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, 45 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 45 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.
- The clinical validation study was conducted in patients 50 years of age and older. ACS Guidelines recommend screening begin at age 45. Cologuard performance in patients ages 45 to 49 years was estimated by sub-group analysis of near-age groups.
- 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 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 30% 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 varying ages. The US Multi-Society Task Force on Colorectal Cancer recommends that screening begin at age 50 (age 45 for African Americans), as the incidence of both CRC and premalignant lesions increases sharply after this age.[5] The 2018 guideline update from the American Cancer Society gave a qualified recommendation to initiate screening at age 45 in all individuals based on increasing incidence of CRC in younger adults.[6]

One in 3 adults 50 years of age or older are not current with recommended CRC screening.[7] Less than half of adults 50-54 years of age and only 17.8% of adults ages 40-49 report recent screening for CRC.[6]

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.[8-11] 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]

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).[12-13] 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.[14-16] 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.[18] 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. [17-18]

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, ("DeeP-C" or "the 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 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

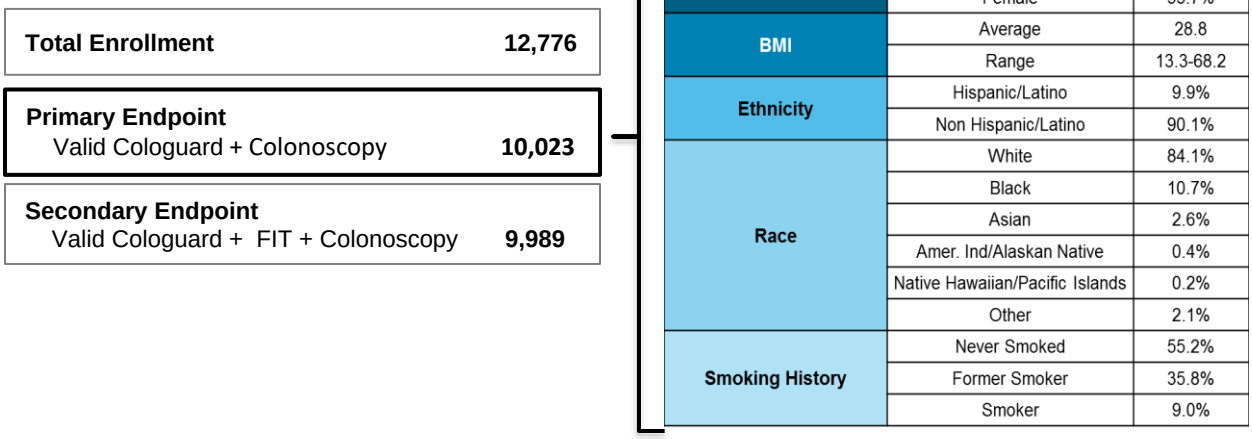
	6.2 – no findings on colonoscopy, no histopathological review

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 notably impact data analyses. The majority of subjects were White (8,422/10,023, 84.1%), although 10.7% of the population were Black or African American subjects (1,071/10,023). Nearly 10% of subjects were Hispanic or Latino (991/10,023, 9.9%). Average BMI was 28.8 and the majority of subjects never smoked (5.531 /10,023, 55.2%).

Figure 1: Clinical Study Demographics



Demographics		
Age (Years)	Average	64.2
	Range	44-84
Gender	Male	46.3%
	Female	53.7%
BMI	Average	28.8
	Range	13.3-68.2
Ethnicity	Hispanic/Latino	9.9%
	Non Hispanic/Latino	90.1%
Race	White	84.1%
	Black	10.7%
	Asian	2.6%
	Amer. Ind/Alaskan Native	0.4%
	Native Hawaiian/Pacific Islands	0.2%
	Other	2.1%
Smoking History	Never Smoked	55.2%
	Former Smoker	35.8%
	Smoker	9.0%

Clinical Performance Measures

The primary and secondary performance measures for the clinical study are summarized in Table 2 below. The primary performance measures were the sensitivity and specificity of Cologuard for CRC, using colonoscopy with histopathology as the reference method. The primary analysis required that the lower bound of the 95% one-sided confidence interval for the sensitivity of Cologuard for CRC exceed 65%. The specificity analysis for CRC required that the lower bound of the one-sided 95% confidence interval exceed 85%.

With respect to the secondary performance measure, Cologuard was compared to FIT using a non-inferiority test for CRC sensitivity and using a superiority test for advanced adenoma (AA) sensitivity. In order for Cologuard to be deemed non-inferior to FIT, the one-sided 95% confidence interval lower bound for the Cologuard – FIT difference in percentages with a positive test among subjects with CRC was required to exceed -5%. Establishing

superiority required a one-sided p-value <0.025 (exact McNemar's comparison test).

Table 2: Clinical Study Primary and Secondary Performance Measures

Primary Performance measures	• Determine the CRC sensitivity and specificity of Cologuard.
Secondary Performance measures	• Compare Cologuard to FIT for CRC and AA sensitivity.

Summary of Clinical Study Results

Results from the clinical study demonstrated that Cologuard successfully met the primary performance measure of the study, establishing a clinically meaningful sensitivity and specificity for CRC. Sensitivity of Cologuard for CRC was 92.3% (60/65) with a one-sided 95% confidence interval lower bound of 84.5, substantially exceeding the protocol-specified threshold of 65%. In addition, Cologuard successfully demonstrated a clinically meaningful specificity according to the protocol-specified criteria. The specificity of Cologuard was 86.6%, with a one-sided 95% confidence interval lower bound of >86.0%.

Clinical study results demonstrated superiority of Cologuard to FIT for sensitivity in detecting CRC. Secondary performance measures included an analysis of performance Cologuard and FIT using colonoscopy as a reference. Cologuard correctly detected 60 of the 65 total CRC cases identified by colonoscopy (92.3%). FIT captured only 48 of the 65 CRC cases identified by colonoscopy (73.8%). FIT identified only a single cancer that was not identified by Cologuard. Cologuard, meanwhile, identified 13 cancers that were missed by FIT. Cologuard was compared to FIT using a non-inferiority test for CRC sensitivity. In addition, Cologuard demonstrated superiority over FIT with respect to sensitivity for CRC using an exact McNemar's comparison test as the one-sided p-value (p=0.0018) was well below the p <0.025 threshold for superiority. The lower bound of the one-sided confidence interval for the Cologuard – FIT difference was 0.080, substantially exceeding the protocol-specified non-inferiority threshold of -0.05.

Establishing superiority for AA sensitivity required a one-sided p-value <0.025 (exact McNemar's comparison test). Cologuard demonstrated superiority for AA sensitivity, with a p-value of <0.0001, substantially below the threshold for superiority of p<0.025. FIT identified only 29 AA cases that were not captured by Cologuard, while Cologuard identified 170 AA cases that were not positive on the FIT test.

Analysis was also performed to calculate the Cologuard negative predictive value (NPV) for Category 1 (CRC) and Category 2 (AA). Clinical results show that a negative patient result for Cologuard gives 99.94% assurance that the patient does not have cancer and a 94.79% chance that the patient does not have an advanced adenoma.

Cologuard and FIT Performance Comparison

Cologuard was superior to FIT for both CRC and AA detection. Cologuard also demonstrated high sensitivity for detection of lesions and polyps which historically have been difficult to capture with FIT, including early stage CRC, proximal lesions, and higher risk precancerous lesions. Cologuard demonstrated a numerically greater sensitivity than FIT for detection of CRC and AA across lesion subgroups. Sensitivity results are summarized in Table 3 and Table 4 below. As noted above, Cologuard specificity was 86.6% and FIT specificity was 95%. These specificity measures excluded CRC and AA for both tests.

Cologuard sensitivity for stage I cancer was 89.7% compared to 65.5% for FIT (p=0.039). Sensitivity for stage II cancer was 100.0% for Cologuard compared to 76.2% for FIT (p=0.062). CRC sensitivity was also compared to FIT by size of the lesion, with higher detection at each lesion size than FIT. When analyzed by lesion location, Cologuard showed 90.0% sensitivity for proximal cancer compared to 66.7% for FIT (p=0.039). Cologuard also detected higher risk precancerous lesions, including high grade dysplasia (69.2% Cologuard, 46.2% FIT, p=0.004) and sessile serrated polyps (43.0% Cologuard, 5.1% FIT, p<0.001). Cologuard and FIT were both better at detecting precancerous lesions as lesion size increased from 0.5 cm to ≥3 cm (value for trend for both was p<0.001).

Table 3: Cologuard and FIT Cancer Sensitivity

Subgroup	n=	Cologuard Sensitivity	FIT Sensitivity
Cancer Stage			
CRC, all stages (p=0.018)	65	92.3%	73.8%
Stage I (p=0.039)	29	89.7%	65.5%
Stage II (p=0.062)	21	100.0%	76.2%
Stage III	10	90.0%	90.0%
Stage IV	4	75.0%	75.0%
Stage I-III (p=0.002)	60	93.3%	73.3%
Cancer Size			
< 5 mm	0	0	0
5-9 mm	5	80.0%	60.0%
10-19 mm	14	92.9%	85.7%
20-29 mm	12	91.7%	66.7%
≥30 mm	34	94.1%	73.5%
Cancer location			
Proximal (p=0.039)	30	90.0%	66.7%
Distal (p=0.062)	35	94.3%	80.0%

*Cologuard specificity was 86.6% and FIT specificity was 95%. These specificity measures excluded CRC and AA for both tests.

Table 4: Cologuard and FIT Advanced Adenoma Sensitivity

Subgroup	Cologuard n=	Cologuard Sensitivity	FIT n=	FIT Sensitivity
Pre-malignant Neoplasia				
AA, all subcategories (p<0.001)	760	42.4%	757	23.8%
High grade dysplasia (p-0.004)	39	69.2%	39	46.2%
Sessile serrated ≥10 mm (p<0.001)	100	43.0%	99	5.1%
AA location				
Proximal (p<0.001)	433	33.0%	431	15.5%
Distal (p<0.001)	326	54.6%	325	34.8%
Lesion Size	p value for trend<0.001		p value for trend<0.001	
< 5 mm	10	20.0%	10	20.0%
5-9 mm	56	32.1%	56	14.3%
10-19 mm	577	39.0%	574	20.9%
20-29 mm	79	64.6%	79	43.0%
≥30 mm	38	68.4%	38	42.1%

*Cologuard specificity was 86.6% and FIT specificity was 95%. These specificity measures excluded CRC and AA for both tests.

Cologuard Subgroup Analysis: please note that the clinical study was not designed to evaluate subgroups and subgroup analysis should be interpreted with that in mind.

The clinical study results were analyzed according to various demographic characteristics, including gender, age, and race/ethnicity as summarized in Table 5 below. Although CRC sensitivity was higher for males versus females and higher in Whites and Asians compared to Black/African Americans, AA sensitivity and specificity remained consistent across subgroups, with only a few differences likely attributed to a lower number of subjects from all subpopulations in the study.

Cologuard CRC sensitivity was higher for males versus females. Meanwhile, specificity of Cologuard was similar for females as compared with males. Specificity was 87.3% (4,398/5,037) for females, compared with 85.8% (3,569/4,161) for male subjects. Advanced adenoma detection showed similar results between males and females.

For age, Cologuard sensitivity for CRC was consistently high across all age groups. Sensitivity for patients 65 years of age and older ranged from 88.9% to 100.0%. Although sensitivity was 75% for subjects age 60-64, the number of CRC cases was particularly small in this age group (n = 4); only one CRC case was not detected by Cologuard. With respect to AA, sensitivity was similar across all age groups, with sensitivity as high as 46.8% for subjects between the ages of 70 and 79. Cologuard specificity for CRC was also high across all age groups. Specificity was in the 80% range or above for most age groups, aside from subjects > 75 years old. Specificity for AA was also similar across age groups.

Cologuard CRC sensitivity was very high among White subjects, but lower among Black or African American subjects) and high among the small number of Asian CRC cases. However, the results observed in Black/African American subjects may have been affected by the low overall number of cancer cases in that subpopulation. Sensitivity among Hispanic or Latino subjects was high, although the sample size was small.

Cologuard sensitivity for AA was similar for White and Black/African American subjects. Sensitivity was also similar among Hispanic/Latino subjects. AA sensitivity was lower among Asian subjects and very high for American Indian or Alaskan Natives, compared with other groups. Only the American Indian and Alaskan Native subpopulations showed higher sensitivity in AA detection. Differences between racial and ethnic subpopulation results may be affected by the small number of subjects in the African American and American Indian or Alaska Native subpopulations. Cologuard specificity was high across all racial and ethnic groups, with rates > 85% for most groups.

Table 5: Cologuard Performance by Subgroup

Subgroup	CRC Sensitivity	AA sensitivity	Specificity
Gender			
Male	34/34 (100%)	201/450 (44.7%)	3569/4161 (85.8%)
Female	26/31 (83.9%)	121/310 (39%)	4398/5037 (87.3%)
Age			
<60 yrs	7/7 (100.0%)	65/171 (38.0%)	2491/2703 (92.2%)
60-64 yrs	3/4 (75.0%)	24/57 (42.1%)	681/765 (89.0%)
65-69 yrs	19/20 (95.0%)	125/301 (41.5%)	2871/3352 (85.7%)
70-74 yrs	16/18 (88.9%)	72/154 (46.8%)	1292/1566 (82.5%)
75-79 yrs	6/6 (100.0%)	29/62 (46.8%)	480/617 (77.8%)
>79 yrs	9/10 (90.0%)	7/15 (46.7%)	152/195 (77.9%)
Race			
White	53/55 (96.4%)	271/641 (42.3%)	6639/7726 (85.9%)
Black or African American	5/8 (62.5%)	36/85 (42.4%)	879/978 (89.9%)
Asian	1/1 (100.0%)	4/13 (30.8%)	229/245 (93.5%)
American Indian or Alaska Native	0/0	3/4 (75.0%)	24/32 (75.0%)
Native Hawaiian or Other Pacific Islander	0/0	0/0	21/23 (91.3%)
Other	1/1 (100.0%)	7/16 (43.8%)	171/189 (90.5%)
Ethnicity			
Hispanic or Latino	8/9 (88.9%)	23/59 (39.0%)	837/923 (90.7%)
Not Hispanic or Latino	52/56 (92.9%)	298/700 (42.6%)	7127/8272 (86.2%)

Performance in Age Group 45 to 49

The American Cancer Society Colorectal Cancer Screening Guideline (2018) lowered the recommended age to start colorectal cancer screening from 50 to 45 for patients at average risk for CRC and included the use of the multi-target stool DNA test (Cologuard) for cancer screening within that recommendation, along with other stool-based non-invasive tests and structural (visual) examination options, depending on patient preference and test availability.[19] The ACS based their recommendation on colorectal cancer (CRC) incidence and mortality rates, results from microsimulation modeling that demonstrate a favorable benefit-to-burden balance of screening beginning at age 45, and the expectation that screening will perform similarly in adults ages 45 to 49 as it does in adults ages 50 and older.

Retrospective analysis of Cologuard test results in patients 45 to 49

Retrospective data were collected to evaluate whether Cologuard performance in samples from patients ages 45 to 49 years is comparable to that achieved in samples obtained from patients ages 50 and older. Through September 2018, there had been 2241 completed Cologuard tests (through Exact Sciences Laboratories) aged 45 to 49 years. It is unknown if these patients were at average risk. Of these tests, 7.4% (165/2241) had a positive result and 92.6% (2076/2241) had a negative result, indicating the specificity in this age group is ≥92.6%, which is comparable to the specificity of patients ages 50 to 59 from the DeeP-C study. Follow-up data were not available from the 2241 completed Cologuard tests to confirm colorectal cancer outcomes for either positive or negative results.

Ordering Cologuard

Cologuard is available for physicians to order through the Exact Sciences Laboratories online portal at www.CologuardTest.com or through paper requisition. Cologuard includes a compliance program and provides attentive service to physicians and patients with live operators. For any questions about Cologuard or specific questions on how to order the test, please contact Exact Sciences Laboratories.

Exact Sciences Laboratories
145 E. Badger Rd, Suite 100
Madison, WI 53713
844-870-8870

Sample Collection

- Samples for use with Cologuard must be collected with the Cologuard Collection Kit (Exact Sciences, 100026), including a stool sample for DNA testing (Container) and a stool sample for Hemoglobin testing (Tube).
- Patients should not provide a sample if they have diarrhea or blood in their urine or stool from bleeding hemorrhoids, bleeding cuts or wounds on their hands, rectal bleeding, or menstruation.
- Patients should familiarize themselves with detailed information contained in Cologuard Patient Guide and collection instructions before completing sample collection.
- The use of this kit requires sitting down on the toilet and standing up from the toilet. Patients should have someone available to help them sit down or stand up if needed.
- To ensure the integrity of the sample, the laboratory must receive 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.

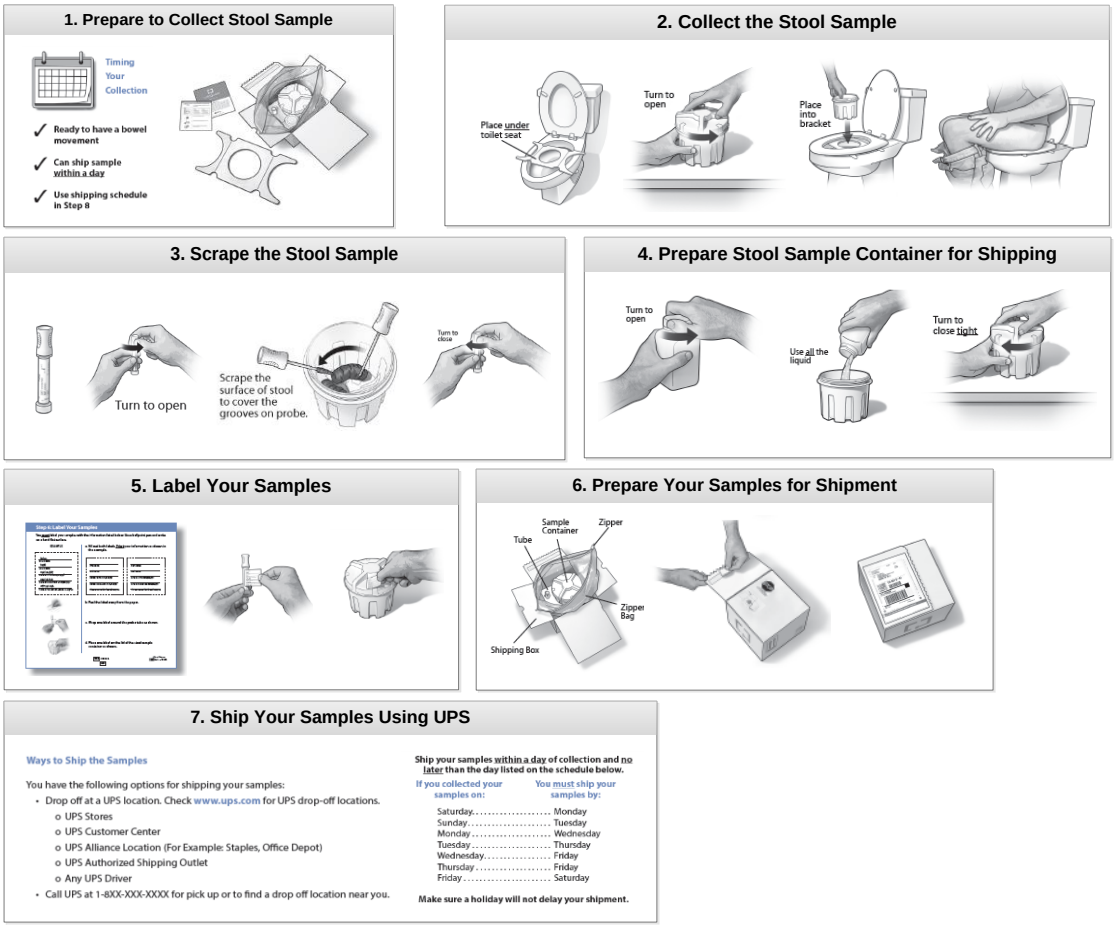
Interfering Substances

There are no known interfering substances with Cologuard. The molecular and hemoglobin assays of the test were challenged independently with the substances that could potentially be found in patient samples, including common lotions and creams, feminine over the counter products, stool softeners, anti-diarrhea products, laxatives, anti-acids, upset stomach relief products, urine, alcohol, common vegetables and fruits, fats, and lipids. There was no observed interference with any substance in either assay. The hemoglobin assay was also tested with antibiotics, anti-inflammatories, anti-fungal drugs, pain relievers, and decongestants with no observed interference. The molecular assay was additionally tested with animal genomic DNA of commonly edible animals (both high and low levels) with no observed interference.

Instructions for Sample Collection

Once the Cologuard test has been ordered, the collection kit will be sent to the patient at their home. Detailed instructions for patient specimen collection are provided in the Cologuard Patient Guide as part of the collection kit. Full closure of the stool collection container should be emphasized to patients to ensure receipt of a usable sample for testing. A toll-free number is also provided with the patient guide to ensure that any patient questions are addressed. An overview of the collection process is provided in the figure below.

Figure 5: Patient sample collection process



Interpretation of Cologuard Results

A negative test result means that the test did not detect abnormal DNA and/or blood in the sample. A test can also have a negative result that is incorrect (false negative). For that reason, it is important to continue a regular screening schedule with your patients. A positive Cologuard test means that the test detected abnormal DNA and/or blood that could be caused by precancer or cancer in the colon or rectum. A test can also have a positive test that is incorrect (false positive). Any positive result should be followed by a diagnostic colonoscopy. In some cases Cologuard may not generate a result. If this occurs a new patient sample may be requested.

References

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