Food and Drug Administration
Medical Devices Advisory Committee

Molecular and Clinical Genetics Panel
Shield
Guardant Health, Inc.
May 23, 2024

Introduction:

On, May 23, 2024, a panel heard presentations from Guardant Health and the FDA and discussed and answered questions on the information related to the premarket approval application for the Shield test by Guardant Health, Inc. Voting members of the panel also voted on the panel's response to questions from FDA for the Shield test regarding its safety, effectiveness, and benefit versus risk profile. The device in question 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. The proposed indications for use are: 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 a diagnostic colonoscopy or for surveillance colonoscopy in high-risk individuals. The test is performed at Guardant Health, Inc.

Guardant Health Presentation

1. Benefits of CRC screening and need for additional screening options:

As the fourth most diagnosed cancer and the second leading cause of cancer-related death, colorectal cancer (CRC) is well suited to screening because early detection significantly improves patient survival. Leading organizations recommend that screening begin at age 45 for all adults at average risk, and only 58% of eligible US adults are up to date with CRC screening, which is well below the target of 80%. Colonoscopy is the most effective method for the prevention of colorectal cancer, given the ability to detect and remove advanced adenomas (AAs) with this procedure. However, adherence rates for both colonoscopy and noninvasive stool-based tests are impacted by various barriers and Guardant Health sees a need for an effective blood-based screening alternative to enhance patient access, to increase the number of individuals receiving a CRC screening evaluation.

2. Overview of Shield development program:

The Shield test is based on the identification of DNA fragments, known as cell-free DNA (cfDNA) because it originates from the tumor and is released into the bloodstream following cell death. The tumor-derived ctDNA has unique genomic and epigenomic alterations i which can be distinguished from DNA released into the blood noncancerous cells. Shield relies on well-established sequencing technologies to detect cfDNA carrying tumor associated alterations in circulation.

3. ECLIPSE study design and effectiveness and safety results:

ECLIPSE was a prospective, US-based, multicenter study designed to evaluate the performance of Shield to detect colorectal cancer in average risk individuals. There were two co-primary objectives to evaluate the performance of Shield compared to the clinical reference standard, which is colonoscopy and biopsy of any lesions. The primary endpoints were sensitivity of Shield for CRC and specificity of Shield for advanced neoplasia (AN), defined as CRC or AA. Shield met the primary objectives, demonstrating CRC

sensitivity of 83.1% when compared to colonoscopy and demonstrating 89.6% specificity for the absence of AN compared to colonoscopy. In terms of safety, Shield has a low direct risk that includes known risks associated with the required blood draw. Indirect risks include the consequences of a false positive or false negative for CRC. There were no unanticipated adverse device effects observed across all participants enrolled in the ECLIPSE study.

4. Clinician's perspective:
Options for CRC screening are currently limited to colonoscopy and stool-based tests. Patients typically do not decline stool-based tests during the decision-making encounter, but these often result in noncompliance when the patient leaves the office and never completes the screening. While colonoscopy is the prioritized screening option due to its ability to both detect and prevent CRC, many patients prefer a noninvasive option and in order to achieve guideline recommended screening targets, an innovative, convenient, effective alternative option is needed.

5. Conclusion:
Shield's performance in terms of sensitivity for CRC and specificity for AN is within the range of screening choices; but is on the lower end of the range of widely used stool options for AA sensitivity. The additional choice of a blood test is expected to increase the number of individuals who complete screening, and by following a strategy that includes physician and provider education to facilitate informed patient decision-making, adherence rates for CRC screening are likely to increase with the additional option of a blood-based test.

Questions to Guardant Health
Various representatives of Guardant Health responded to questions about the Shield test including, but not limited to, the following:

- Longitudinal adherence
- Frequency and interval of testing
- Specimen requirements for the test assay
- CRC screening benefit from advanced polyp detection versus detection of asymptomatic cancer
- Detection of false positives with Shield
- Rate of invalid tests
- Defining advanced neoplasia and advanced adenoma
- Symptoms patients in the trial did or did not experience
- Performance of the test across multiple racial groups
- Sojourn time from stage one to three CRC
- Performance of the device across multiple comorbidities
- Differences in assay systems

FDA Presentation
The FDA review team for the Shield test from Guardant Health summarized the FDA's review of the premarket application. FDA presented background information on colorectal cancer, advanced adenoma, screening, and the device in question. Approximately one third of screen-eligible patients do not undergo screening for CRC, which is a curable disease if detected early. Increased screening rates may translate into significant reduction of CRC-associated morbidity and mortality. The FDA review team discussed current screening guidelines and recommendations with respect to testing strategy and age. Screening and detection of both CRC and adenomatous polyps and other precancerous lesions are considered to contribute to the reduction of CRC incidence and ultimately clinical benefit through a reduction in

mortality. The test is not indicated for individuals who have a personal or family history of CRC, among other contraindications. FDA discussed key Guardant-proposed limitations for the Shield test to be included in product labeling. FDA discussed the algorithm used by the device to classify samples as either "abnormal signal detected" or "normal signal detected."

FDA presented information on the clinical study design, patient accountability, primary effectiveness results, age adjusted device performance, and additional statistical analyses that were conducted to evaluate the performance of Shield. A total of 24,876 subjects were enrolled from 265 sites across the US. Inclusion criteria included patients at average risk for CRC aged 45 to 84 years old. . FDA conducted additional statistical analyses and concluded that the sensitivity and specificity data as presented did not create favorable bias to the performance. The overall performance of the Shield test was a CRC sensitivity of 83.1%, AA sensitivity of 13.2%, and AN specificity of 89.6%.

FDA then discussed review considerations for the discussion questions, including the Shield test's false negativity rate for CRC and AA and additional statistical analyses. There are several existing FDA-approved devices for CRC screening in the average risk population for developing colorectal cancer with varying levels of performance and adherence. The majority of CRCs arise from colonic adenomas. Advanced adenomas can progress to cancer at an annual rate of up to 5%, depending on a variety of factors. Approximately 45% of stage one CRCs were missed by the Shield test, and all CRCs smaller than ten millimeters were missed.

Questions to FDA

FDA's review team responded to questions about the Shield test and its premarket application, including, but not limited to, the following:

- Meaning of the term "trend" referenced in sponsor's presentation
- Meaning of first line vs second line indications.
- FDA rationale for the second line indication of the Epi proColon device
- FDA's process in evaluation of sensitivity and specificity, as opposed to frequency of testing
- Clinical performance of other tests that were approved by FDA in context of stage one cancers

Open Public Hearing

Seventeen individuals presented statements during the open public hearing portion of the event.

1. Dr. Girish Putcha of Precision Medicine and Diagnostics discussed the concept of average risk, the absence of hyperplastic polyps in summaries from the sponsor and FDA, and the tiering of tests. Dr. Putcha emphasized the importance of apples-to-apples comparisons when evaluating clinical performance in the intended use population and its adherence.

2. Mr. Dennis Barnes, a patient and advocate for colorectal cancer screening, shared about the importance of screening for all types of cancer.

3. Dr. Andrew Albert, a gastroenterologist, offered a clinician's perspective on testing options and the need for patient adherence. He supported the option of having a test patients will be comfortable with.

4. Ms. Candace Henley, founder of the Blue Hat Foundation, addressed the life-saving nature of CRC screenings across diverse communities and supported the addition of new screening options that cater to the diverse needs of all populations.

5. Ms. Mary Beth Kropp, the widow of a colorectal cancer patient, shared her journey with the disease and her desire for diagnostic options to be available so that more individuals will comply with screening guidelines.

6. Dr. Robert Azurin, a family medicine doctor who performs Guardant Shield tests, discussed the various CRC screening options on the market and his personal experience with a family member who was diagnosed with colorectal cancer.

7. Ms. Jody Hoyos, CEO of the Prevent Cancer Foundation, spoke on the potential of blood-based screening options as a tool in the fight against colorectal cancer.

8. Ms. Patricia James, a Shield test user, shared her story of family and personal history with cancer and the significance of easy options for early detection and screening for her health and wellbeing.

9. Dr. Tiago Biachi, a medical oncologist at Moffitt Cancer Center, spoke in support of a blood-based test for screening for colorectal cancer and mentioned the trend of younger patients being diagnosed with the disease in recent years.

10. Mr. Andrew Spiegel, CEO of the Global Colon Cancer Association, expressed his perspective on new blood-based screening options as a positive innovation, the need for screening compliance to improve in underserved communities, and the life-saving potential of new screening types.

11. Mr. Trevor Maxwell, a current colon cancer patient and founder of Man Up to Cancer, advocated for the approval of the Shield test due to its life-saving potential. He also touched on male adherence trends for cancer screening.

12. Mr. John Gormly, a colon cancer survivor, shared his perspective that the Shield test played a key role in his diagnosis and was a factor in his success in fighting the disease.

13. Dr. Len Lichtenfeld, a medical oncologist and strategic advisor, presented his thoughts on various aspects of screening options and expressed a hope that incorporating the Shield test into the screening options available to clinicians would have the effect of decreasing the burden of colorectal cancer on the population.

14. Ms. Wenora Johnson, a colorectal cancer survivor, shared her excitement and hope at the prospect of the Guardant Shield test. She discussed the disparities in screening compliance in communities of color and expressed that more screening options could result in more screening being completed and better health outcomes.

15. Dr. Gregory Robertson, an internal medicine physician, shared his experiences with discussing CRC screening options with patients and the desire for every patient and provider to have Shield in their arsenal when it comes to colon cancer screening.

16. Mr. Michael Sapienza, CEO of the Colorectal Cancer Alliance and the son of a deceased colorectal cancer patient, expressed his interest in the Shield test becoming available to aid underserved individuals, improve adherence, and expand access to testing.

17. Mr. Chris Evans, president of the Colon Cancer Coalition, shared his perspective that introduction of a blood-based choice for colorectal cancer screening will increase screening rates and ultimately save lives.

Panel Deliberation

Panel members asked questions of both the sponsor and FDA regarding the presentation of the Shield test and its premarket application. Questions included, but were not limited to, the following topics:

- Labeling of Epi proColon device
- Interim analysis on numbers of adenomas and performance of assay
- Further analysis on stage one difference
- Upward trends in young onset colorectal cancer and potential for changes in recommended screening age
- Difference in definition of a screening test versus a diagnostic test
- Potential labeling of Shield test
- Proportions of patients who go on to get colonoscopies after noninvasive screening results are positive
- Impacts on frequency of colonoscopy use for screening if a blood-based test were available
- Conversion of false negatives to positives or vice versa with repeat screening
- Reasoning behind sponsor's choice not to do repeat testing in two-year follow-up period
- The absence of serial data to suggest the Shield test would change the trajectory of disease

The panel members then further discussed the information presented and the sponsor's statements and claims as they relate to the FDA questions for discussion.

FDA Questions and Vote

FDA asked three voting questions of panel members. The questions are included below with the results of the voting members' responses:

Question 1: Is there reasonable assurance that the Shield test is safe for use in patients who meet the criteria specified in the proposed indication? Please vote either yes, no, or abstain.

Response: The panel voted 8 yes, 1 no, 0 abstentions.

Question 2: Is there reasonable assurance that the Shield test is effective for use in patients who meet the criteria specified in the proposed indication? Please vote either yes, no or abstain.

Response: The panel voted 6 yes, 3 no, 0 abstentions.

Question 3: Do the benefits of the Shield test outweigh the risk for use in the patients who meet the criteria specified in the proposed indication? Please vote either yes, no or abstain.

Response: The panel voted 7 yes, 2 no, 0 abstentions.

The panel further discussed the reasoning behind each of their votes as well as any changes to labeling, restrictions for use, or other controls that would have made a difference in their answers. Several

responses mentioned the need for careful labeling and concerns as to the effectiveness of the Shield test as compared to other options.

Adjournment

FDA and the panel chair expressed their mutual gratitude for all parties' contributions to this Guardant Health panel meeting and were dismissed.

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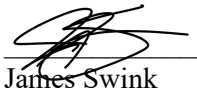
I approve the minutes of the meeting as recorded in this summary.

Andrea Ferreira-Gonzalez, PhD
Chairperson

I certify that I attended this meeting on May 23rd, 2024
and that these minutes accurately
reflect what transpired.



James Swink