shield™ Colorectal Cancer Screening Test

Intended Use / Indications for Use

The Shield test is a qualitative, in vitro diagnostic test intended to detect colorectal cancer derived alterations in cell-free DNA from blood collected in the Guardant Shield Blood Collection Kit.

Shield is indicated for colorectal cancer screening in individuals at average risk for the disease, age 45 years or older. Patients with a positive result should be followed by colonoscopy. Shield is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals.

This test is performed at Guardant Health, Inc.

Precaution

Based on data from clinical studies, Shield has limited detection (55%-65%) of Stage I colorectal cancer and does not detect 87% of precancerous lesions. One out of 10 patients with a negative Shield result may have a precancer that would have been detected by a screening colonoscopy. Shield demonstrated high detection of Stage II, III, and IV colorectal cancer.

Contraindications

The Shield test is NOT indicated for use for patients that have the following:

- Personal history of colorectal cancer (CRC), adenomas, or other related cancers
- Family history of CRC, defined as having one or more first-degree relative (parent, sibling, or child) diagnosed with CRC at any age
- Positive result on another colorectal cancer screening method within the last six months, or:
    - 12 months for fecal occult blood test (FOBT) or fecal immunochemical test (FIT)
    - 36 months for FIT-DNA test
- Personal history of any of the following high-risk conditions for colorectal cancer:
    - Inflammatory Bowel Disease (IBD), including chronic ulcerative colitis (CUC) and Crohn's disease
    - Familial adenomatous polyposis (FAP)
    - Other hereditary cancer syndromes including but not limited to:
        - Hereditary non-polyposis colorectal cancer syndrome (HNPCC) or "Lynch Syndrome", Peutz- Jeghers Syndrome, MUTYH Polyposis (MAP), Gardner's Syndrome, Turcot's (or Crail's) Syndrome, Cowden's Syndrome, Juvenile Polyposis, Cronkhite-Canada Syndrome, Neurofibromatosis and Familial Hyperplastic Polyposis

IVD **Rx Only**

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Summary

The Shield test is a blood test developed by Guardant Health for the qualitative detection of colorectal cancer derived alterations in individuals at average risk for the disease, age 45 years or older. The test is performed in the Guardant Health CLIA laboratory and returns a qualitative result of positive or negative.

Patients with a positive result may have colorectal cancer or advanced adenomas and should be followed by colonoscopy.

The test can be considered in a manner similar to guideline-recommended non-invasive CRC screening modalities and is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy of high-risk individuals.

Shield is a non-invasive, blood-based CRC screening test and can be completed during any healthcare encounter, alongside other blood tests.

Shield has 83% CRC sensitivity and 90% specificity for advanced neoplasia (AN) as demonstrated in the ECLIPSE clinical study. Shield has a false positive rate of 10%, meaning one of 10 people who do not have Advanced Neoplasia (colorectal cancer or advanced adenoma) will have a false positive test result. Shield has a false negative rate of 17%, meaning 17 of 100 people who have colorectal cancer will incorrectly have a negative result.

Shield has limited ability for the detection of advanced adenomas [13.2% (147/1116); two-sided 95% confident interval (CI) (11.3, 15.3)].

In the ECLIPSE clinical study, Shield's CRC sensitivity by cancer stage was 54.5% for Stage I (12/22), 95% CI (34.7%, 73.1%), 100% for Stage II (14/14) (87.5%,100.0), 100% for Stage III (18/18) (82.4%,100.0%), and 100% for Stage IV (9/9) (70.1%,100.0%). Shield did not detect any CRC lesions smaller than 10mm (0/6, 95% CI 0.0%-39.0%) and detected 91.4% of CRC lesions at least 10mm (53/58, 95% CI 81.4% - 96.3%).

When discussing CRC screening with your patients, you should share the benefits and risks of all screening modalities and work with your patients to find the option that is most appropriate for their overall health, prior screening history, preferences, and schedule constraints.

Limitations

- Providers should discuss the most appropriate screening test to use with patients depending on their medical history and individual circumstances. The Shield test is not intended as a screening test for individuals who are at high risk for colorectal cancer.
- Shield has limited ability to prevent the development of colorectal cancer from advanced precancerous lesions and lower detection rates for Stage I colorectal cancer, given the current data available.
    - Shield has lower performance of stage I colorectal cancer [54.5% (12/22); 95% confidence interval (CI) (34.7%, 73.1%)]. The majority [6/10] of missed Stage I cancers were less than 10mm. Shield did not detect colorectal cancer lesions smaller than 10mm [0% (0/6); 95% CI 0.0% - 39.0%].
    - Shield may fail to detect as many as 88.7% of patients with advanced precancerous lesions which can later become neoplastic because of its limited ability for the detection of advanced adenomas [13.2% (147/1116); 95% CI (11.3, 15.3)].
    - Shield has a false negative rate of 17% for colorectal cancer, meaning 17 of 100 people who have colorectal cancer will incorrectly have a Shield negative result.
    - Shield has a false positive rate of 10%, meaning one of 10 people who do not have Advanced Neoplasia (colorectal cancer or advanced adenoma) will have a false positive test result.
- Colorectal cancer screening guideline recommendations vary for persons over the age of 75. The decision to screen patients over the age of 75 should be made on an individualized basis in consultation with a healthcare provider.
- A positive Shield test result suggests patients may have colorectal cancer or advanced adenoma. Patients with a positive result should be followed by colonoscopy.
- A negative Shield test result does not guarantee absence of colorectal cancer or advanced adenoma. Patients with a negative result should continue participating in colorectal cancer screening programs, at the appropriate guideline recommended intervals.
    - One out of 10 patients testing negative will be falsely reassured that they are negative for advanced adenoma, given the negative predictive value for advanced adenoma of 90%.
    - One out of 1000 patients testing negative will be falsely reassured that they are negative for colorectal cancer, given the negative predictive value of 99.9%.
- A false positive result may occur when the Shield test generates a positive result while a colonoscopy will not find colorectal cancer or advanced adenoma. A false negative result may occur when the Shield test does not detect a colorectal tumor signal while a colonoscopy identifies a colorectal cancer.
- The performance of Shield has been established in a prospectively designed, cross-sectional study. The benefits and risks of programmatic colorectal cancer screening (i.e., repeated testing over an established period of time) with Shield has not been studied.
- Non-inferiority or superiority of Shield sensitivity as compared to other recommended screening methods for colorectal cancer or advanced adenoma has not been established.
- Cross-reactivity was observed in analytical studies using samples from subjects with non-colorectal cancers, including gastric, pancreatic, liver, bladder, breast, lung, prostate, ovarian, melanoma and kidney cancers.
- Consult the Guardant Shield Blood Collection Kit (BCK) instructions for use (LBL-000324), for precautions and limitations specific to the collection and shipping of blood samples.

CRC Overview

CRC is the second leading cause of cancer related death for both men and women in the United States.[1] CRC survival rates dramatically increase when the disease is detected early; the 5-year relative survival rate is 91% in those with localized disease, dropping to 14% in those with metastatic disease.[2]

Current CRC screening guidelines in the average-risk population recommend that screening begin when individuals reach 45 years of age, using guideline-recommended screening tests. Unfortunately, CRC screening adherence remains suboptimal, with approximately 42% of screening-eligible individuals in the U.S. not completing CRC screening in accordance with current guideline recommendations.[2] This low adherence may contribute to over half of individuals being diagnosed after their disease has metastasized.[3,4] As a result, individuals who are not up to date with screening are at increased risk of CRC mortality.[5]

The actual number of CRC cases identified through screening depends on both the ability of the test to detect the disease (sensitivity) and the willingness of the patient to complete a particular screening test (adherence).

Device Description

The Shield test is a blood test developed by Guardant Health for the qualitative detection of colorectal cancer. Shield is a screening test to detect alterations associated with colorectal cancer from whole blood samples collected from individuals at average risk for CRC. These samples are shipped to Guardant Health, where cfDNA is extracted from the plasma component of whole blood and prepared for analysis using next-generation sequencing technology.

The resulting cfDNA data are then analyzed using proprietary bioinformatics algorithms trained to detect the presence of colorectal cancer associated signals. Following final analysis, a test report is generated for the sample.

Shield has 83% CRC sensitivity and 90% specificity for AN as demonstrated in the ECLIPSE clinical study (see “Clinical Study” section below). The Shield test consists of a cell-free DNA (cfDNA) workflow developed for the qualitative detection of colorectal cancer derived markers in the blood. This workflow produces a final test result of positive or negative. A patient with a positive result should be followed by colonoscopy. A patient with a negative result should continue participating in colorectal cancer screening programs. If no result is generated a new blood sample collection may be requested.

Clinical Study

Overview

ECLIPSE was a multi-center, prospective, non-randomized pivotal study to evaluate the clinical performance of the Shield test, in which 10,258 patients were randomly selected for clinical validation from 22,877 subjects enrolled at over 200 sites across the US.

Using colonoscopy with histopathological confirmation, the Shield test achieved sensitivity of 83.1% for CRC and 89.6% specificity for Advanced Neoplasia (CRC or Advanced Adenoma) with no unanticipated adverse device effects. Shield detected 54.5% of stage I (95% CI: 34.7%,73.1%), and 100% of stage II and 100% of stage III and IV CRCs. Specificity was 89.9% in those without any neoplastic findings on colonoscopy. Additionally, as compared to colonoscopy and histopathology, Shield sensitivity for Advanced Adenoma (AA) detection was 13.2%.

Study Design

The study was designed to enroll subjects who were between the ages of 45 and 84 years (inclusive), at average risk for the development of CRC.

All enrolled subjects underwent a blood draw for the Shield test prior to any bowel preparation or intervention.

Subjects then underwent bowel preparation and colonoscopy per standard clinical practice within 6 months of the study related blood draw. Colorectal neoplasia of any grade or severity was confirmed by central histopathological review. Colonoscopy and histology findings were classified as described in **Table 1** based on the lesion of greatest clinical significance. Advanced Neoplasia (AN) includes category 1 and categories 2a to 2e.

Blood samples were tested in the Guardant Health Clinical Laboratory using the Shield test according to clinical laboratory operating procedures.

Table 1: Colonoscopy/Histopathology Diagnosis Category Descriptions

Category	Findings
1	Colorectal cancer, any stage
2	Advanced Adenoma
2a	Carcinoma in situ, any size
2b	High-grade dysplasia, any size
2c	Villous growth % (>25%), any size
2d	Tubular adenoma, ≥10 mm
2e	Serrated lesion, ≥10 mm (includes sessile serrated adenoma/polyp)
3	Non-advanced adenoma, >3 adenomas, <10 mm
4	Non-advanced adenoma, 1 or 2 adenomas, >5 mm, <10 mm
5	Non-advanced adenoma, 1 or 2 adenomas, ≤5 mm

Category	Findings
6	Negative, or other findings
7	Not evaluable

Study Population and Baseline Demographics

The primary analysis population included 7,861 individuals ages 45-84 at average risk for CRC with a colonoscopy diagnosis and valid Shield test result from the 10,258 subjects selected for clinical validation. Study sites were located in every geographic region in the continental U.S. and included a wide variety of care settings in both rural and urban areas.

Subjects in the primary analysis population were 79% White and 12% Black or African American with 13% identifying as Hispanic or Latino. This demographic distribution largely mirrors the U.S. Census population.[6] The average age was 60 years. The majority of subjects had BMI < 30 (59%) and had never used tobacco (70%). Subject accounting and demographics are summarized below in **Figure 1**.

Figure 1: Clinical Study Demographics

Demographics (Clinical Validation Evaluable Dataset = 7,861)					
Age (Years)		**Race**		**BMI**	
Average	60.3	White	78.5%	<30	58.6%
Range	45-84	Black or African American	11.8%	≥30 to <35	23.8%
Gender		Asian	7.1%	35+	17.5%
Female	53.7%	American Indian or Alaska Native	0.2%	Not Available	0.1%
Male	46.3%	Native Hawaiian or Other Pacific Islander	0.2%	**Smoking History**	
Ethnicity		Other	1.7%	Never	70.2%
Hispanic/Latino	13.3%	Multiple	0.3%	Current	9.4%
Non-Hispanic/Latino	86.2%			Former	20.4%
Not Available	0.5%				

Clinical Performance Measures

The co-primary and secondary performance measures for the clinical study are summarized in **Table 2** below. Two co-primary performance measures were pre-defined for this study:

- Shield sensitivity for CRC and specificity for AN in average-risk individuals relative to colonoscopy and histopathological diagnosis. CRC sensitivity (assessed on subjects in Category 1) was considered acceptable if the lower bound of the 2-sided 95% Wilson confidence interval (CI) exceeded 65%.
- AN specificity (assessed on subjects in Category 3-6) was considered acceptable if the lower bound of the 2-sided 95% Wilson CI exceeded 85%.

Table 2: Clinical Study Primary and Secondary Performance Measures

Co-primary Performance Measures	• Determine Shield sensitivity for CRC and specificity for AN relative to colonoscopy and histopathological diagnosis
Key Secondary Performance Measure	• Evaluate Shield sensitivity for AA relative to colonoscopy and histopathological diagnosis

Summary of Clinical Study Results

Effectiveness Results and Safety

The primary and secondary performance characteristics of Shield are shown in **Table 3** below.

Table 3: Shield Sensitivity and Specificity

Shield Result	CRC (N=65)	AA (N=1116)	Non-AN (N=6680)	Total (N=7861)
Positive	54	147	698	899
Negative	11	969	5982	6962
Total	**65**	**1116**	**6680**	**7861**
CRC Sensitivity = % (2-sided 95% Wilson CI)	**83.1% (72.2%, 90.3%)**			
AA Sensitivity = % (2-sided 95% Wilson CI)	13.2% (11.3%, 15.3%)			
AN Specificity = % (2-sided 95% Wilson CI)	**89.6% (88.8%, 90.3%)**			
AN Specificity (negative, no findings (Category 6) = % (2-sided 95% Wilson CI)	89.9% (89.0%, 90.7%)			

As shown in **Table 3**, Sensitivity of Shield for CRC was 83.1% with a 2-sided 95% CI lower bound of 72.2%. Shield specificity for AN was 89.6% with a 2-sided 95% CI lower bound of 88.8%. The specificity of Shield for colonoscopy negative for AN was 89.9%.

Subgroup Analysis

The clinical study results are reported according to various demographic and baseline characteristics including gender, age, and race/ethnicity as summarized in **Table 4** below. Shield performance was similar among the subgroups with the exception of two trends. Lower specificity was observed with increased age. Higher AA sensitivity was observed with increased age, but increased sensitivity for highest grade AA lesions, or lesions with the highest malignant potential, was observed in all age groups (**Table 5**).

Table 4: Shield Performance by Demographic and Baseline Characteristics

Subgroup	CRC Sensitivity (N=65) % (n/N)	AA Sensitivity (N=1,116) % (n/N)	AN Specificity (N=6,680) % (n/N)
Gender			
Female	86.7% (26/30)	13.3% (68/511)	90.1% (3314/3677)
Male	80.0% (28/35)	13.1% (79/605)	88.8% (2668/3003)
Age Group			
45-49	75.0% (3/4)	3.6% (2/56)	95.5% (554/580)
50-59	76.9% (10/13)	8.6% (33/385)	93.0% (2470/2657)
60-69	88.2% (30/34)	15.1% (63/417)	89.7% (1785/1989)
70-79	76.9% (10/13)	18.7% (47/252)	80.9% (1136/1405)
80+	100.0% (1/1)	33.3% (2/6)	75.5% (37/49)
Race			
American Indian or Alaska Native	(0/0)	0% (0/2)	83.3% (10/12)
Asian	75.0% (3/4)	17.9% (10/56)	84.4% (422/500)
Black or African American	90.0% (9/10)	13.2% (16/121)	92.1% (737/800)
Native Hawaiian or Other Pacific Islander	(0/0)	0% (0/2)	94.1% (16/17)
White	81.6% (40/49)	13.0% (119/917)	89.8% (4672/5201)
Other	100.0% (1/1)	6.3% (1/16)	84.2% (101/120)
Multiple	100.0% (1/1)	50.0% (1/2)	80.0% (16/20)
Not Available	(0/0)	(0/0)	80.0% (8/10)
Ethnicity			

Subgroup	CRC Sensitivity (N=65) % (n/N)	AA Sensitivity (N=1,116) % (n/N)	AN Specificity (N=6,680) % (n/N)
Hispanic or Latino	90.9% (10/11)	18.9% (24/127)	87.3% (791/906)
Not Hispanic or Latino	81.5% (44/54)	12.5% (123/984)	89.9% (5162/5741)
Not Available	(0/0)	0% (0/5)	87.9% (29/33)

Results are additionally reported by lesion characteristic covariates below in Table 5. Shield performance was similar across covariates with the exceptions of the expected trends toward higher CRC and AA sensitivity with greater lesion size and severity. While sensitivity for Stage I CRC was 54.5% (12/22, 95% CI 34.7%, 73.1%), sensitivity for Stage II CRC was 100% (14/14, 95% CI 78.5%, 100.0%), Stage III CRC was 100% (18/18, 95% CI 82.4%, 100.0%), and Stage IV CRC was 100% (9/9, 95% CI 70.1%, 100.0%).

Sensitivity for advanced adenomas with higher malignant potential, specifically those with features of high-grade dysplasia or villous architecture was 22.6% and 17.9%, respectively. Sensitivity for advanced adenomas 30mm or greater in size was 23.6%.

Table 5: Shield Performance by Lesion Covariates

Subgroup	CRC Sensitivity (N=65) % (n/N)	AA Sensitivity (N=1,116) % (n/N)	AN Specificity (N=6,680) % (n/N)
Lesion Size (mm)			
<5 mm	0.0% (0/1)	0.0% (0/4)	N/A
5-9 mm	0.0% (0/5)	18.8% (9/48)	N/A
10-19 mm	87.5% (7/8)	11.9% (102/859)	N/A
20-29 mm	83.3% (10/12)	13.6% (18/132)	N/A
30+ mm	94.7% (36/38)	23.6% (17/72)	N/A
Missing	100.0% (1/1)	100.0% (1/1)	N/A
CRC Stage			
I*	54.5% (12/22)	N/A	N/A
II	100.0% (14/14)	N/A	N/A
III	100.0% (18/18)	N/A	N/A
IV	100.0% (9/9)	N/A	N/A

Subgroup	CRC Sensitivity (N=65) % (n/N)	AA Sensitivity (N=1,116) % (n/N)	AN Specificity (N=6,680) % (n/N)
Stage Unknown	50.0% (1/2)	N/A	N/A
I-III	81.5% (44/54)	N/A	N/A
AN Specificity Histopathology Diagnosis Subcategories			
Nonadvanced Adenoma, ≥3 adenomas, <10 mm (Category 3)	N/A	N/A	87.7% (284/324)
Nonadvanced Adenoma, 1 or 2 adenomas, > 5 mm, <10 mm (Category 4)	N/A	N/A	89.0% (614/690)
Nonadvanced Adenoma, 1 or 2 adenomas, ≥5 mm (Category 5)	N/A	N/A	89.1% (1027/1152)
Negative, no findings (Category 6)	N/A	N/A	89.9% (4057/4514)
AA Sensitivity Histopathology Diagnosis Subcategories			
Advanced Adenoma, Carcinoma in situ, any size	N/A	0.0% (0/1)	N/A
Advanced Adenoma, with High-grade dysplasia (HGD), any size	N/A	22.6% (7/31)	N/A
Advanced Adenoma with villous component (>=25%), any size	N/A	17.9% (37/207)	N/A
Tubular Adenoma >= 10 mm in size	N/A	12.0% (82/685)	N/A
Serrated lesion >=10 mm in size	N/A	11.0% (21/191)	N/A

*Assumes 5 incompletely staged by AJCC malignant polyps are Stage 1 disease.

Patient Testing with the Shield Test

To order the Shield test, a Test Requisition Form (TRF) must be fully completed and signed by the ordering physician or other authorized medical professional. The order can be placed through the provider online portal found on www.ShieldCancerScreen.com or through paper requisition. The blood collection kit (BCK) is used in the collection and transportation of blood samples and can be obtained by submitting a kit

request on the online portal. Refer to the Guardant Shield BCK Instructions for Use for further details about collecting blood samples and shipping samples to the Guardant Health Clinical Laboratory.

For any questions about the test or the Guardant Shield BCK, contact Guardant Health Client Services (Tel: 855.722.7335, or Email: ScreeningSupport@guardanthealth.com).

Interpretation of Results

A test report will be returned to both the ordering healthcare provider and the patient with a final result of positive or negative. Patients are advised to contact their healthcare provider to discuss the Shield Result.

A positive result means the Shield test result raises concern for the presence of colorectal cancer or advanced adenoma. A colonoscopy evaluation is necessary to determine whether CRC is present. A negative result means the Shield test result indicates a signal associated with colorectal cancer was not detected.

The sensitivity of the Shield test for detection of colorectal cancer is 83.1%. This means that approximately 17% of patients with CRC will have a “false negative” Shield result, meaning that colorectal cancer was actually present but was not detected by the test.

The specificity of the Shield test in detecting Advanced Neoplasia (which includes both colorectal cancer and advanced adenomas) is 89.6%. This means that approximately 10% of individuals without any colorectal neoplasia will have positive results that were a “false positive,” meaning that neither colorectal cancer nor advanced adenoma was actually present.

The sensitivity of the Shield test for detecting advanced adenoma is 13.2%. 86.8% of patients with an advanced adenoma will have a “false negative” result. The Shield test is not intended to be used to screen for the presence of advanced adenomas.

Patients should be referred for a colonoscopy evaluation to confirm whether colorectal cancer or an advanced adenoma is present following a positive result. Also, patients with a negative result should continue participating in colorectal cancer screening programs, at the appropriate guideline recommended intervals as one out of 10 patients testing negative will be falsely reassured that they are negative for advanced adenoma, given the negative predictive value for advanced adenoma of 90%. One out of 1000 patients testing negative will be falsely reassured that they are negative for CRC, given the negative predictive value of 99.9%. These are lesions that may have been detected by a screening colonoscopy.

Patient Education Through Shared Decision-Making

It is important to engage in a shared decision-making discussion with your patients to determine the best CRC screening option among all available options. Adherence to CRC screening is known to improve when patients are offered multiple options. Adherence to blood-based testing is expected to be higher than that to other CRC screening options.

When talking with patients about screening for CRC, providers should share the benefits and risks of all screening modalities and work with their patients to find the option that is most appropriate for their overall health, prior screening history, preferences, and schedule constraints.

Colonoscopy should be discussed with all patients, given the test's ability to detect and potentially remove colorectal lesions.

The Shield test can be considered in a manner similar to guideline-recommended non-invasive CRC screening options.

The following information should be shared with patients:

Detection of early-stage disease is important in the reduction of colorectal cancer mortality. Shield has limited ability to prevent the development of colorectal cancer given the current data available. Shield has limited ability to detect advanced adenomas, the precursor lesions that over time, may develop into colorectal cancer. This may impact the ability to prevent the development of CRC. Based on data from clinical studies, Shield correctly identified 13.2% of individuals with an advanced adenoma. This means that 86.8% of individuals with an advanced adenoma incorrectly received a negative result. Shield did a better job identifying Stage II, III, and IV colorectal cancer (100% of individuals with these cancers were correctly identified with Shield) than Stage I colorectal cancer (55% of individuals with these cancers were correctly identified with Shield). This means that 45% of individuals with Stage I colorectal cancer were not identified with Shield. The majority of Stage I cancers not detected by Shield (6 of 10) were less than 10mm in size. Shield did not detect any CRC lesions less than 10mm in size (0/6) but detected 91.4% of CRC lesions at least 10mm. One out of 10 patients testing negative will be falsely reassured that they are negative for advanced adenoma, given the negative predictive value for advanced adenoma of 90%. One out of 1000 patients testing negative will be falsely reassured that they are negative for CRC, given the negative predictive value of 99.9%.

As part of this decision-making process, it is important to communicate to patients that a negative result does not preclude a CRC or advanced adenoma diagnosis and that they should continue participating in colorectal cancer screening programs. Patients with a positive result should be referred for diagnostic colonoscopy.

References

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