FDA Executive Summary

Prepared for the
November 29, 2023, meeting of the
Molecular and Clinical Genetics Devices Panel of the
Medical Devices Advisory Committee
Virtual

The committee will discuss and make 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.

Discussion and Recommendations for In Vitro Diagnostic Devices

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I. Introduction, Purpose, and Structure of the Panel Meeting

The Division of Molecular Genetics and Pathology (DMGP) in the Office of Health Technology 7, Office of *In Vitro* Diagnostics (OHT-7), Office of Product Evaluation and Quality (OPEQ), Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA), has regulatory oversight of molecular genetics and pathology *in vitro* diagnostics (IVDs), including tests for cancer diagnosis and screening.

FDA is convening this Molecular and Clinical Genetics Panel (the Panel) of the Medical Devices Advisory Committee meeting on November 29, 2023, to discuss and make recommendations regarding the design of multi-cancer detection (MCD) screening tests (MCD 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 tests. No MCD tests have been granted FDA authorization to date. The meeting will be entirely virtual over the course of one day with introduction and background provided by the FDA, a segment for open public comment, and topics for discussion and deliberation by the Panel.

MCD tests are most commonly intended to be used for cancer screening in asymptomatic individuals who may benefit from interventions at earlier stages. While traditional cancer screening tests have been specific to a single cancer indication, these technologies are intended to detect multiple cancers at once, which presents regulatory challenges for assessing the tests' benefit-risk profiles.

FDA approves a medical device based on its determination of a reasonable assurance of safety and effectiveness of the device. For IVDs, safety and effectiveness are generally determined by assessing an IVD's analytical validity and clinical validity. Cancer screening has both risks and benefits. The device manufacturer (or sponsor of the premarket submission) must provide information that demonstrates the probable benefits of using the device outweigh any probable risks in order to be authorized for marketed use. Demonstrating that the probable benefits of MCD tests outweigh the probable risks may be challenging for tests used in the asymptomatic population. FDA must carefully consider and weigh both.

The Panel will not be asked to formally vote on their recommendations regarding MCD tests or to any specific device currently under development. However, their expert advice will be considered for future regulatory discussions and review of submissions.

II. Background

a. Regulation of IVDs

Per 21 CFR 809.3, *in vitro* diagnostic devices are defined as[1]:

> "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body…"

FDA regulations applicable to IVDs are based on the FDA classification of the device. The current approach to classification is a product of several laws, most prominently the 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (FD&C Act). [2] Medical devices, including IVDs, are classified based on the level of

[1] All citations or references to the Code of Federal Regulations in this document are available at: https://www.ecfr.gov/current/title-21.
[2] https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls

risk to patients. The three regulatory classes for device categorization are based on the level of control necessary to assure the safety and effectiveness of a device:

> Class I: Devices of low to moderate risk for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
>
> Class II: Devices of moderate to high risk which require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
>
> Class III: Devices of high risk for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness.

Figure 1 depicts a decisional chart detailing how FDA generally classifies medical devices based on the risks associated with the device and by evaluating regulatory controls that provide a reasonable assurance of the device's safety and effectiveness. For the purposes of this panel meeting, FDA will focus solely on Class III devices.

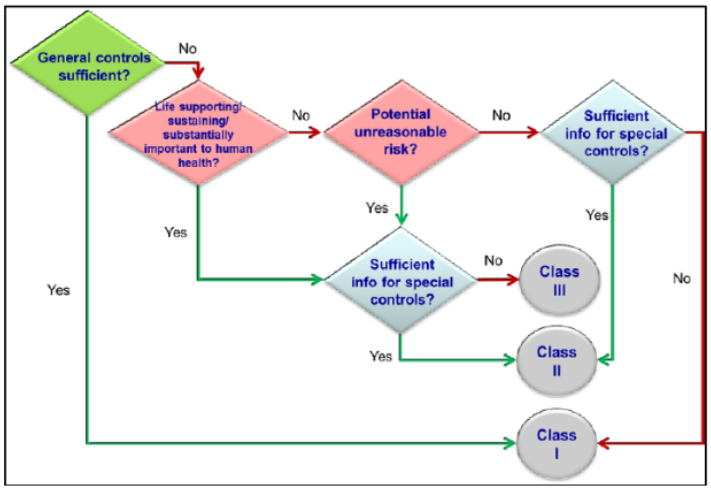

Figure 1: Device Classes. Under section 513(a) of the FD&C Act, FDA generally classifies medical devices based on the risks associated with the device and by evaluating regulatory controls that provide a reasonable assurance of the safety and effectiveness of the device.

b. Class III Devices

Class III devices are those for which insufficient information exists to determine that general (Class I) and special controls (Class II) can provide reasonable assurance of the safety and effectiveness, and where these devices are life supporting or life sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents unreasonable risk of illness or injury.[3] Class III devices require 'premarket approval' (PMA) and IVDs classified into Class III generally have greater FDA oversight and regulatory requirements than Class II devices.[4]

c. Current Regulation of Cancer Screening Assays

Due to the risks associated with false positive and false negative results, cancer screening tests for asymptomatic populations are regulated as Class III devices, subject to premarket approval.

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[3] Section 513(a)(1)(C) of the FD&C Act.
[4] More detailed information regarding pre-market PMA applications is available at: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma

In the last 10 years, FDA has approved IVDs for screening asymptomatic populations for cervical cancer and colorectal cancer. Such IVDs require a prescription and are intended for the detection of biological substances in blood and other body fluids that suggest the presence of cancer. Cancer screening tests have an intended use similar to the following:

> *[test name] is intended for the qualitative detection of [cancer] associated [markers] and for the presence of [biomarker] in human [specimen]. A positive result may indicate the presence of [cancer] and should be followed by diagnostic [test name]. [test name] is indicated to screen adults of either sex, 50 years or older, who are at typical average risk for [cancer]. [test name] is not a replacement for diagnostic [test name] or surveillance [test name] in high-risk individuals*.

d. Clinical Setting for Cancer Screening

In the United States (U.S.) as of 2020, the latest year for which CDC cancer incidence data are available, over 1.7 million cases of cancer are reported yearly with over 600,000 dying from their cancer that year.[5] There are no screening tests for the general population for over 70% of the incident cancers occurring in the U.S.[6], presenting a great opportunity for the development of such tests. For the remaining 30% of incident cancers, the U.S. Preventive Services Task Force recommends tests, at A and B levels, for lung, breast, colorectal and cervical cancers for screening in select age ranges in the asymptomatic population.[7]

III. Panel Topics

a. Topic 1: Clinical study design considerations for FDA submissions, including evaluation of cancer specific performance

To determine whether there is a reasonable assurance of safety and effectiveness for an IVD, FDA evaluates among other things, whether there is valid scientific evidence to demonstrate that the IVD is analytically and clinically valid. The data necessary to demonstrate that the IVD is clinically valid depends on the intended use of the IVD. To demonstrate clinical validity of cancer screening tests, device manufacturers typically collect data from a prospective clinical study designed to evaluate the clinical performance of the IVD in the intended use population. In these studies, study participants undergo testing by the candidate IVD and diagnostic procedures, which includes pathology review of biopsied tumors identified by diagnostic procedures such as imaging.

MCD tests present a potential opportunity to improve cancer detection with the hope of decreasing death due to cancer. However, it is important to note that the gap in health equity may be exacerbated with use of MCD tests in underserved and underrepresented populations due to limited access to follow up care related to financial or limited resource barriers.

To determine the clinical performance of a candidate MCD test, results from the MCD test should be compared to the cancer status of the patient. Sensitivity and specificity are calculated to determine the diagnostic accuracy of the IVD. Positive and negative predictive values are calculated to determine the probability that a test positive or test negative result, respectively, are correct. There are no fully effective methods for determining clinical truth in test negatives for many cancers and for this reason the most accurate measurement that can be determined is the positive predictive value which reflects the accuracy of all test positives. Please discuss what are appropriate methods to determine the cancer status of each patient, especially in the context of cancers detected without established screening methods. What type of diagnostic workup is recommended for confirmation of the MCD result, especially for those patients with MCD test negative results? Is time to diagnosis an issue for consideration depending upon the cancer type? In the context of a positive MCD test result, where multiple possibilities are

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[5] CDC Cancer Data and Statistics, https://www.cdc.gov/cancer/dcpc/data/index.htm); accessed Oct. 24, 2023.
[6] Cancer statistics, 2022. R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal. CA Cancer J Clin. 2022 Jan;72(1):7-33. doi: 10.3322/caac.21708. Epub 2022 Jan 12
[7] USPSTF, https://www.uspreventiveservicestaskforce.org/uspstf/cancer screening; accessed Oct. 24, 2023.

revealed by imaging, should we consider that a lack of confirmation with a negative tissue biopsy be due to a sampling error and recommend additional biopsies or other diagnostic methods? At what point would a repeat biopsy (liquid or tissue) be recommended? For study participants that receive a negative MCD test result, how much follow-up (diagnostic tests, time, effort), if any, is needed to verify that these are true negatives? In either type of MCD test results, the diagnostic pathways have not been standardized making it more difficult to determine benefits or risks. The FDA seeks input from the Panel to help with recommendations in this clinical area.

Potentially confounding variables are assessed to identify potential sources of bias in the study. For MCD tests, the clinical performance of the test is evaluated for different types of cancers simultaneously and studies may neglect to assess performance of the test in patients with other nonmalignant comorbidities such as inflammatory bowel disease, diabetes, emphysema, gastroesophageal reflux disease (GERD), or cancer specific risk factors (i.e., those that may be a risk factor for one cancer but not for another); for example, cirrhosis, hepatitis B or C status in liver cancer, human papilloma virus (HPV) in head and neck squamous cell carcinomas (HNSCC), and smoking. Please discuss the need for assessing nonmalignant comorbidities and cancer specific risk factors in the clinical performance study for MCD tests and any recommendations you have for how this should be done.

Some MCD tests may claim that they are for "early" detection of cancer. In these cases, data should be provided to support that claim. First, the term "early" should be defined. Second, it should be clear whether "early" applies to all cancers the MCD test is intended to detect or only to certain cancers in the intended use. Please discuss recommendations regarding data necessary to support an early detection claim.

For a MCD test, acceptance criteria for the clinical performance study may depend on the intended use of the test, as well as the cancer type. The multi-cancer approach raises many difficult questions and introduces complexities in test development and validation. For example, we anticipate that the sensitivity of MCD tests for detecting different cancer types may vary. It may be challenging to appropriately design and validate MCD tests for multiple different cancer types simultaneously due to differences amongst different cancers (e.g., biology, natural history, and prevalence). We ask the Panel to consider and recommend how to scientifically manage this complexity in the evaluation of MCD tests.

Because MCD tests can be intended to detect multiple cancers, including those that have a low prevalence in the U.S., a large study is likely needed to demonstrate clinical validity. Even screening for prevalent cancers in the general population may necessitate large studies when considering the statistical power needed to capture and evaluate each individual cancer type. Please consider and discuss the benefit vs. burden of conducting a large prospective clinical study for the varying prevalence of different cancers that could be detected by a MCD test.

Although a control arm in clinical trials is typically not required in clinical validation, a control arm has the power to show benefit of a MCD test which would otherwise be challenging to determine due to the variable performance across cancers. We ask the Panel to please recommend whether a control arm should be included in the clinical performance study design for MCD tests and if so, the reasons for it. If the Panel recommends a control arm, please comment on whether study participants in the control arm should have blood drawn at the same pre-specified times as study participants in the interventional arm and when MCD testing would be performed for those in the control arm, if at all.

In addition to the potential value of a MCD test to detect more cancers which would not have occurred otherwise, the convenience of blood-based non-invasive testing may also improve compliance with cancer screening in general. However, where there are acceptable alternative screening methods, false negative results may lead individuals to forgo more effective screening programs, ignore symptoms, and/or bias physicians in their differential diagnoses. Therefore, patients with false negative results could remain undiagnosed and untreated if they forgo recommendations for regular interval screening. Undiagnosed and untreated individuals with cancer are likely to experience an increase in morbidity and mortality due to the later stage of detection. In the absence of understanding how the MCD tests perform relative to the alternatives, these tests may fail to improve sensitivity and only lead to decreased specificity (increase in false positive results needing follow-up). There are well-

established screening methods for lung, breast, cervical, prostate, and colorectal cancer. Please comment on the extent of your concern that individuals will forgo well-established screening methods for these cancers. Please discuss whether a head-to-head comparison to acceptable alternative screening methods is needed to help understand test performance.

b. Topic 2: Use of Tissue of Origin (TOO) assays to help identify tumor location versus other methods, patient work up considerations following positive results, and follow-up for patients with negative results

A MCD test is designed to indicate whether or not cancer was detected in the person but may not be designed to inform the location of the tumor. In such cases an additional test may be needed to help determine the tumor of origin (TOO). Biomarkers detected by a TOO test may have specific features that are unique to the cancers from which they were shed and can be used to help determine the TOO. This is different than traditional metrics for evaluating the performance of single cancer screening tests which automatically drive the direction of the diagnostic workup. Here, TOO tests help direct the principle diagnostic follow-up procedures ordered by the physician. For example, a TOO test may suggest the cancer signal detected is from the breast which may then lead the physician to order a diagnostic mammogram. In the absence of a TOO test, a physician will need to consider whether to order a variety of serum based and imaging tests to identify the source until a tumor is found or reasonably determine that no tumor is present. If a cancer is not detected, this may lead the patient into an unnecessary odyssey of diagnostic tests to resolve the original test result. Such testing can lead to invasive procedures, radiation exposure, and anxiety for the patient being evaluated. Further, such findings can lead to overdiagnosis and overtreatment.

We ask the Panel for feedback on the following questions: Without a TOO test used in conjunction with the MCD test, are there acceptable alternatives to determine the specific TOO? Consider whether general imaging (x-rays, PET scans, MRI, CT scans, PET-CT scans, etc.) in asymptomatic patients are expected to generate false positives that exceed the true positives, especially for smaller, early cancers. Do these imaging modalities have a place in the workup of TOO, in the MCD test positive but asymptomatic population?

For MCD tests that may be able to report TOO output, the evaluation of diagnostic accuracy becomes more complex. For example, with a TOO test in conjunction to the MCD test indicating a lung cancer but upon workup a breast cancer is actually diagnosed – is this considered a true or false positive for the TOO? In comparison, for a simple clinical situation where a cancer signal is generated from the MCD test but lacks a TOO test, if the workup detects no cancer, then the initial MCD test result would be considered a false positive. Also consider whether the TOO test (i.e., finding the cancer origin) needs to be evaluated for its own accuracy and what are the parameters to define that accuracy in the context of a MCD test with or without a corresponding TOO test? Please deliberate if there is a clinical benefit to a MCD test without a TOO output that likely would rely on imaging to identify the location of a tumor.

c. Topic 3: Benefit/risk considerations, including postmarket study considerations

FDA approves a medical device based on a determination that there is a reasonable assurance of safety and effectiveness for the device. To support that there is a reasonable assurance of safety and effectiveness, the device manufacturer or sponsor of the PMA submission should provide the FDA with information that demonstrates that the probable benefits of using the device outweigh any probable risks. Probable benefits and probable risks for IVDs are informed by the analytical and clinical performance of test. MCD tests may provide a non-invasive method to detect more cancers and improve patient outcomes. Acceptable performance characteristics of an IVD depends largely on the consequences of an incorrect result, i.e., false positive and false negative results. Consequences of false positive and false negative results may differ widely for different cancer types and these consequences could be compounded when MCD tests are used.

Given the current absence of cancer screening programs for most cancers, the more significant risk may be related to false positive test results. The risks associated with an initial positive MCD test result include the number and type of diagnostic workups needed to confirm the result (i.e., possible unnecessary testing and treatment). For this reason, it may be prudent to recommend that MCD test developers optimize specificity at the expense of sensitivity. Additionally, because of the lack of diagnostic guidelines and pathways for MCD tests, there is concern false positives present significant risk due to the diagnostic odyssey that may follow. Harms could range from invasive procedures that could lead to bleeding, infection, or organ and tissue damage to increased patient anxiety and mental health reverberations to family members. And for true positives, at what point does overtreatment become a concern; in particular, for indolent cancers. These may have a different diagnostic pathway and clinical treatment effort. In this situation, there could be increased risk of harm from the treatment itself over that from the disease. Also found within the diagnostic pathway, whether the positive test results are true or not, is the clinical issue of incidentalomas, asymptomatic tumors found incidentally through the diagnostic process. These are a part of overall risk or accumulate excess risk in the diagnostic pathway and may necessitate clinical care on their own. The greater the investigations to determine the tumor's origin, greater is the increased of risk of incidentalomas and the problem of prioritizing resources against the original and possibly primary clinical concern.

How does the Panel recommend FDA weigh the harms of false negatives and false positives? Please comment on what the acceptable false positive rate is for a MCD test and whether this should be generalizable across all cancers or be cancer specific when the test includes a TOO result. Also, please comment on whether MCD test performance should be compared directly to well-established alternative screening methods, e.g., mammograms and colonoscopies, to inform the benefits and risks of MCD tests for those subpopulations.

Stage shift could be considered as a surrogate endpoint in the clinical validation of a MCD test. However, an increase in earlier stage cancers being discovered should be commensurate with a decrease in detection of later stage cancers. In one report modeling for breast, lung, ovarian, and prostate cancer, stage shift seemed to not have significant mortality benefit and varied across cancers.[8] FDA requests the Panel to consider the available evidence and their experiences and comment on whether there is sufficient scientific evidence to support use of stage shift as a surrogate endpoint for establishing clinical validity of MCD tests.

It can be expected that some of the cancers intended to be detected by the MCD test will be rare. We would like the Panel to comment on whether cancers with insufficient numbers of cancer cases to determine performance in the pivotal clinical studies should be included in authorized labeling with limitations or remain unclaimed but able to be reported until additional studies are performed that can demonstrate the cancer specific sensitivity and/or specificity.

[8] Stage Shift as an Endpoint in Cancer Screening Trials: Implications for Evaluating Multicancer Early Detection Tests. L. Owens, R. Gulati, R. Etzioni. Cancer Epidemiol Biomarkers Prev. 2022 Jul 1;31(7):1298-1304.

IV. Panel Questions

The FDA seeks recommendations from the Molecular and Clinical Genetics Panel in three main topics: clinical study design, tissue of origin tests and benefit/risks are they relate to MCD tests. In this context, the Panel is asked to please discuss the following:

Topic 1: Clinical study design considerations for FDA submissions, including evaluation of cancer specific performance

1. What are critical study design considerations when planning an MCD clinical validation with respect to:
   - What are the advantages and disadvantages of different study designs?
   - Type of clinical trial – is a control arm necessary?
   - Size and enrollment strategies?
   - What considerations need to be given for data subjects from non-US sites?
   - Appropriate age for an MCD?
   - How should high risk patients be defined for an MCD and is it acceptable to enrich with high-risk patients?
2. Please define how early detection should be defined for an MCD test and discuss data and considerations necessary to support an "early" cancer detection claim.
3. Aggregating multiple cancers into one study has its advantages but the benefit/risk is likely unique to each cancer. Please discuss the benefits and limitations of a single aggregated study.
   - Given the various differences across cancers (shed rates, natural history, variety of histologies, risk of follow-up, etc.), should physicians be informed of per cancer performance?
   - Please discuss what aggregate and per cancer validation for MCDs would entail.
     - Minimum number of positive cancer cases for each cancer?
     - Minimum sensitivity for early stage?
     - Minimum sensitivity for each cancer?
4. If per cancer evaluation is recommended, for those cancers with alternative recommended screening tests:
   - How should the evaluation of the test for cancers with current screening methods be assessed? Should performance be compared to recommended screening?
   - Please discuss the risks of having an MCD test that does not perform as well as alternative screening methods.
   - If the MCD performance is significantly lower for a particular cancer with a well-established alternative screening method, should that cancer type be contraindicated for the test though able to be reported if positive?
5. What are the critical data collection and assessments needed to address potential bias?
   - Please discuss the data elements that should be collected to address comorbidities for aggregated and per cancer performance.
   - How should comorbidities and other conditions which may lead to false positive results be addressed in aggregate and per cancer? (e.g., cirrhosis, emphysema, inflammatory bowel disease, diabetes, smoking, obesity)
6. Should specificity be calculated on a per cancer basis?

Topic 2: Use of Tissue of Origin (TOO) assays to help identify tumor location versus other methods, patient work up considerations following positive results, and follow-up for patients with negative results

1. When an MCD test identifies a cancer signal, a tissue of origin (TOO) assay provides a starting point for follow-up to identify the tumor source.

- Which methods, either clinical and/or laboratory are acceptable to determine the possible TOO of a cancer signal detected by an MCD test?
- What are the risks of using CT or PET-CT scans for repeated testing?
- What is acceptable clinical performance of a TOO test, either as a diagnostic component of the original MCD assay or as a standalone test?

2. If an MCD test does not have a TOO component of the original MCD assay:
   - What are the acceptable diagnostic alternatives to determine the tissue of origin?
   - Are these alternative methods reasonable to ascertain truth?
3. What is clinical truth? For tests with other methods, for tests without other methods?
   - How should truth be obtained for test negatives?
   - For those without alternative methods, is there a minimum follow-up period and should a second test be taken at the end of the follow period (e.g., 1 year, 2 years, 3 years)?

Topic 3: Benefit/risk considerations, including postmarket study considerations

1. FDA must be able to support that the probable benefits of a test are greater than the probable risks to determine the test is safe and effective. Please discuss the following:
   - What is critical to determining benefit? How should we weigh the benefit of potentially screening more patients?
   - What performance is necessary for overall performance to make this determination?
     - Minimum specificity?
     - Minimum sensitivity?
     - What are the risks of false negatives and false positives?
2. What is the definition of early-stage and what supportive data is needed for a test to be defined as early-stage detection test?
3. Should MCD test developers prespecify a fixed specificity to support a low false positive rate?
4. Please describe the anticipated follow up for a positive result in terms of diagnoses, number of procedures and repeat testing?
5. What is the anticipated frequency physicians would order an MCD test? Does this depend on having received a positive or negative test result?
6. What are the harms from unresolved positive results and are there risk mitigation strategies?
7. What are the risks and harms from overdiagnosis and are there potential risk mitigation strategies?
8. Please comment on the significance of time to diagnosis.
9. Is evaluation of stage shift necessary for evaluation of benefit?
   - Is there a logical basis for investigating stage shift in the overall cohort?
   - Per cancer? Stage shift may have different benefit across different cancers.
   - What type of metric should be used to evaluate stage shift?
10. Under what conditions is the use of real-world evidence (RWE) to support clinical validation of an MCD test acceptable?
    - Expand upon per-cancer assessment
    - Validate rare cancers
    - Evaluate reduction in cancer stages and/or stage shift
    - Establish a valid interval for testing
11. What considerations are critical when allowing the use of RWE to support the aforementioned?