FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

# Brief Summary of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee

**May 23, 2024**

## Introduction:

The Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee for the Food and Drug Administration met on May 23, 2024 to discuss, make recommendations, and vote on information regarding the premarket approval application for the Shield test by Guardant Health, Inc. 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.

## FDA Questions/Panel Deliberations:

### FDA Question

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, or is it more appropriate for specific populations (e.g., patients who decline colonoscopy or other CRC screening tests).

### Panel Deliberations

The Panel discussed "first line" vs "second line claim" and the rationale behind the possible second line claim. The Panel discussed use of colonoscopy vs other primary CRC screening tests, and noted multiple reasons the optimal test is a colonoscopy which is used for both

screening and prevention but recognized the value on alternative acceptable screening methods for patients not compliant with colonoscopy screening. The discussion focused on the value of a CRC screening program was early detection and prevention and discussed the performance of Shield for detection of advanced adenomas (AA) and Stage I cancer relative to the performance of other CRC screening methods with a first line claim (i.e., Cologuard) vs second line (i.e., EpiProcolon), as well as the use of fecal immunochemical test (FIT) and guaiac fecal occult blood tests (gFOBT) for AA and CRC screening. The Panel discussed the risk of using Shield as a primary CRC screening option considering this test might fail to detect AA when CRC development can be prevented, and lack of detecting Stage I cancer may lead to failure to treat cancer early. However, performance comparisons to FIT and the common and widespread use of FIT in CRC screening were noted, and that performance of Shield fits within performance of other non-invasive stool-based tests used for primary CRC screening. For this reason, several panelists noted that it would be important to determine whether false negative results for this test would be detected with an appropriate interval of repeat testing or lead to worse outcomes.

Panel was in agreement that test performance appears to be reliable for screening for colorectal cancer, stages 2, 3, and 4, and that there is a benefit of having blood test with higher adherence by patients who fail to obtain colonoscopy or a hesitant to use stool based testing, noting availability of blood-based testing may also improve programmatic screening in marginalized populations.

The Panel discussed the CRC development timeline and raised a question about substitution of colonoscopy with alternative, non-invasive CRC screening tests. Several panelists noted current lack of evidence to show that increased testing with Shield would lead to improved outcomes, and publications of studies designed to evaluate whether the number of colonoscopies decreased or increased with availability of non-invasive CRC screening tests were noted.

**FDA Question**

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 comment on potential mitigations that may be available to mitigate clinical risks of the Shield test's AA sensitivity.

**Panel Deliberations**

The Panel continued to discuss the risks of Shield given that the Shield AA sensitivity is lower than other approved non-invasive CRC screening tests. Panel discussions focused on complexity of cancer prevention and data describing the rate of progression from AA to late stage cancer. It was noted that the data suggest this is not rapid and that repeat testing and adherence might be meaningful with Shield however it was reiterated that this information is unknown.

If Shield were to be approved as a first line CRC screening test, the Panel suggested that it is important for labeling to make clear that test is indicated for CRC screening, not for both CRC and AA screening, and that Shield showed high performance to detect CRC stage 2 and later stages. Therefore, possible mitigation would be very clear labeling for the product. Labeling and limitations together with education will be critical.

The panel members felt strongly that patient and physician education regarding the limitation of Shield as a preventative test are critical for the use of Shield. Panelists discussed that the primary goal of a CRC screening program is prevention and improved outcome. The inability of Shield to detect AA as well as colonoscopy or some alternative stool-based tests is an important discussion physicians should have with their patients. The value of informed consent regarding this test was noted. Some panelists expressed concern about conflation of the test by both physicians and patients regarding this type of screening tests as preventative and highly accurate. It was emphasized that the test labeling and education materials need to be very clear. and help patients understand prevention in the shared decision making. It was noted that although negative predictive value (NPV) of the test is extremely high, it does not capture the significance of false negatives because high NPV is driven by the low prevalence of disease. There should be controls placed when labeling the test and have appropriate education materials since the value in this test is for those people who do not have adequate access or are choosing not to obtain a colonoscopy. The panel members discussed value of education and what kind of education should be put in place. Infographics in breast cancer education were brought up by the panelists as an example of an area where there are lots of various tests and physician discussions with patients on the benefit/risk of the test. Panelists reiterated that education materials need to ensure people understand limitations, and not assume the answer they get from the test is final answer. Otherwise, patients might be falsely reassured with negative results. There was suggestion that the inability to detect adenomas should be included in the intended use statement.

Possible additional mitigations include a need for clarity of blood vs stool test, and that this blood screening test is indicated for CRC, not for polyps.

**FDA Question**

3. If the device were to be found safe and effective based on existing data, please discuss whether FDA should consider asking for 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) of using the test. In the event this device were approved, please discuss whether a PAS would be helpful, and the types of information, if any, that would be important to collect during such a study.

**Panel Deliberations**

Panel discussed possible post market / longitudinal studies, repeat testing and what should be the schedule and frequency for repeated testing. Panel expressed consensus that there should be data collected on repeat testing at multiple intervals and discussed whether repeat testing would lead to the improvement of outcomes. Further studies and repeated testing could be helpful

since currently there is no available data for repeated Shield testing in 1-3 years. The Panel recommended that different, multiple intervals should be studied to understand the performance.

Incidental findings were brought up, and whether assessing possible follow-up on those can be incorporated in further studies, and whether there should be possible recommendations for further testing.

Panel was adamant about the need for a post approval study for the Shield test. There should be more information about false positives longitudinally. In addition, Panel opined there should be studies about operating characteristics of this test in real word settings, which would be the primary care setting where the test would be used. These studies could show the operating performance in a real world setting, which could either show dramatically improved or decreased performance characteristics.

A user comprehension study on whether patients and providers have accurate understanding of educational materials should also be considered.

Regarding possible mitigations using education materials, the Panel recommended to balance benefit risk through patient education, labeling. etc. Labeling should clearly note that this test is not able to help prevent cancers by identifying pre-malignant lesions. Post marketing data can provide further insight.

Additional summative comments regarding risk mitigation were provided after voting, including:

- Labeling should make it clear that indication is CRC, and not for the detection of adenoma, and not designed as a strategy to prevent the onset of CRC from advanced adenomas.
- Since there is limited sensitivity for stage 1 CRC, labeling should make it clear that the test reliably detects CRC stages 2-4 but not stage 1.
- Test labeling should make clear that negative result does not reassure that patient doesn't need colonoscopy.
- Clear labeling is the key, test should be indicated for CRC screening in asymptomatic individuals.
- Provider and patient education could be considered appropriate mitigation for risks.
- There should be further studies to address eventual effect on mortality; also, there should be more investigation on characteristics of lesions that were detected or undetected by the test.
- Additional studies need to be done in CRC screening programs in primary care setting.
- Availability of this test will raise adherence component of CRC screening, and possibly impact CRC mortality.
- Consider consenting patients to the risks and benefits of the test.

## Vote:

The panel voted on the safety, effectiveness, and risk benefit ratio of Guardant Shield.

On Question 1, the panel voted 8 yes, 1 no, 0 abstain that the data shows that there is reasonable assurance that Shield is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 6 yes, 3 no, 0 abstain that there is reasonable assurance that Shield is effective for patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 7 yes, 2 no, 0 abstain that the benefits of Shield do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

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Transcripts may be downloaded from: May 23, 2024: Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee

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