24 Hour Summary
Molecular and Clinical Genetics Panel
Advisory Committee Meeting
November 29, 2023

Introduction:

A meeting of the Molecular and Clinical Genetics Panel ("the Panel") of the Medical Devices Advisory Committee was convened on November 29, 2023, to discuss and make recommendations related to multi-cancer detection (MCD) screening devices (tests).

On November 29, 2023, the Panel discussed and made recommendations on the design of multi-cancer detection (MCD) in vitro diagnostic devices (tests) as well as potential study designs and study outcomes of interest that could inform the assessment of the probable benefits and risks of MCD screening tests. The committee's discussion and recommendations from this meeting will help inform future Agency regulatory efforts for these novel tests.

FDA Questions/Panel Deliberations:

Topic I

The Panel generally believes that the clinical validation studies should be randomized controlled studies with a comparison to a control arm that is receiving currently accepted alternative cancer (standard of care) screening for cancers with these methods available. The Panel believes that the use of MCD tests should not replace the current alternative cancer screening methods.

Some on the Panel discussed that the use of an MCD test in a randomized clinical trial should have cancer-specific mortality as a primary endpoint while others on the panel did not agree. The Panel generally believes that the stage (i.e., stage shift) or disease state (i.e., intent for curative treatment is available or not) at which the cancer was detected with the use of an MCD test may be used as to support an "early" cancer detection claim.

The Panel agreed with the FDA that determining ground truth for test positives and test negatives is a critical point in the clinical trial study design as this information drives assessment of the performance of the assay (i.e., positive predictive value or PPV, sensitivity, specificity).

The Panel recommended that clinical trial designs should be:

- Pre-specified with respect to follow-up diagnostic pathways and a statistical analysis plan such as evaluation of specificity on a per cancer basis.
- Designed with intention based on the intended use and indications for use of the MCD test.
- Designed to include historically underrepresented and underserved populations such as ethnic/racial minorities and rural populations.

Topic II

The Panel believes that MCD tests should have a tissue-of-origin (TOO) component to the device as it would guide targeted diagnostic work-up and minimize the risks associated with whole body imaging and multiple follow-up diagnostic procedures (e.g., radiation exposure, financial burden, psychological harm).

The Panel discussed concerns related to:

- Access of care to follow-up diagnostic imaging tools such as positron emission tomography (PET) scans especially in rural geographic areas in the United States.
- Limitations of the currently available imaging tools (PET, computed tomography or CT scans, and PET-CT scans) with regards to their ability to detect different types and sizes of tumors, incidental findings, and indolent tumors.

The Panel agreed that the follow-up diagnostic pathways for a positive test should be pre-specified and well-defined in the clinical trials. The Panel emphasized that this is particularly important from a health equity perspective as patients in rural areas will have additional barriers to care that will need to be considered in the planning of these clinical trials. The Panel recommended that patients who test negative with the MCD test should continue with all currently recommended cancer screenings or be monitored over a certain period for cancers without an accepted alternative cancer screening method.

The Panel believes that there are inherent differences in the biology and natural history of different types of cancer which drives the considerations for diagnostic pathways, ascertainment of clinical truth, and interval to screening with an MCD test. Data collected from properly designed randomized clinical trials would be most useful to guide the recommendations. Additionally, the Panel believes that MCD test developers should provide clear guidelines and educational tools along with their properly validated MCD test to help with clinical implementation of this novel technology.

Topic III

The Panel generally believes that the probable benefits and risks associated with a false positive MCD test result will need to be assessed on a cancer-by-cancer basis due to differences in risk profiles between follow-up diagnostic procedures (e.g., invasive versus noninvasive). The Panel believes that proper physician education and pretest counseling for patients - particularly setting realistic expectations with patients - may be able to mitigate some risks associated with false positive/negative results and overdiagnosis (i.e., identification of indolent tumors). Generally, the Panel agreed that depending on the prevalence of cancer in the target population for these MCD tests, >99% specificity may be required for these types of tests to maintain a high PPV.

The Panel discussed that the anticipated follow up for a positive MCD result should be:

- Worked up as quickly as possible, however patients should be informed in advance that the resolution of whether a positive result is cancer may take months.
- Guided by a TOO component to the MCD test and detailed in the marketing authorization approved by FDA based on data collected from the clinical validation studies.
- Complemented with educational tools and resources to provide guidance for patients and clinicians.

The Panel believes FDA should consider the following:

- Time to diagnosis following a positive MCD test result is a health equity issue particularly for underserved populations who may receive a positive MCD test result but are unable to receive a diagnosis due to systemic, financial, and geographic barriers. Therefore, cancer screening constitutes both the MCD test and all the follow up care until diagnostic resolution.
- Interval testing for an MCD test will be driven by data collected from MCD clinical trials and will also depend on the intended use population(s) such as asymptomatic versus high risk individuals.
- Real-world data (RWD) and real-world evidence (RWE) may be used to support clinical validation of an MCD test in select situations such as in the post-market setting. Additionally, the Panel recommended that a patient registry be established for patients who undergo testing specifically to support the standardized collection of key information. However, the Panel expressed concern about the use of RWD/RWE in other scenarios. For example, the Panel does not believe that RWD/RWE can be used to determine the reduction of cancer-specific mortality with the use of an MCD test.

Open Public Hearing (OPH)

In the morning OPH session, the Panel heard presentations from clinicians and other stakeholders. Roger Royse and Valerie Caro spoke to their patient experiences with MCDs. Joshua Ofman spoke on behalf of GRAIL LLC, Sana Raoof spoke on behalf of Memorial Sloan Kettering Cancer Center, Alberto Gutierrez on behalf of NDA Partners LLC, Robert Smith on behalf of the American Cancer Society, Dax Kurbegov on behalf of the Sarah Cannon Cancer Institute of HCA Healthcare, Mylynda Massart on behalf of the University of Pittsburgh Medical Center, Tomasz Beer on behalf of Exact Sciences, Ruth Etzioni on behalf of the Fred Hutch Cancer Center, Girish Putcha on behalf of Precision Medicine and Diagnostics LLC and Gary Puckrein on behalf of the National Minority Quality Forum.

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Transcripts:

Transcripts may be downloaded from:
November 29, 2023: Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee Meeting Announcement - 11/29/2023 | FDA

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