Molecular and Clinical Genetics Panel Meeting
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FDA Presentation

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Premarket Approval (PMA) Application
Guardant Health
Shield

Device Overview and Clinical study

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• Kenneth Morabito	BIMO Review
• Freddy Tita-Nwa	GMP reviewer
• Donna Roscoe	Acting Division Director
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Purpose of Meeting

To obtain input on:

- Safety and effectiveness of the Shield test system
- Whether the benefits outweigh the risks of using Shield for the proposed intended use

Overview of FDA Presentation

Part I: Background and Analytical Studies

- Background for CRC and AA
- Proposed Indications for Use and Contraindications
- Device Overview and Workflow
- Analytical Studies

Part II: Clinical Studies

- Clinical Studies Design and Patient Accountability
- Performance Analyses

Part III: Review Considerations

- Summary of Key Points
- FDA Considerations and Discussion Questions

FDA Presentation Part I

Background and Analytical Studies

- Background for CRC and AA
- Proposed Indications for Use and Contraindications
- Device Overview and Workflow
- Analytical Studies

Disease Background and Review Considerations

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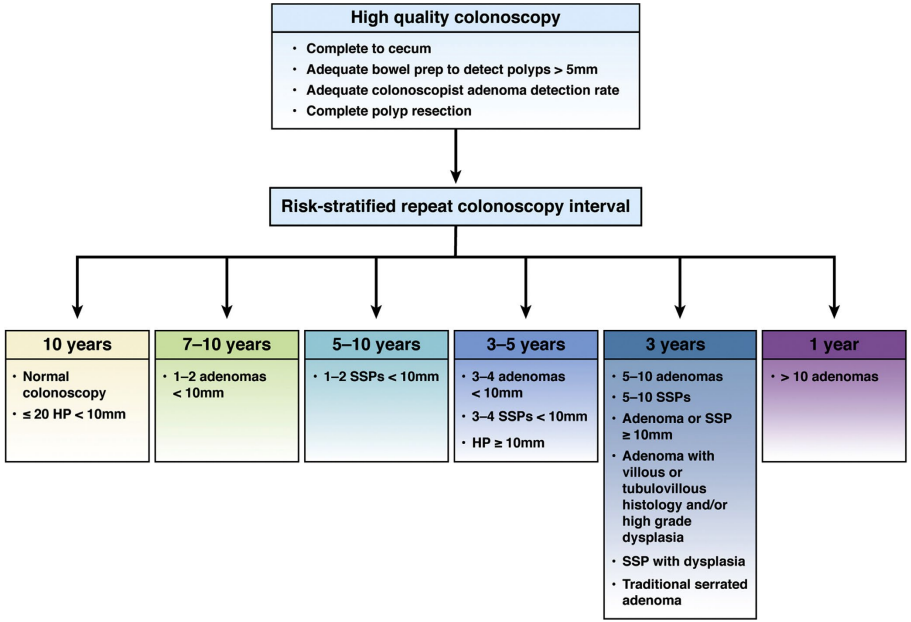
CRC Background

- CRC occurs in ~150,000 patients in the US annually and is associated with over ~50,000 deaths.
- It is the second leading cause of cancer deaths in the US.
- Detecting CRC early may lead to benefit to the public health:
  - localized CRC has approximately 90% 5-year survival rate
  - metastatic CRC has approximately a 15% 5-year survival rate
- Appropriate screening and surveillance strategies may mitigate morbidity and mortality from CRC.

Advanced Adenoma Background

- The majority of CRCs arise from colonic adenomas.
- AA can progress to cancer at an annual rate of up to 5%.
- Detection and removal of AA can reduce the incidence of CRC and the morbidity/mortality associated with CRC.

Follow-Up Surveillance of Adenomas (MSTF)



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

- Patients are triaged into certain intervals of surveillance follow-up based on the size of the adenoma, the histology of the adenoma, the number of adenomas and other factors.
- These surveillance strategies are integral to patient management

CRC Screening in the United States

- ~ 1/3 of screen eligible patients do not undergo screening for CRC.
- ~ 75% of people who died from CRC were not up to date with screening.
- The target for CRC screening is 80% in the US, according to the American Cancer Society/National Colorectal Cancer Roundtable.
- Thus, there is room for improvement of CRC screening uptake in the US.
- Increased screening rates may translate into significant reduction of CRC associated morbidity and mortality.

CRC Screening Guidelines (USPSTF)

- USPSTF evaluates the benefit/risks of screening tests*, and,
- Recommendations are evidence based
- Recommends a variety of modalities for screening, including endoscopic procedures, stool-based methods as well as CT colonography, and,
- Does not currently recommend serum, urine or capsule based methods - limited data
- Recommends considerations be given to variables such as:
  - Frequency of screening needed,
  - Access to screening,
  - Risks associated with the screening procedure,
  - Ability of the patient to complete the pre-procedure bowel preparation,
  - Ability of the patient to undergo anesthesia or sedation,
  - Risk of follow-up procedures for abnormal findings.

*(USPSTF Recommendation Statement, JAMA 2021).

CRC Screening Guidelines (USPSTF)

A variety of testing strategies are currently recommended by the USPSTF, with specified timepoints for repeat testing. These include:

- 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 (CT) colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years + annual FIT
- Colonoscopy screening every 10 years.

CRC Screening Guideline (USPSTF)*

- CRC screening by these guidelines are indicated for those patients 45 or older, who are who are at average risk for colorectal cancer and do not have signs or symptoms of colorectal cancer.
- The USPSTF screening recommendations have varying degrees of strength, depending on the age groups.
- For adults aged 45 to 49 years: **Grade B recommendation: moderate net benefit**
- For adults aged 50 to 75 years: **Grade A recommendation: substantial net benefit**
- For adults aged 76 to 85: **Grade C recommendation: small net benefit.**
  - **Selectively screen adults 76 to 85 years old for CRC, considering the patient's overall health, prior screening history, and patient preferences.**

CRC Screening Guidelines (ACS Statement)

ACS Statement Highlight:

- "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."

Proposed 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 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.

Proposed Contraindications (sponsor)

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, etc.)
- Has a known diagnosis of inflammatory bowel disease

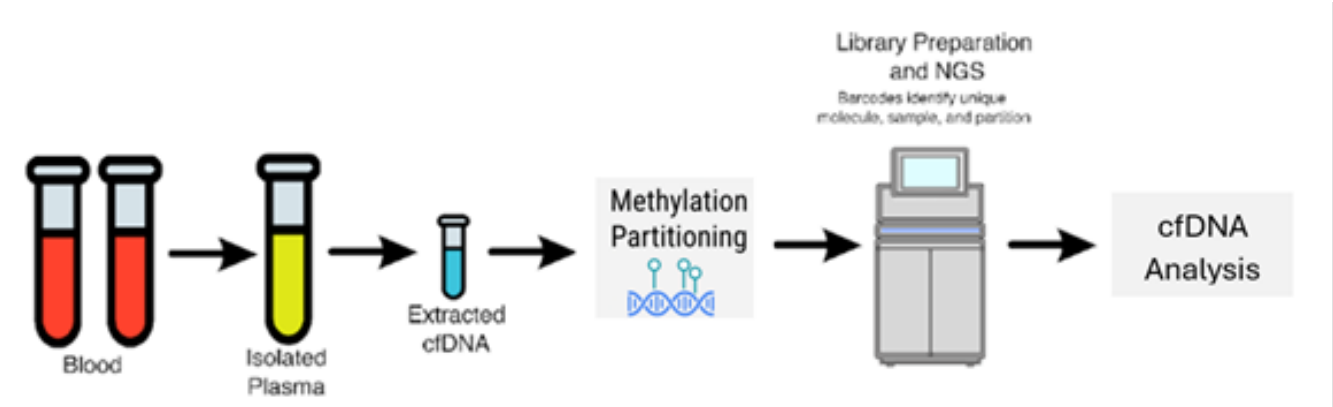
Proposed Key Precautions and Limitations (sponsor)

- 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.

Device Overview and 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. Test workflow includes:

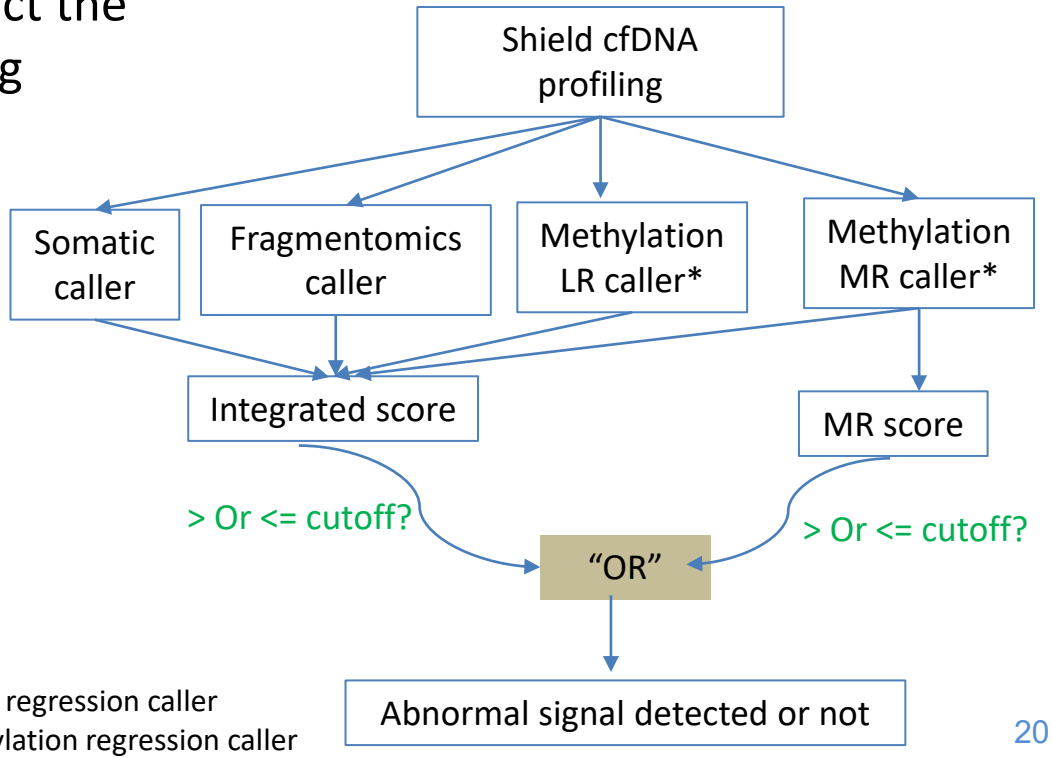
- Whole blood collection and shipment to Guardant Health.
- Plasma isolation from whole blood
- cfDNA extraction from plasma
- DNA sequencing to detect methylation patterns, fragment and genomic alterations
- cfDNA data analyzation



Device panel and algorithm

The Shield Test integrates the signals from three analyte types to predict the presence or absence of circulating tumor DNA (ctDNA):

- Somatic mutations
- Methylation
- Fragmentomics



*LR caller: logistic regression caller
*MR caller: methylation regression caller

Summary of Analytical Studies

- Blood Collection Tube Validation
- Pre-analytical
- Analytical Sensitivity
  - Limit of “Blank”
  - Limit of Detection
- Analytical Specificity
  - Cross-Contamination and Carry-Over
  - In silico primer and probe-specificity
  - Endogenous interfering substances
- Results in Non-Colorectal Cancers and Diseases
- Precision
  - Reproducibility
  - Repeatability
  - Plasma isolation equivalence
  - Reagent lot-to-lot interchangeability
- Robustness
- Sample Stability
- Reagent Stability
- Instrument/Software

FDA Presentation Part II

Clinical study

- Clinical Studies Design
- Patient Accountability
- Primary Effectiveness Results
- Age-Adjusted Sensitivity and Specificity
- Statistical Analyses:
  - Predictive Values
  - Subgroup analyses

ECLIPSE study

The ECLIPSE study ("Evaluation of ctDNA LUNAR Assay* In an Average Patient Screening Encounter") was a registrational study to evaluate the performance of the Shield test to detect colorectal cancer (CRC) in average-risk adults.

* 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.

Clinical Study Design of ECLIPSE

- Prospective enrollment (age 45 - 84)
- 265 sites across the US
- 24,876 subjects enrolled
- Enrollment weighted toward ages 60-84 (63.6%)
- Cross-sectional study design
- Subject underwent colonoscopy within 183 days of sample collection
- Blood sample collection prior to the patient undergoing colonoscopy
- Clinical performance of the Shield test was compared to colonoscopy

ECLIPSE Inclusion Criteria

- Average risk for CRC
- Patient is 45 to 84 years of age
- Intended to undergo screening colonoscopy
- Willing to consent to blood draw pre-bowel preparation and prior to undergoing colonoscopy within 60 days (amended to 6 months) of the date of the investigational blood draw

ECLIPSE Exclusion Criteria*

- Any condition that is considered by a physician or healthcare provider as being of high risk for CRC
  - any diagnosis or personal history of high-risk conditions for colorectal cancer
  - Personal history of CRC
- Family history of CRC, defined as having one or more first-degree relatives (parent, sibling, or child) with CRC at any age.
- Personal history of any malignancy
- Personal history of any high-risk conditions for colorectal cancer, such as inflammatory bowel disease, hereditary cancer syndromes
- Has undergone CRC screening tests
  - 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.
- Known medical condition which, in the opinion of the Investigator, should preclude enrollment into the study.
- Undergoing colonoscopy for investigation of symptoms.
- 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.

* This is an abbreviated list.

Six Histopathological Categories

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 the Table below.

Category	Findings	Class for Reference Result
1	Colorectal cancer, any stage	**CRC**
2	Advanced adenoma	**AA (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	**Non-AN (non-advanced neoplasia)**
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**	

ECLIPSE Study Objectives

Primary Objectives

- Sensitivity for **CRC** based on the lower bound of the two-sided 95% confidence interval >65%.
- **AN** specificity based on the lower bound of the two-sided 95% confidence interval >85%.

Secondary Objectives

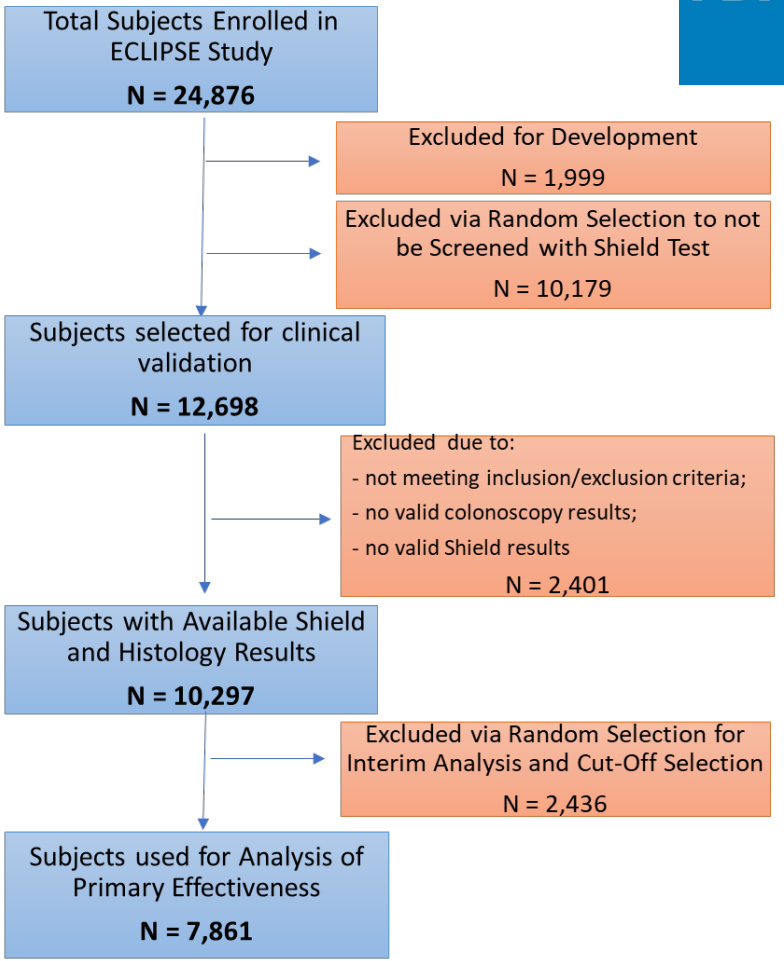
- The secondary objective was to establish the sensitivity of the Shield test in the detection of advanced adenomas in average-risk patients.

ECLIPSE Study Populations

FDA performed subset analyses to evaluate the potential for bias:

- device modifications that were made during the clinical study
- assignment of subjects to different datasets

FDA concluded that the sensitivity and specificity data presented did not create favorable bias to the performance.



Classification Performance of a Test

CRC sensitivity	Proportion of patients in histological category 1 (CRC) who test positive
AA sensitivity	Proportion of patients in histological categories 2 (AA) who test positive
AN specificity	Proportion of patients in histological categories 3-6 (non-AN) that had a negative test result

	Clinical Truth			
	Treated as positive		Treated as negative	
	CRC	**AA**	**Non-AN**	**Total**
Shield Positive	A_1	B_1	C_1	$\mathbf{A_1+B_1+C_1}$
Shield Negative	A_2	B_2	C_2	$\mathbf{A_2+B_2+C_2}$
Total	$\mathbf{A_1+A_2}$	$\mathbf{B_1+B_2}$	$\mathbf{C_1+C_2}$	**N**

- Estimate of sensitivity for CRC is A1/(A1+A2);
- Estimate of sensitivity for AA is B1/(B1+B2);
- Estimate of specificity for AN is C2/(C1+C2).

Primary Effectiveness Results

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

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

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

Note that the AA sensitivity is increasing with age, while AN specificity decreases with age.

Clinical performance by combined age group

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.

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 (95%CIs are overlapping between age groups).

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).

Specificity for 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 AN specificity with an increase of age: the decrease in specificity was statistically significant (all three 95%CIs are not overlapping).

Age-adjusted Performance of the Shield test

The performance of the Shield test is different for three age groups, therefore, the age adjusted overall performance was calculated.

	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 AN	89.6%	**89.5%**

Predictive Values

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

Positive and Negative Predictive Values (PPV and NPV)

	Prevalence of CRC	Prevalence of AA	Percent Positive Shield results	PPV for CRC	PPV for AA	NPV for CRC	NPV for AN
45-49	0.24% (4/1664)	7.39% (123/1664)	4.58%	3.93%	5.76%	99.94%	92.47%
50-59	0.33% (18/5407)	10.49% (567/5407)	7.43%	3.45%	12.09%	99.92%	89.56%
60-69	0.43% (41/9559)	10.78% (1030/9559)	11.11%	3.41%	14.65%	99.94%	89.65%
70-79	0.56% (15/2694)	12.47% (336/2694)	19.41%	2.21%	11.99%	99.84%	87.25%
80+	0.96% (1/104)	6.73% (7/104)	25.81%	3.73%	8.69%	100%	93.95%
Age-adjusted (2020)	**0.42%**	**10.28%**	**11.10%**	**3.10%**	**12.04%**	**99.92%**	**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 subjects with Shield positive results was in range 2.21% to 3.93%.
- The percent of subjects with AA among the subjects with Shield positive results is ranged from 5.76% to 14.65%.
- The percent of subjects with CRC among subjects with negative Shield results is ranged from 0.06% to 0.16%.

Subgroup Analysis
Primary Effectiveness Population

CRC sensitivity stratified by cancer stage

CRC Stage	Sensitivity	95% CI
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%)

- The detection of stage I CRC is 54.5%, while the detection of CRC in later stage (II, III, IV) is 100%.

* There are 5 malignant polyps that are not fully staged in the stage I calculation. Stage I sensitivity, may be summarized as 11/17 (64.7%), excluding those 5 patients.

CRC sensitivity stratified by lesion size

CRC Lesion Size	Sensitivity	95% CI
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%)

The Shield test failed to detect CRC lesions that are less than 10mm (0/6).

AA sensitivity stratified by lesion size

AA Lesion Size	Sensitivity	95% CI
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%)

There is a trend of increasing the sensitivity of AA with increasing lesion size.

AA sensitivity stratified by Histopathology Sub- categories

AA Sensitivity Histopathology Diagnosis Sub- categories	Sensitivity	95% CI
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%)

The detection of AA in different histopathology sub-categories varies between 0% to 22.6%.

AN Specificity stratified by Histopathology Sub-categories

AN Specificity Histopathology Diagnosis Sub- categories	Specificity	95% CI
All	89.6% (5982/6680)	(88.8%, 90.3%)
(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%)

The point estimate of AN specificity was slightly higher in category 6.

FDA Presentation Part III

Review Considerations

- Summary of Key Points
- FDA Considerations and Discussion Questions

Summary of Key Points (CRC)

Shield can detect 83% of the CRCs, from a non-invasive blood test; however, it will miss 17% of CRC.

- 17% false negativity for CRC were mainly in Stage I CRC
- The sensitivity for Stage I CRC is 54.5% (12/22)*
- The Shield test failed to detect all CRCs that are less than 10mm in size.
- The sensitivity for Stage II, III, IV is 100%

* Of note, Stage I sensitivity, may be summarized as 11/17 (64.7%), excluding those 5 CRC patients in the Stage I calculation that were not completely staged.

Summary of Key Points (AA)

The Shield test detected 13% of the advanced adenomas

- Shield will miss 87% of advanced adenomas.
- The detection of AA varied between 0% to 22.6% in different histopathology sub-categories
- Shield detects 22.6% of AA with high-grade dysplasia and 17.9% of AA with a villous component. These histologies are more aggressive types of AA.

Summary of Key Points (PPV /NPV)

- PPVs for CRC in different age groups ranged from 2.21% to 3.93% (3.10% overall).
- PPVs for AA in different age groups ranged from 5.76% to 14.65% (12.04% overall).
- The overall NPV for CRC is 99.92%.
  - Thus, at the population level, this test can reassure the majority of patients testing negative, that they do not have CRC.
- The overall NPV for AN is 89.86%.
  - One out of 10 patients testing negative will be falsely reassured that they are negative for AA.
  - One out of 1000 patients testing negative will be falsely reassured that they are negative for CRC.

FDA Considerations and Discussion Questions

Review Considerations

- Discussion Question 1 → Appropriate Scope of Claims
  - CRC sensitivity of 83.1%, advanced adenoma (AA) sensitivity of 13.2%, and advanced neoplasia (AN) specificity of 89.6%.

- Discussion Question 2 → AA performance and potential mitigations
  - Advanced adenoma (AA) sensitivity of 13.2%

- Discussion Question 3 → The need of a post approval study (PAS) about benefits and risks of programmatic colorectal cancer screening (i.e., repeated testing over an established period of time)

Points/background for Discussion Question 1

- Performance of approved non-invasive CRC screening tests
- Performance of recommended CRC screening tests by guidelines
- Performance of Guardant Shield test
- Adherence Rates

CRC In Vitro DIAGNOSTIC LANDSCAPE

Performance of several FDA approved devices for CRC screening in the average risk population for developing colorectal cancer

- 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.
- Epi proColon, has a different claim that may be considered "Second line" and is indicated for individuals at average risk for CRC who decline recommended screening methods, such as colonoscopy or other first line CRC screening tests.

FIT tests

- authorized by the FDA for the detection of hemoglobin in stool
- do not explicitly have FDA authorization for CRC screening.
- Some clinical practice guidelines (e.g., from USPSTF) recommend use of FIT tests in CRC screening.

CRC In Vitro DIAGNOSTIC LANDSCAPE

	Cologuard	Epi proColon
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% (19%, 25%) (134/621)
Specificity (95% CI) (fractions)	86.6% (85.9%, 87.3%) (7936/9167)	78.8% (76.7%, 80.8%) (1182/1500)

The performance of FIT tests for CRC screening has been reported in multiple publications.

- Pooled CRC sensitivity of 79% (95% CI 0.69-0.86) with a specificity of 94% (95% CI 0.93-0.95).
- CRC sensitivity of 73.8% (95% CI 61.5%-84.0%), AN specificity of 94.9% (95% CI 94.4%-95.3%,), and AA sensitivity of 23.8% (95% CI 20.8%-27.0%).

High-sensitivity FOBT has a sensitivity of 50-75%, AA sensitivity of 7-21% and specificity 96-99%.

Guardant's proposed indication for the Shield test is for colorectal cancer screening in individuals at average risk of the disease, most similar to a "first line" claim.

Shield performance in patients of 50 years or older

Since the 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.

	Shield Performance	
Intended Use Population Age	For 45+ years	For 50+ years
Sensitivity-CRC (95% CI) (fraction)	**83.1%** (72.2%, 90.3%) (54/65)	**83.6%** (72.4%, 90.8%) (51/61)
Sensitivity-AA (95% CI) (fraction)	**13.2%** (11.3%, 15.3%) (147/1116)	**13.7%** (11.7%, 15.9%) (145/1060)
Specificity-non-AN (95% CI) (fraction)	**89.6%** (88.8%, 90.3%) (5982/6680)	**89.0%** (88.2%, 89.7%) (5428/6100)

Summative Points for Shield

- A non-invasive blood test with 83% sensitivity for CRC detection.
- CRC detection sensitivities for Stage II, III and IV CRC are 100%
- False negativity for CRC is 17%; false negativity for Stage I CRC is 45.5%; false negativity for AAs is 87% .
- The PPV for CRC of 3.10%.
- The PPV for CRC+AA is 15.14%, given the specificity of the test >89%.
  - the balance of false positives to true positives is 5.6 to 1.
- The NPV for CRC is 99.92%; NPV of AN is 89.86%.

Adherence Rates

- On 10,000 clinical orders, the Shield LDT showed a 96% adherence rate.
  - This may be influenced by bias in the form of early adopters opting for this test. A real-world estimate of adherence, has yet to be demonstrated.
- The adherence to the Shield test is likely to be higher than for colonoscopy and other CRC screening tests.

Points /background for Discussion Question 2

- AA background
  - The majority of CRCs arise from colonic adenomas.
  - AA can progress to cancer at an annual rate of up to 5%.
  - Detection and removal of AA can reduce the incidence of CRC and reduce the morbidity/mortality associated with CRC.

- Detection of AA by Guardant Shield test is 13.2%
  - The detection of AA varied between 0% to 22.6% in different histopathological sub-categories.
  - Shield detects 22.6% of AA with high-grade dysplasia and 17.9% of AA with a villous component. These histologies are more aggressive types of AA.

Points /background for Discussion Question 3

- **The Shield test missed 17% of CRCs and, all CRCs missed were Stage I**
- **The NPV for CRC was 99.92%.**
- **The NPV for advanced neoplasia (CRC/AA) was 89.86%.**
- **USPSTF currently recommends repeat testing at certain times for the screening strategies below*.**
  - 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.

*Clinicians and patients may consider a variety of factors in deciding which test may be best for each person.

Thank You

Questions?