Molecular and Clinical Genetics Devices Panel
of the
Medical Devices Advisory Committee

In Vitro Diagnostic Multi-Cancer Detection Tests

Office of Health Technology 7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

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*** Virtual***

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Panel Questions

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Purpose of this Panel Meeting

The committee will discuss and make recommendations on:

- Clinical validation study design elements critical to multi-cancer detection (MCD) tests
- Determination of clinical truth and design elements needed for MCD in vitro diagnostic devices
- 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.

Panel Topics

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

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

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

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Topic 1

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

Clinical Study Design: Trial Design

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.

Clinical Study Design Consideration: Per Cancer

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?

Clinical Study Design Consideration: Per 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?

Clinical Study Design: Data Collection & Analyses

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?

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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

Tumor of Origin

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?

Clinical Study Design: Clinical 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)?

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Topic 3

Benefit/risk considerations,

including postmarket study considerations

Benefit-Risk Questions

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?

Benefit-Risk Questions

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?

Benefit-Risk Questions

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?

Benefit-Risk Questions: Real World Evidence

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?


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