfully demonstrating superiority for CRC (p=0.0018) and AA (p<0.0001) sensitivity.

Study Design

The study was designed to enroll subjects of either sex between the ages of 50 and 84 years (inclusive), who were at average risk for development of colorectal cancer and asymptomatic for gastrointestinal symptoms warranting diagnostic colonoscopy. In addition, subject enrollment was age-weighted toward a slightly older population to increase the point prevalence of colorectal cancer in this study. 64% of subjects in the actual study population were of age 65-84.

Subjects participating in the pivotal trial provided a stool sample and subsequently underwent colonoscopy within 90 days of study enrollment. Subjects collected stool samples for Cologuard and FIT testing at home. Subjects then underwent colonoscopy per standard of care. Subjects and physicians remained blinded to the results of Cologuard and the FIT. Results from Cologuard and the FIT test were compared to the results of the colonoscopy examination and histopathologic diagnosis of all significant lesions either biopsied or removed.

Negative colonoscopy findings were categorized as negative (Table 1, category 6.2). Histopathological results from biopsied tissue or excised lesions were categorized based on the most clinically significant lesion present (i.e. the index lesion) by a central pathologist according to the pre-specified standards outlined in Table 1. Sensitivity analysis was performed using positive findings in categories 1 and 2 while specificity was calculated using categories 3 through 6 (all findings excluding CRC and AA).

Table 1: Category definitions

Category	Findings
1	CRC, all stages (I-IV)
2	Advance adenoma, including the following subcategories: 2.1 – Adenoma with carcinoma in situ/high grade dyplasia, any size 2.2 – Adenoma, villous growth pattern (>25%), any size 2.3 – Adenoma > 1.0 cm in size, or 2.4 – Serrated lesion, > 1.0 cm in size
3	1 or 2 adenoma (s), >5 mm in size, or < 10 mm size, non-advanced
4	> 3 adenomas, <10mm, non-advanced
5	1 or 2 adenoma(s), ≤5 mm in size, non-advanced
6	Negative – No neoplastic findings 6.1 – negative upon histopathological review 6.2 – no findings on colonoscopy, no histopathological review

Study Population and Baseline Demographics

Study enrollment and population demographics are summarized in Figure 1. A total of 10,023 subjects with colonoscopy and Cologuard data were included in the primary analysis population. This population included 65 subjects with CRC. Analysis was conducted to rule out bias associated with the subjects excluded from the analysis population.

The average age of subjects included in the primary analysis was 64.2 years, and there were a slightly higher percentage of female subjects (5,378/10,023, 53.7%) as compared with male subjects (4,645 /10,023, 46.3%). Two 49-year-old subjects and one 44-year old subject were included in the study, which is inconsistent with the intended user population. Each of these subjects was a true negative on Cologuard and their inclusion did not

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