FDA Executive Summary

Prepared for the
May 23, 2024 Meeting of the
Molecular and Clinical Genetics Panel of the Medical Devices
Advisory Committee

Pxxxxxx
Shield
Guardant Health, Inc.

Introduction

This is the **FDA Executive Summary** for the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Panel meeting on the Shield blood based colorectal cancer screening test developed by Guardant Health. The device is a qualitative *in vitro* diagnostic test intended to detect colorectal cancer derived alterations in cell-free DNA (cfDNA) from plasma isolated from the whole blood collected in the Guardant blood collection tubes for individuals at average risk of the disease, age 45 years or older.

On March 10, 2023, Guardant Health, Inc. submitted a Premarket approval application (PMA) requesting approval of the class III device under Pxxxxxx. This submission has been reviewed by the Division of Molecular Genetics and Pathology (DMGP), in the Office of In Vitro Diagnostic Devices (OHT7), in the Office of Product Evaluation and Quality (OPEQ) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This document summarizes FDA's review of the PMA highlighting the areas for which we are seeking the panel's opinion. These topics will include the device performance and clinical experience to date. At the conclusion of the panel review and discussion of the data presented, FDA will seek panel recommendation regarding the potential benefit versus risk of using the Shield test in the context of the proposed intended use and whether Guardant has provided adequate information to support the safe and effective use of the device.

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1 PROPOSED INDICATIONS FOR USE

The sponsor has proposed the following Indications for Use statement:

> 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 Blood Collection Kit.
>
> Shield is intended for colorectal cancer screening in individuals at average risk of the disease, age 45 years or older. Patients with an "Abnormal Signal Detected" may have colorectal cancer or advanced adenomas and should be referred for colonoscopy evaluation. Shield is not a replacement for diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals.
>
> The test is performed at Guardant Health, Inc.

1.1 Contraindications

The sponsor has proposed following Contraindications:

The Shield test is not indicated for an individual who:

- Has a personal history of colorectal cancer (CRC)
- Has a family history of CRC, defined as having one or more first-degree relative (parent, sibling, or child) diagnosed with CRC at any age
- Has a known hereditary / germline risk of CRC (for example, Lynch syndrome or Hereditary Non-Polyposis CRC, or Familial Adenomatous Polyposis)
- Has a known diagnosis of inflammatory bowel disease

1.2 Precautions and Limitations

The sponsor has proposed following Precautions and Limitations:

- For prescription use only. This test must be ordered by a qualified medical professional.
- The Shield test should be considered alongside other CRC screening modalities, like colonoscopy, and is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.
- Shield has limited ability for the detection of advanced adenomas.
- Screening for CRC is recommended for people over 45 years old and providers should discuss the most appropriate 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 of CRC.
- CRC 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.

- An Abnormal Signal Detected Shield test result suggests the presence of colorectal cancer or advanced adenoma. Patients with an Abnormal Signal Detected result should be referred for colonoscopy evaluation.
- A Normal Signal Detected Shield test result does not preclude the presence of colorectal cancer or advanced adenoma, and patients should continue adhering to participating in guideline recommended screening programs.
- A false positive result may occur when the Shield test generates an Abnormal Signal Detected 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 positive result.
- Consult the Guardant Shield Blood Collection Kit (BCK) instructions for use which are included in the Guardant Shield BCK for Cancer Screening (LBL-000324) for precautions and limitations specific to the collection and shipping of blood samples.

2 DEVICE DESCRIPTION

The Shield test is an *in vitro* diagnostic test which employs the following:

2.1 Guardant Shield Blood Collection Kit – Cancer Screening

The Guardant Shield Blood Collection Kit (BCK) comprises all components used in the collection, stabilization, packaging, and transportation of whole blood samples and is the only test component intended for external distribution (i.e., the Shield test itself is performed in Guardant's clinical laboratory). The kit will contain four Guardant-labeled blood collection tubes and packaging material with instructions for kit storage, sample collection, and shipping after samples are collected. See **Figure 1** below.

Figure 1: Guardant Shield Blood Collection Kit

2.2 Assay Reagents

The Shield Test includes reagents for cfDNA extraction, methylation partitioning, library preparation, enrichment, autopooling and sequencing reactions. Additionally, the test uses general laboratory reagents in the assay. Most reagents are manufactured at Guardant Health, and they are prepared/configured into plates or tubes, depending on the reagent type.

2.3 Instrumentation

The Shield Automated Assay consists of the instrumentation and customized automated methods for processing samples according to the Shield workflow. Instrumentation is included to perform the following functions: automated pipetting, mixing and heating; and cfDNA extraction, measurement, and sequencing.

2.4 Software

The Shield Test includes software used for sample processing, data analysis, and report generation. The Shield software is comprised of two software subsystems:

- Guardant Assay Platform: The Guardant Assay Platform (GAP) is a software package that supports the execution of assay specific workflows. It provides common infrastructure and functionalities that are assay agnostic. This infrastructure facilitates the execution of the assay by providing the user a graphic interface for managing samples, executing the test, viewing status, receiving notifications, and viewing results. Built as a platform, the GAP does not contain or provide any data analytics algorithms, assay logic, or business rules.
- Guardant Screening Software: The Guardant Screening Software (GSS) is a software package that implements the Shield screening assay specific workflows and analytics. The GSS runs and is supported by the infrastructure GAP provides. GSS contains all the data analytics, algorithms, assay logic, and business rules for the Shield Test.

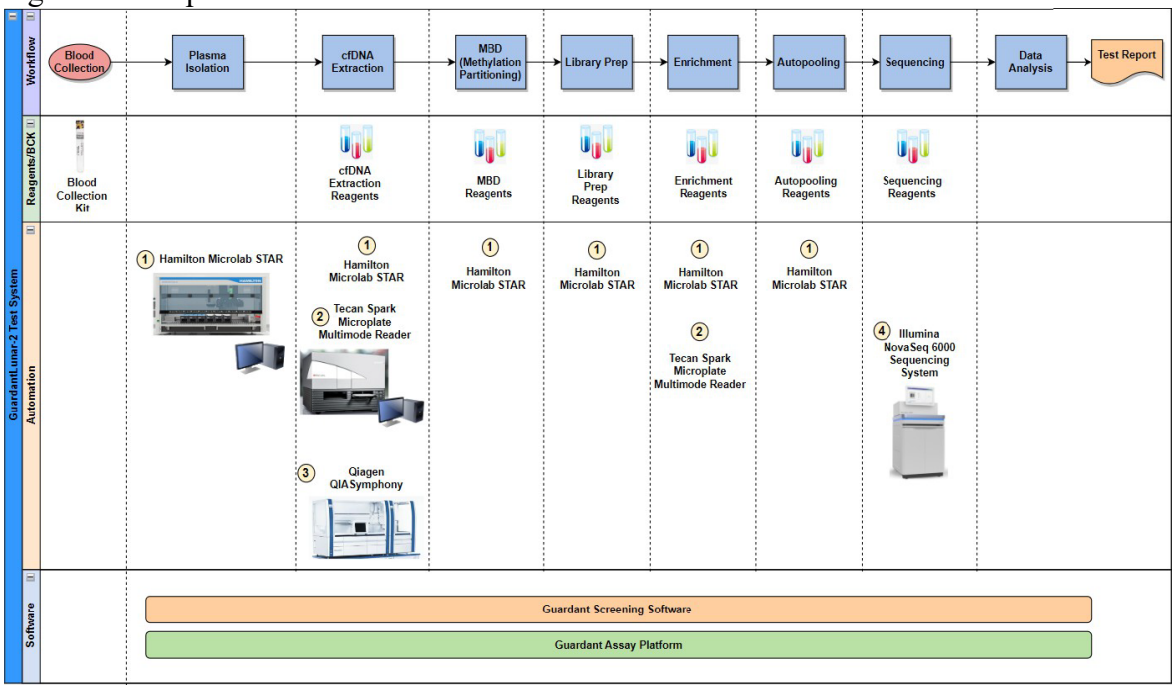
2.5 Test Workflow

2.5.1 Test Workflow

The Shield is a next generation sequencing based qualitative test to detect genomic and epigenomic alterations in cell-free DNA (cfDNA) isolated from blood. The Shield test begins with the collection of whole blood in 4 Guardant cfDNA blood collection tubes that are provided as part of the Guardant BCK. The patient specimen is then shipped to Guardant Health. Plasma is isolated from whole blood in each tube and then pooled. The cfDNA is extracted from a minimum of 2 mL of plasma for processing through the DNA sequencing workflow. The sequencing workflow is designed to enrich for DNA shed from neoplastic lesions and to detect unique epigenetic modifications in these cells. Epigenomic modifications may be detected as either altered methylation patterns in cfDNA sequence, or as changes in cfDNA fragment size distribution along the genome. In the cfDNA workflow, cfDNA is prepared in a manner that allows for simultaneous analysis of genomic and epigenomic changes. A library is prepared and enriched for informative genomic regions, followed by sequencing of the enriched library. The resulting cfDNA data are analyzed using proprietary bioinformatics algorithms designed to detect the presence of colorectal neoplasm-associated signals.

Figure 2. below provides a system overview and how the sub-system components are integrated into the workflow for processing whole blood samples and generating test results.

Figure 2. Components and workflow overview



2.5.2 Calling Algorithm and Result Reporting

The data from the sequencing generates four results outputs: Four of these (Fragmentomics caller Mixture Score, Methylation Caller Logistics Regression Score, Somatic mutation caller, and Methylation Caller or "MR Score")) are combined into the "Integrated Score", and the Methylation Caller or "MR Score" is also evaluated independently. The cfDNA MR Score and cfDNA Integrated Scores, are compared to predefined cutoffs to generate positive vs negative results for each cfDNA MR Call and cfDNA Integrated Call. If either of these calls is positive, then the result is positive. A negative call only occurs when both the cfDNA Integrated Call and the cfDNA MR Call are negative. These results classify samples as either "Abnormal Signal Detected" or "Normal Signal Detected".

3 PRE-CLINICAL STUDIES

Guardant has conducted the following nonclinical (analytical validation) studies to evaluate the analytical performance of the Shield test:

- Limit of Blank
- Limit of Detection
- Precision
- Accuracy

- In silico primer and probe-specificity
- Cross-Reactivity with Non-Colorectal Cancers and Diseases
- Endogenous interfering substances
- Cross-Contamination and Carry-Over
- Reagent lot-to-lot interchangeability
- Robustness /Assay Workflow and cfDNA input guardbanding
- Blood collection tube (BCT) within-lot repeatability
- Plasma isolation equivalence
- General lab instrument and reagent evaluation
- Sample and Reagent Stability

The data from above mentioned studies was provided and reviewed by FDA. This data will not be discussed during the panel meeting.

4 REGULATORY HISTORY AND BACKGROUND INFORMATION

The Shield test has not been marketed as an IVD in the United States or any foreign country. An earlier version of the test was launched on May 2, 2022, in the US, and is currently offered by Guardant as a laboratory-developed test (LDT).

4.1 BACKGROUND INFORMATION ON TARGET DISEASE

4.1.1 Colorectal Cancer

Colorectal cancer occurs in approximately 150,000 patients in the United States annually and is associated with over 50,000 deaths annually (SEER) and is the second leading cause of cancer deaths in the United States annually (Siegal et al., 2024). Despite gains in screening for CRC, via colonoscopy, and other non-invasive stool-based tests, approximately one-third of screen eligible patients do not undergo screening for CRC (Richardson et al., 2022). Furthermore, it is estimated that more than 75% of people who died from CRC were not up to date with screening (Doubeni et al., 2018). Detecting CRC early may lead to significant benefit to the public health, as localized CRC has a nearly a 90% 5-year survival rate, while metastatic CRC has only approximately a 15% 5-year survival rate (Ref 1, SEER). Appropriate screening and surveillance strategies for CRC and advanced precancerous lesions, can mitigate morbidity and mortality associated with this disease.

The majority of CRCs arise from colonic adenomas, the major precursor for CRC. Adenoma prevalence can be as high as 40%, with advancing age and male sex associated with higher prevalence (Bonnington et al., 2016). Advanced adenoma (AA) is commonly defined as an adenoma with size ≥10 mm, with tubulovillous or villous histology, or with high-grade dysplasia in the absence of invasive CRC (Gupta et al., 2020). Advanced adenomas have greater potential to develop into a cancer than non-advanced precancerous lesions and

progress to cancer at an annual rate of up to 5% (Brenner et al., 2007). Given the 90% early-stage colorectal cancer survival rate, detection and removal of advanced adenomas to reduce the risk of colorectal cancer (CRC) may lead to further improvement in survival rates. Advanced adenomas are stratified by risk based on their histology and size and are used to guide more frequent screening and surveillance per clinical guidelines as shown in the Table 1 and Figure 3 below, adapted from US Multi- Society Task Force Recommendations (Gupta et al., 2020).

Table 1. US Multi-Society Task Force Recommendations for Post-Colonoscopy Follow-Up in Average-Risk Adults with Normal Colonoscopy or Adenomas
(Adapted from Gupta et al., 2020)

Baseline colonoscopy finding	Recommended interval for surveillance colonoscopy	Strength of recommendation	Quality of evidence
Normal	10 y	Strong	High
1–2 tubular adenomas <10 mm	7–10 y	Strong	Moderate
3–4 tubular adenomas <10 mm	3–5 y	Weak	Very low
5–10 tubular adenomas <10 mm	3 y	Strong	Moderate
Adenoma ≥10 mm	3 y	Strong	High
Adenoma with tubulovillous or villous histology	3 y	Strong	Moderate
Adenoma with high-grade dysplasia	3 y	Strong	Moderate
>10 adenomas on single examination[e]	1 y	Weak	Very low
Piecemeal resection of adenoma ≥20 mm	6 mo	Strong	Moderate

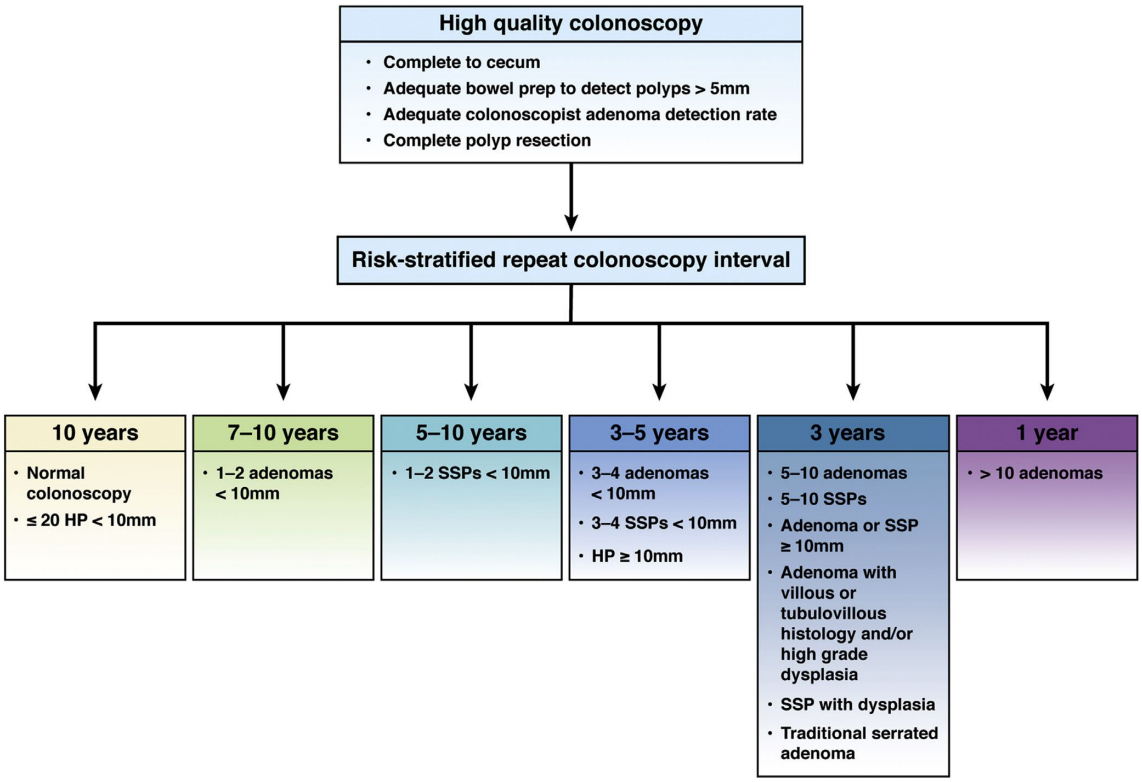


Figure 3. Recommendations for post-colonoscopy follow-up in average risk adults (from Gupta et al., 2020).

Appropriate screening and surveillance strategies for CRC and advanced pre-cancerous lesions, can mitigate morbidity and mortality associated with this disease.

4.1.2 Current Colorectal Cancer Screening Guidelines

There are several guideline-recommended CRC screening methods, including non-invasive stool tests, and invasive options such as flexible sigmoidoscopy and colonoscopy.

A number of professional societies and organizations have developed guidelines for CRC screening. Although the details of the recommendations differ, there is agreement that screening for average-risk persons should start at age 45 with repeat testing over time according to the American Cancer Society (ACS, 2018), and the US Preventive Services Task Force (USPSTF Recommendation Statement, JAMA 2021) colorectal cancer screening guidelines. There is an associated net benefit of screening according to the United States Preventive Services Task Force (USPSTF) in average risk patients 45-75 years of age (Grade A recommendation (50-75 years old) and Grade B recommendation (45-49 years old)). Also, there is a USPSTF Grade C recommendation for CRC screening in patients 76-85 years old; upon patient and physician discussion of the patient's overall health, prior screening history, and preferences, CRC screening may be offered in this age group (USPSTF Recommendation Statement, JAMA 2021). Also, it is important to acknowledge American Cancer Society's statement that "Screening with any one of multiple options is associated with a significant reduction in CRC incidence through the detection and removal of adenomatous polyps and other pre-cancerous lesions and with a reduction in mortality through incidence reduction and early detection of CRC." Thus, screening and detection of both CRC and adenomatous polyps and other pre-cancerous lesions, are considered to contribute to the reduction in CRC incidence, and ultimately clinical benefit through a reduction in mortality. The USPSTF has carefully examined the available screening modalities, and notes that "The risks and benefits of different screening tests vary. Because of limited available evidence, the USPSTF recommendation does not include serum tests, urine tests, or capsule endoscopy for colorectal cancer screening." (USPSTF Recommendation Statement, JAMA 2021). However, the USPSTF delineates key screening options that are available, which include, the following recommended screening strategies:

- High-sensitivity guaiac fecal occult blood test (HSgFOBT) or fecal immunochemical test (FIT) every year
- Stool DNA-FIT every 1 to 3 years
- Computed tomography colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years + annual FIT
- Colonoscopy screening every 10 years.

Of note, while the USPSTF studied the blood based methylated-Septin9 in the 2016 recommendation on CRC screening (USPSTF Recommendation Statement, JAMA 2016), it does not in the most recent 2021 recommendation. The Guardant Shield test presents a new blood based screening option that is the subject of this panel discussion. Blood based CRC

screening tests may have the benefit of higher adherence / compliance; however, depending on the blood based screening test's performance, there may be an increased risk that patients may fail to have colorectal cancer detected at earlier stage because they have chosen to forgo screening colonoscopies in favor of the convenience of the blood based method. The probable benefits and risks of this device for screening the average risk population need to be carefully considered.

4.2 CRC In Vitro DIAGNOSTIC LANDSCAPE

There are several existing FDA approved devices for CRC screening in an average risk population for developing colorectal cancer (e.g., Cologuard, Epi proColon). A summary of the CRC screening performance for these devices is provided in Table 2. Estimates of sensitivity for CRC and AA along with two-sided 95% confidence intervals (95%CI) are provided below in Table 2; specificity estimates along with two-sided 95%CI were also provided for patients without (CRC or AA). Some in vitro diagnostic CRC screening tests, such as Exact Cologuard test, may be considered "First line" tests which are indicated as a primary screening option for individuals at average risk for CRC who are typical candidates for CRC screening. Other CRC screening tests, such as Epi proColon, have a different claim that may be considered "second line" and are indicated for individuals at average risk for CRC who decline recommended screening methods, such as colonoscopy or other first line CRC screening tests. Guardant's proposed indication for Shield test is for colorectal cancer screening in individuals at average risk of the disease, most similar to a "first line" claim.

Table 2. Performance of Alternative FDA Authorized Tests Used for CRC Screening, Including Percent Sensitivity and Specificity with 2-sided 95% CI and Fractions

	Cologuard[1]	**Epi proColon[2]**
Intended Use	CRC and AA	CRC only; limited
Specimen type	Stool	Blood
Sensitivity - CRC (95% CI) (fraction)	**92.3%** (83.0%, 97.5%) (60/65)	**68.2%** (53.4%, 80.0%) (30/44)
Sensitivity - AA (95% CI) (fraction)	**42.4%** (38.8%, 46.0%) (321/757)	**22%**[4] (19%, 25%) (134/621)
Specificity (95% CI) (fractions)	**86.6%** (85.9%, 87.3%) (7936/9167)	**78.8%** (76.7%, 80.8%) (1182/1500)

[1]Cologuard SSED (P130017) https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017B.pdf
[2] Epi proColon SSED (P130001) https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130001B.pdf

FIT tests are authorized by the FDA for the detection of hemoglobin in stool and do not explicitly have FDA authorization for CRC screening. Some clinical practice guidelines (e.g., from USPSTF) recommend uses for FIT tests in CRC screening. The performance of FIT tests for CRC screening has been reported in multiple publications. For example, in a meta-analysis of 19 studies (one-time FIT screening) in asymptomatic average-risk, authors report that the pooled sensitivity of FIT was 79% (95% CI 0.69-0.86) for CRC with a specificity of 94% (95% CI 0.93-0.95) (Lee et al., 2014; Robertson et al., 2017). Similar results were reported in a study reported by Imperiale et. al (NEJM, 2014), in which FIT sensitivity for detecting colorectal cancer was 73.8% (95% CI 61.5%-84.0%, 48 of 65 CRC detected), specificity was 94.9% (95% CI 94.4%-95.3%, 8695 out of 9167 non-advanced

neoplasia), and AA sensitivity of 23.8% (95% CI 20.8%-27.0%' 180 of 757 AA detected).

5 PIVOTAL CLINICAL STUDY

The ECLIPSE study ("Evaluation of ctDNA LUNAR Assay In an Average Patient Screening Encounter") was a registrational study to evaluate the performance of LUNAR-2[1] blood test to detect colorectal cancer (CRC) in average-risk adults. This study was a multi-site, prospective, non-randomized, observational study designed to evaluate the clinical performance of Shield in patients 45 – 84 years of age who were of average risk for CRC. Patients eligible for CRC screening and intending to undergo colonoscopy were enrolled in the study. The study enrolled a total of 24876 subjects from 265 sites across the US between October 8, 2019, and the data cutoff on September 30, 2022. Blood samples were collected from all patients who consented to enroll in the study and met eligibility criteria. Blood collection was performed prospectively using Guardant Blood Collection Kits from all enrolled subjects prior to the patient undergoing standard of care colonoscopy and were processed and analyzed at Guardant Health. Performance of the Shield test was compared against the reference method of colonoscopy. Central pathology reviews were conducted for lesion classification. The lesion of greatest clinical significance was used to classify each subject into one of the histopathology categories listed in Table 3. These categories were used to designate the reference result for the purpose of determining test sensitivity and specificity, positive predictive value and negative predictive value.

Table 3. Colonoscopy/Histopathology Diagnosis Category Descriptions

Category	Findings	Class for Reference Result
1	Colorectal cancer, any stage	**CRC**
2	Advanced adenoma	**AA**
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	**Non-AN**
4	Non-advanced adenoma, 1 or 2 adenomas, >5 mm, <10 mm	
5	Non-advanced adenoma, 1 or 2 adenomas, ≤5 mm	
6	Negative, or other findings	
7	Not evaluable	

[1] The test was originally named "LUNAR-2"at the time of the clinical study, and was renamed to "Shield" at the time of the PMA submission.

5.1 Enrollment Criteria

5.1.1 Inclusion Criteria

Patients who met the following criteria were considered for inclusion in this study:

- Aged 45 to 84 years at time of consent.
- Intended to undergo screening colonoscopy.
- Considered by a physician or healthcare provider as being of average risk for CRC.
- Willing to consent to blood draw pre-bowel preparation administration prior to undergoing colonoscopy within 60 days (amended to 6 months) of the date of the investigational blood draw.
- Willing and able to participate in required study activities.

5.1.2 Exclusion Criteria

Patients who met any one of the following criteria were excluded from this study:

- Undergoing colonoscopy for investigation of symptoms.
- Has undergone colonoscopy within preceding 9 years.
- Positive FIT/fecal occult blood test result within the previous 6 months.
- Has completed Cologuard or Epi proColon testing within the previous 3 years.
- Personal history of CRC.
- Personal history of any malignancy (patients who have undergone surgical removal of skin squamous cell cancer may be enrolled provided the procedure was completed at least 12 months prior to the date of provision of informed consent for the study).
- Known diagnosis of inflammatory bowel disease.
- Currently taking any anti-neoplastic or disease-modifying anti-rheumatic drugs.
- Family history of CRC, defined as having one or more first-degree relatives (parent, sibling, or child) with CRC at any age.
- Known hereditary/germline risk of CRC (for example, Lynch syndrome or hereditary nonpolyposis CRC, or familial adenomatous polyposis).
- Any major physical trauma (e.g., disruption of tissue, surgery, organ transplant, blood product transfusion) within the 30 days leading up to the provision of informed consent.
- Known medical condition which, in the opinion of the Investigator, should preclude enrollment into the study.
- Participation in a clinical research study in which an experimental medication has been administered or may be administered within the 30 days leading up to providing informed consent or may be administered through the time of colonoscopy.

5.2 Clinical Study Objectives

5.2.1 Primary Objectives

The primary objective of this study was to establish the performance characteristics of the Shield test sensitivity for CRC (category 1, Table 3) and specificity of non-advanced neoplasia (categories 3, 4, 5, and 6), Table 3) in average-risk patients against the reference standard defined by colonoscopy/histopathology diagnosis. Acceptance criteria for the primary endpoints were based on the acceptance criteria for sensitivity of CRC and specificity for non-CRC:

- Guardant's performance goal for the sensitivity for CRC was based on the lower bound of the two-sided 95% confidence interval >65%.
- Guardant's performance goal for AN specificity was based on the lower bound of the two-sided 95% confidence interval >85%.

5.2.2 Secondary Objectives

The secondary objective was to establish the sensitivity of the Shield test in the detection of advanced adenomas in average-risk patients. Guardant did not include a performance goal for the secondary endpoint of AA sensitivity.

6 CLINICAL PERFORMANCE STUDY RESULTS

6.1 Accountability of Clinical Performance Study

Samples were collected from a total of 24876 subjects at 265 sites for the Shield test. The disposition of the specimens and colonoscopy results from patients enrolled into the clinical study is as follows:

- Of the total 24876 subjects, 1999 subjects from a prespecified enrollment time window were used toward the device development.
- Of the remaining 22877 subjects, 10179 subjects were randomly selected not to be screened with the Shield test. The remaining 12698 subjects included all CRC subjects and a proportion of non-CRC subjects selected through random down-sampling to match US Census age distribution.
- Of the 12698 subjects, 10297 subjects met study inclusion / exclusion criteria and have valid colonoscopy within 183 days and have valid Shield results. This population included 65 subjects with CRC.
- Of the 10297 subjects, 2436 were randomly selected for interim specificity analysis and cut-offs selection, therefore, 7861 subjects were included in pivotal clinical validation dataset.
- The total number of patients in the final clinical validation evaluable dataset consisted of **7861** subjects with valid colonoscopy and valid Shield test results that were analyzed in the primary analysis dataset.

A sample flowchart for the whole validation dataset is shown in Figure 4 below.

Figure 4. Patient accountability diagram showing breakdown of patient samples and colonoscopy results with sequential application of exclusions between the total available for primary analysis and those not included in the primary analysis.

The percent of Shield Invalid results was 3.1% (345/11211) with 95%CI: (2.8%, 3.4%). Invalid results were excluded from the data analysis.

Guardant initiated enrollment into the ECLIPSE study on October 8, 2019 with database cutoff on September 30, 2022. The Guardant LUNAR-2 device was initially designed to include only a cfDNA assay workflow. In July 2021, the device was updated to include a protein workflow with the aim of improving the detection of advanced adenomas (hereafter, the 2021 device version). The first module for the PMA application for the Shield device was submitted on April 18, 2022. The device review therefore originally requested approval of the 2021 device version. Guardant stated that due to the pre-analytical instability of the protein analyte, a decision was made in October 2022 to define a configuration of the device that removed the protein component of the workflow and reverted to the initial cfDNA-only device configuration. This cfDNA-only device (the Shield test) utilizes the same cfDNA assay workflow, calling algorithms, and classification scores that were part of the 2021 device version. The changes in the Shield device from the 2021 version include: the exclusion of the protein assay workflow, exclusion of the protein reagents and instrumentation, and update to the cutoffs for the cfDNA classification scores due to the removal of the protein assay results. The Shield device changes were made after Guardant

initiated testing of the specimens from patients enrolled into the trial but prior to unblinding of the colonoscopy/biopsy results. During the PMA review, FDA reviewed additional analyses performed to evaluate whether device modifications that were made during the clinical study, and the subjects and specimens from the original enrolment that were assigned to different datasets (e.g., modify the cut-off, interim analyses, preliminary specificity assessment), introduced any bias when assessing device performance. In general, the performance reported by Guardant using the final Shield cfDNA cutoff was comparable to a published methodology that considered a pre-specified fixed target for specificity in the primary analysis dataset (Kondratovich et al, 2005). An additional analysis comparing performance of the primary dataset excluding and including the interim analysis population demonstrated that there were no significant differences in clinical performance observed between subgroups. FDA concluded that the sensitivity and specificity data presented are representative of the device performance.

6.2 Study Population Demographics

The demographic and baseline characteristics for subjects in the primary analysis dataset considered by Guardant (7861 subjects constituting final clinical validation evaluable dataset) are presented in Table 4. There was generally a balance of male and female study participants, and the average age was 60 years. 79% of the subjects were White, 12% were Black or African American, and 13% were of Hispanic or Latino. The majority of subjects (70.2%) never smoked.

Table 4. Demographics and Baseline Characteristics of Subjects by Procedural and Lesion Findings

Characteristic	All (N=7,861)	CRC (N = 65)	AA (N = 1116)	Non-AN (N = 6680)	Non-CRC (N = 7796)
Age (years)					
n	7861	65	1116	6680	7796
Mean (SD)	60.3 (9.14)	63.2 (8.26)	61.6 (8.67)	60.0 (9.20)	60.3 (9.14)
Median	60	63	62	60	60
Min, Max	45, 84	45, 82	45, 82	45, 84	45, 84
Age Group, n (%)					
45-49	640 (8.1)	4 (6.2)	56 (5.0)	580 (8.7)	636 (8.2)
50-59	3055 (38.9)	13 (20.0)	385 (34.5)	2657 (39.8)	3042 (39.0)
60-69	2440 (31.0)	34 (52.3)	417 (37.4)	1989 (29.8)	2406 (30.9)
70-79	1670 (21.2)	13 (20.0)	252 (22.6)	1405 (21.0)	1657 (21.3)
80+	56 (0.7)	1 (1.5)	6 (0.5)	49 (0.7)	55 (0.7)
Gender, n (%)					
Female	4218 (53.7)	30 (46.2)	511 (45.8)	3677 (55.0)	4188 (53.7)
Male	3643 (46.3)	35 (53.8)	605 (54.2)	3003 (45.0)	3608 (46.3)
Race, n (%)					

Characteristic	All (N=7,861)	CRC (N = 65)	AA (N = 1116)	Non-AN (N = 6680)	Non-CRC (N = 7796)
American Indian or Alaska Native	14 (0.2)	0	2 (0.2)	12 (0.2)	14 (0.2)
Asian	560 (7.1)	4 (6.2)	56 (5.0)	500 (7.5)	556 (7.1)
Black or African American	931 (11.8)	10 (15.4)	121 (10.8)	800 (12.0)	921 (11.8)
Native Hawaiian or Other Pacific Islander	19 (0.2)	0	2 (0.2)	17 (0.3)	19 (0.2)
White	6167 (78.5)	49 (75.4)	917 (82.2)	5201 (77.9)	6118 (78.5)
Other	137 (1.7)	1 (1.5)	16 (1.4)	120 (1.8)	136 (1.7)
Multiple	23 (0.3)	1 (1.5)	2 (0.2)	20 (0.3)	22 (0.3)
Missing	10 (0.1)	0	0	10 (0.1)	10 (0.1)
Ethnicity, n (%)					
Hispanic	1044 (13.3)	11 (16.9)	127 (11.4)	906 (13.6)	1033 (13.3)
Not Hispanic or Latino	6779 (86.2)	54 (83.1)	984 (88.2)	5741 (85.9)	6725 (86.3)
Missing	38 (0.5)	0	5 (0.4)	33 (0.5)	38 (0.5)
BMI category, n (%)					
<30	4610 (58.6)	38 (58.5)	619 (55.5)	3953 (59.2)	4572 (58.6)
>=30 & <35	1873 (23.8)	14 (21.5)	283 (25.4)	1576 (23.6)	1859 (23.8)
35+	1375 (17.5)	13 (20.0)	213 (19.1)	1149 (17.2)	1362 (17.5)
Missing	3 (0.0)	0	1 (0.1)	2 (0.0)	3 (0.0)
Tobacco Use, n (%)					
Never	5522 (70.2)	41 (63.1)	711 (63.7)	4770 (71.4)	5481 (70.3)
Current	737 (9.4)	9 (13.8)	158 (14.2)	570 (8.5)	728 (9.3)
Former	1601 (20.4)	15 (23.1)	247 (22.1)	1339 (20.0)	1586 (20.3)
Missing	1 (0.0)	0	0	1 (0.0)	1 (0.0)
Alcohol Use, n (%)					
Never	3449 (43.9)	30 (46.2)	471 (42.2)	2948 (44.1)	3419 (43.9)
Current	4004 (50.9)	28 (43.1)	583 (52.2)	3393 (50.8)	3976 (51.0)
Former	406 (5.2)	7 (10.8)	62 (5.6)	337 (5.0)	399 (5.1)
Missing	2 (0.0)	0	0	2 (0.0)	2 (0.0)
Illicit Drug Use, n (%)					
Never	7481 (95.2)	63 (96.9)	1052 (94.3)	6366 (95.3)	7418 (95.2)
Current	148 (1.9)	0	26 (2.3)	122 (1.8)	148 (1.9)
Former	229 (2.9)	2 (3.1)	38 (3.4)	189 (2.8)	227 (2.9)
Missing	3 (0.0)	0	0	3 (0.0)	3 (0.0)

6.3 Effectiveness Data

6.3.1 Primary Effectiveness Analysis

Shield clinical performance was evaluated in the primary analysis dataset of 7861 subjects with valid colonoscopy diagnosis and valid Shield test.

Because analyses were done separately for CRC and AA screening performance, the clinical effectiveness data can be understood in the following way (shown in Table 5 below):

Table 5. Clinical performance table

	CRC	**AA**	**Non-AN**	**Total**
Shield Positive	A_1	B_1	C_1	$A_1+B_1+C_1$
Shield Negative	A_2	B_2	C_2	$A_2+B_2+C_2$
Total	A_1+A_2	B_1+B_2	C_1+C_2	N

- Estimate of sensitivity for CRC is $A_1/(A_1+A_2)$;
- Estimate of sensitivity for AA is $B_1/(B_1+B_2)$;
- Estimate of specificity for non-AN is $C_2/(C_1+C_2)$.

The two-sided 95% confidence intervals were calculated using the Wilson score method recommended in the CLSI document EP12-Ed3.

The clinical performance data for 7861 subjects is presented in Table 6 below.

Table 6. Device Sensitivity and Specificity

		Colonoscopy/Histopathology			
		CRC	**AA**	**Non-AN**	**Total**
Shield Test Result	Abnormal Signal Detected (Positive)	54	147	698	899
	Normal Signal Detected (Negative)	11	969	5982	6962
	Total	65	1116	6680	7861

CRC Sensitivity = % (n/N) (two-sided 95% CI)	83.1 (54/65), (72.2, 90.3)
AA Sensitivity = % (n/N) (two-sided 95% CI)	13.2 (147/1116), (11.3, 15.3)
AN Specificity = % (n/N) (two-sided 95% CI)	89.6 (5982/6680), (88.8, 90.3)

a) CRC sensitivity was evaluated as the proportion of CRC subjects that had a positive Shield test result (Abnormal Signal Detected); the estimate of the CRC sensitivity was **83.1%** (54/65) with two-sided 95%CI: (**72.2%,** 90.3%).
b) AA sensitivity was evaluated as the proportion of AA subjects that had a positive Shield result (Abnormal Signal Detected): the estimate of the AA sensitivity was **13.2%** (147/1116) with 95%CI: (**11.3%**, 15.3%).
c) Non-AN specificity was evaluated as the proportion of non-AN subjects that had a negative Shield test result (Normal Signal Detected); the estimate of the non-AN specificity was 89.6% (5982/6680) with two-sided 95%CI: (88.8%, 90.3%).

6.3.2 Subgroup Analyses

The ECLIPSE study results were also analyzed according to various demographic characteristics, as well as lesion size and location.

6.3.2.1 Performance of Shield Test (CRC Sensitivity, AA Sensitivity, non-AN Specificity) Stratified by Age Groups

Summarized performance of the Shield Test for following age groups: 45-49, 50-59, 60-69, 70-79 and 80+ are presented in Table 7 below.

Table 7. Clinical performance by age group in primary analysis dataset.

Age Group	Clinical performance in primary analysis dataset, n=7861		
	Sensitivity		Specificity
	CRC	AA	non-AN
45-49	**75.0%** (30.1%, 95.4%) 3/4	**3.6%** (1.0%, 12.1%) 2/56	**95.5%** (93.5%, 96.9%) 554/580
50-59	**76.9%** (49.7%, 91.8%) 10/13	**8.6%** (6.2%, 11.8%) 33/385	**93.0%** (91.9%, 93.9%) 2470/2657
60-69	**88.2%** (73.4%, 95.3%) 30/34	**15.1%** (12.0%, 18.9%) 63/417	**89.7%** (88.3%, 91.0%) 1785/1989
70-79	**76.9%** (49.7%, 91.8%) 10/13	**18.7%** (14.3%, 23.9%), 47/252	**80.9%** (78.7%, 82.8%) 1136/1405
80+	**100.0%** (20.7%, 100.0%) 1/1	**33.3%** (9.7%, 70.0%) 2/6	**75.5%** (61.9%, 85.4%) 37/49

Age Group	Clinical performance in primary analysis dataset, n=7861		
	Sensitivity		Specificity
	CRC	AA	non-AN
Combined data of the clinical study	**83.1%** (72.2%, 90.3%) 54/65	**13.2%** (11.3%, 15.3%) 147/1116	**89.6%** (88.8%, 90.3%) 5982/6680

Because of small sample sizes in the low and high age groups, three age categories were considered: Group 1 (45-59 years), Group 2 (60-69 years) and Group 3 (70+) to evaluate potential differences in the Shield test performance with regard to age. Data is shown in Tables 8-10 below.

i) Table 8. Sensitivities for CRC for Group 1, Group 2 and Group 3 were following:

Sensitivity for CRC		
	Estimate	95%CI
Group 1 (45-59)	76.5% (13/17)	(52.7%, 90.4%)
Group 2 (60-69)	88.2% (30/34)	(73.4%, 95.3%)
Group 3 (70+)	78.6% (11/14)	(52.4%, 92.4%)

Differences in sensitivities were not statistically significant because the confidence intervals are overlapping between age groups.

ii) Table 9. Sensitivities for AA for Group 1, Group 2 and Group 3 were following:

Sensitivity for AA		
	Estimate	95%CI
Group 1 (45-59)	7.9% (35/441)	(5.8%, 10.8%)
Group 2 (60-69)	15.1% (63/417)	(12.0%, 18.9%)
Group 3 (70+)	19.0% (49/258)	(14.7%, 24.2%)

There is a trend of increasing the sensitivity of AA with increasing age. Sensitivity increased from 7.9% to 15.1% between groups 1 and 2 (95%CIs are not overlapping). However, the difference in sensitivity between groups 2 and 3, while 15.1% to 19.0% was not statistically significant.

iii) Table 10. Specificity for non-AN for Group 1, Group 2 and Group 3 were following:

Specificity for non-AN		
	Estimate	95%CI
Group 1 (45-59)	93.4% (3024/3237)	(92.5%, 94.2%)
Group 2 (60-69)	89.7% (1785/1989)	(88.3%, 91.0%)
Group 3 (70+)	80.7% (1173/1454)	(78.6%, 82.6%)

There is a tendency of decreasing the specificity for non-AN with an increase of age: the decrease in specificity was statistically significant (all three 95%CIs are not overlapping).

iv) Age-adjusted Performance of the Shield test:
The performance of the Shield test is different for three age groups, therefore, in the calculation of the overall sensitivity for CRC, overall sensitivity for AA and overall specificity for non-AN, the age distribution should be considered.

At the beginning of the clinical study, all subject age groups (45 years or older) were enrolled at a natural prevalence, and later an enrollment was halted in subjects 45 to 59 years and continued only in subjects 60 years or older to increase the prevalence of the CRC in the clinical study. Because the study was enriched for older age patients, it was prospectively planned to select subjects to be tested with the Shield tests by random down sampling to match US 2020 census age distribution. An adjusted analysis for the overall Shield sensitivity for CRC, the overall sensitivity for AA and the overall specificity for non-AN using age grouping performance to assess the distribution of age categories from the US Census population in 2020 is shown in Table 11.

Table 11. Age-adjusted performance.

	Age distribution in the Clinical Study data	Age distribution in USA population, 2020
Group 1: 45-59	47.0%	47.8%
Group 2: 60-69	31.0%	29.4%
Group 3: 70+	22.0%	22.8%
	Performance in combined data of clinical study	Age adjusted performance*
Sensitivity for CRC	83.1%	80.8%
Sensitivity for AA	13.2%	12.9%
Specificity for non-AN	89.6%	89.5%

*For example, sensitivities for CRC for group1, 2 and 3 were 76.5%, 88.2% and 78.6% correspondingly. In the US 2020 population, age distribution was 47.8%, 29.4% and 22.8% correspondingly. The prevalence for CRC was 0.30%, 0.43% and 0.64% correspondingly. Then age-adjusted sensitivity for CRC is calculated as (0.478*0.0030*76.5%+0.294*0.0043*88.2%+0.228*0.0064*78.6%)/(0.478*0.0030+0.294*0.0043+0.228*0.0064)=80.8%.

In summary, since, in the clinical study, an age distribution was different from the age distribution according to 2020 census information, age-adjusted performance estimates were summarized in the Table 12 below. In addition, since intended use population for the Shield test is patients of 45 years or older; for a comparison purpose to the performance of previously approved FDA tests, the performance of the Shield Test is also presented for patients of 50 years or older.

Table 12. Comparison of Clinical Performance Summarized by Population Age Including Age-Adjusted Percent Sensitivity and Specificity, with two-sided 95% CI

	Shield Performance			
Intended Use Population Age	For 45+ years		For 50+ years	
	For 45+ years, Clinical study	For 45+years, age adjusted	For 50+ years, Clinical study	For 50+ years, age adjusted
Sensitivity -CRC (95% CI) (fraction)	**83.1%** (72.2%, 90.3%) (54/65)	**80.8%**	**83.6%** (72.4%, 90.8%) (51/61)	**81.3%**
Sensitivity	**13.2%**	**12.9%**	**13.7%**	**13.8%**

-AA (95% CI) (fraction)	(11.3%, 15.3%) (147/1116)		(11.7%, 15.9%) (145/1060)	
Specificity -non-AN (95% CI) (fraction)	**89.6%** (88.8%, 90.3%) (5982/6680)	**89.5%**	**89.0%** (88.2%, 89.7%) (5428/6100)	**88.6%**

6.3.2.2 Performance of Shield Test (CRC Sensitivity, AA Sensitivity, non-AN Specificity) Stratified by Lesion Covariates

Table 13. Clinical performance by lesion covariates (sensitivity and specificity) in primary analysis dataset

Lesion covariates	Category	Sensitivity	95% CI
CRC Stage	All	83.1% (54/65)	(72.2%, 90.3%)
	Stage I	54.5% (12/22)	(34.7%, 73.1%)
	Stage II	100.0% (14/14)	(78.5%, 100.0%)
	Stage III	100.0% (18/18)	(82.4%, 100.0%)
	Stage IV	100.0% (9/9)	(70.1%, 100.0%)
	Stage Unknown	50.0% (1/2)	(9.5%, 90.5%)
CRC Lesion Size	All	83.1% (54/65)	(72.2%, 90.3%)
	<5 mm	0.0% (0/1)	(0.0%, 79.3%)
	5-9 mm	0.0% (0/5)	(0.0%, 43.4%)
	10-19 mm	87.5% (7/8)	(52.9%, 97.8%)
	20-29 mm	83.3% (10/12)	(55.2%, 95.3%)
	30+ mm	94.7% (36/38)	(82.7%, 98.5%)
	Unknown	100.0% (1/1)	(20.7%, 100.0%)
AA Lesion Size	All	13.2% (147/1116)	(11.3%, 15.3%)
	<5 mm	0.0% (0/4)	(0.0%, 49.0%)
	5-9 mm	18.8% (9/48)	(10.2%, 31.9%)
	10-19 mm	11.9% (102/859)	(9.9%, 14.2%)
	20-29 mm	13.6% (18/132)	(8.8%, 20.5%)
	30+ mm	23.6% (17/72)	(15.3%, 34.6%)
	Unknown	100.0% (1/1)	(20.7%, 100.0%)
AA Sensitivity Histopathology Diagnosis Sub-categories	All	13.2% (147/1116)	(11.3%, 15.3%)
	Advanced Adenoma, Carcinoma in situ (CIS), any size	0.0% (0/1)	(0.0%, 79.3%)
	Advanced Adenoma, with High-grade dysplasia (HGD), any size	22.6% (7/31)	(11.4%, 39.8%)
	Advanced Adenoma with villous component (>= 25%), any size	17.9% (37/207)	(13.3%, 23.7%)
	Tubular Adenoma >= 10 mm in size	12.0% (82/685)	(9.7%, 14.6%)
	Serrated lesion >= 10 mm in size (includes Sessile serrated adenoma/sessile serrated polyp (SSA/SSP)	11.0% (21/191)	(7.3%, 16.2%)
	Unknown	0.0% (0/1)	(0.0%, 79.3%)
Lesion covariates	Category	Specificity	95% CI

Non-AN Specificity Histopathology	All	89.6% (5982/6680)	(88.8%, 90.3%)
Diagnosis Sub-categories	(Category 3) Non-advanced Adenoma, >= 3 adenomas, < 10 mm	87.7% (284/324)	(83.6%, 90.8%)
	(Category 4) Non-advanced Adenoma, 1 or 2 adenomas, > 5 mm, < 10 mm	89.0% (614/690)	(86.4%, 91.1%)
	(Category 5) Non-advanced Adenoma, 1 or 2 adenomas, <= 5 mm	89.1% (1027/1152)	(87.2%, 90.8%)
	(Category 6) Negative, no findings	89.9% (4057/4514)	(89.0%, 90.7%)

6.3.3 Positive and Negative Predictive Values (PPV and NPV)

Analysis was also performed to calculate the positive and negative predictive values (PPV and NPV) for Shield (Table 14).

- The positive predictive value (PPV) for CRC is a fraction of patients with CRC among the patients with positive Shield test results. The PPV for AA is a fraction of patients with AA among the patients with positive Shield test results.
- The negative predictive value (NPV) for CRC is a fraction of patients without CRC among the patients with negative Shield test results. The NPV for AN (CRC or AA) is a fraction of patients without AN among the patients with negative Shield test results.

The PPV for any CRC screening test is impacted by the very low prevalence of CRC in the general population with an average risk (listed in Table 14, by age).

Prevalence of CRC in the clinical validation dataset of 7861 patients was higher than the prevalence of the CRC in the general population at average risk due to including only CRC cases from the entire clinical validation dataset, down-sampling for other pathology categories (AA, non-AN), and further exclusion of interim specificity and cutoff determination dataset. Unbiased estimates of the CRC prevalence in different age groups were calculated using the data of all subjects with colonoscopy results and these unbiased estimates of the CRC prevalence were used in calculation of predictive values presented in the table below.

- For example, for patients of age group 45-49, prevalence of CRC was 0.24%.
- 4.58% of the patients of 45-49 age group have positive Shield test results.
- 3.93% of the patients who had positive Shield results had CRC (PPV for CRC of 3.93%), and 5.76% of the patients who had positive Shield results had AA (PPV for AA of 5.76%).
- 99.94% of patients with negative Shield results did not have CRC (NPV for CRC of 99.94%), and 92.47% of patients with negative Shield results were negative for AN (NPV for AN of 92.47%).

Table 14. Predictive Values of Shield %, two-sided 95% CI. PPV is colored green, NPV is colored blue, and the fraction of CRC or AA among the patients with negative Shield test results is colored orange.

	Prevalence of CRC	**Prevalence of AA**	**Percent Positive Shield results**		**%CRC**	**%AA**	**%non-AN**
45-49	0.24% (4/1664)	7.39% (123/1664)	4.58%	Among Shield Positive Results	3.93%	5.76%	90.31%
				Among Shield Negative Results	0.06%	7.47%	92.47%
50-59	0.33% (18/5407)	10.49% (567/5407)	7.43%	Among Shield Positive Results	3.45%	12.09%	84.46%
				Among Shield Negative results	0.08%	10.36%	89.56%
60-69	0.43% (41/9559)	10.78% (1030/9559)	11.11%	Among Shield Positive Results	3.41%	14.65%	81.95%
				Among Shield Negative results	0.06%	10.29%	89.65%
70-79	0.56% (15/2694)	12.47% (336/2694)	19.41%	Among Shield Positive Results	2.21%	11.99%	85.81%
				Among Shield Negative results	0.16%	12.59%	87.25%
80+	0.96% (1/104)	6.73% (7/104)	25.81%	Among Shield Positive Results	3.73%	8.69%	87.58%
				Among Shield Negative results	0.00%	6.05%	93.95%
Age-adjusted (2020)	0.42%	10.28%	11.10%	Among Shield Positive Results	3.10%	12.04%	84.86%
				Among Shield Negative results	0.08%	10.06%	89.86%

- The prevalence of CRC is increasing with an increase of age from 0.24% in 45-49 age group to 0.96% in 80+ group.
- The percent of positive Shield results is also increasing with an increase of age from 4.58% in 45-49 age group to 25.81% in 80+ group.
- The percent of CRC among the Shield positive results was in range 2.21% to 3.93%.
- Among Shield positive results, percent of subjects with AA is ranged from 5.76% to 14.65%.
- Percent of subjects with CRC among subjects with negative Shield results is ranged from 0.06% to 0.16%.

6.3.4 Conclusions

The pivotal study design was focused on patients of average risk who agreed to participate in screening by colonoscopy. It was not designed to yield performance information when

used as a substitute for colonoscopy or non-invasive colorectal cancer screening methods in settings of heightened clinical concern including high risk patients (e.g., predisposition due to genetics or gastrointestinal disease), diagnostic colonoscopy (e.g., patients with signs or symptoms), or surveillance colonoscopy (e.g., patients with personal history of colon cancer or polyps). Performance of the device in patients who refused screening colonoscopy cannot be determined from this study.

The performance of Shield has been established in a prospectively designed, blinded, cross-sectional study. The performance of Shield (i.e., benefits and risks of programmatic colorectal screening (i.e., repeated testing over an established period of time) with Shield has not been studied. Non-inferiority or superiority of Shield programmatic sensitivity as compared to other recommended screening methods for colorectal cancer has not been established.

Shield sensitivity for CRC in the primary analysis dataset is 83.1% with 95% CI: (72.2% to 90.3%), and specificity for non-AN is 89.6% with 95% CI: (88.8% to 90.2%). Additionally, sensitivity performance for CRC is shown across age groups, racial/ethnic groups, and in both men and women.

The risk of the Guardant blood based test for advanced adenomas is that the test will fail to detect a patient with advanced adenoma which can later become neoplastic, losing the opportunity to prevent or prolong the onset of colorectal cancer. The benefit of the Guardant test is that it may increase compliance with CRC screening and detect earlier stage colorectal cancer, which may potentially cure the patient and also potentially prolong survival when treated.

7 QUESTIONS FOR PANEL DISCUSSION

FDA seeks the Panel's input on whether the information submitted by Guardant is adequate to support the safety and effectiveness of the Shield for the proposed intended use. The key issues for this clinical study are listed below:

1. Shield is intended for colorectal cancer screening in individuals at average risk of the disease, age 45 years or older, as a primary screening option. The Guardant test demonstrated colorectal cancer (CRC) sensitivity of 83.1%, advanced adenoma (AA) sensitivity of 13.2%, and advanced neoplasia (AN) specificity of 89.6%. Please discuss:

    a. Based on the clinical performance of this device, the benefits and risks of the device for CRC screening, including considerations for the appropriate patient population and clinical scenario for this device.

    b. Does the clinical performance support use of the Shield test as a primary screening option (similarly to other non-invasive CRC screening options), or is it more appropriate for specific populations (e.g., patients who decline other CRC screening tests).

2. Patients with AA have a high risk of developing CRC cancer. The Guardant ECLIPSE study demonstrated 83.1% sensitivity for CRC, but only 13.2% sensitivity for the detection of AA. Please discuss:

    a. The benefits and risks of a CRC screening test with 13.2% sensitivity for AA.

    b. If risks are present, please discuss whether there are potential mitigations which might be deployed to ensure physicians and patients are able to make informed choices regarding screening test options to mitigate clinical risks of the Shield test's AA sensitivity.

3. If the device is determined to be safe and effective based on existing data, please discuss whether a post approval study (PAS) to gather additional information about benefits and risks of programmatic colorectal cancer screening (i.e., repeated testing over an established period of time) would be beneficial. Please discuss the types of information that would be important to collect during such a study.

FDA looks forward to a productive Panel discussion regarding these issues.

8 QUESTIONS FOR BALLOT VOTE

The following questions relate to the approvability of Shield:

1. Is there reasonable assurance that the Shield test is safe for the proposed indications for use?

2. Is there reasonable assurance that the Shield test is effective for the proposed indications for use?

3. Do the benefits of the Shield test outweigh the risks for the proposed indications for use?

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