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***

U.S. FOOD & DRUG ADMINISTRATION

Welcome and Introduction

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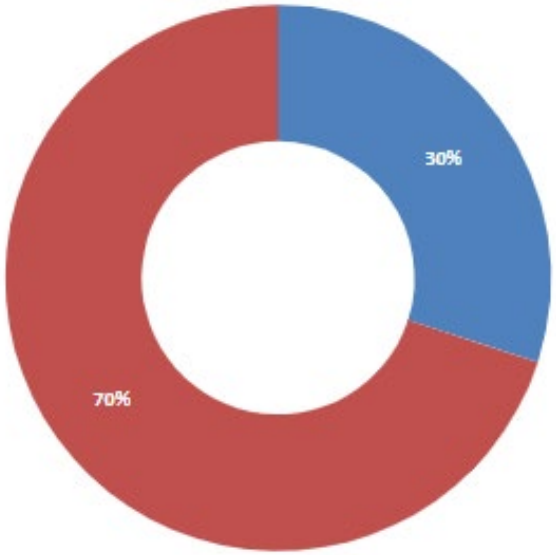
Introduction

- FDA mission to advance and protect public health
- Almost 2 million cancers diagnosed in the US this year*
- Current screening programs have helped lower the mortality rate for certain cancers
- FDA heavily invested in improving outcomes for patients with cancer
- Created the Oncology Center of Excellence
- Health Equity Initiatives

*American Cancer Society

Routine Screening Exists for 30% of Cancers

~70% of Incident Cancers
Have no standard of care (SOC) screening tests



~30% of Incident Cancers
Have recommended preventative screening tests:

- Colorectal
- Cervical
- Breast
- Lung
- Prostate

➢ Estimated 14% of these incident cancers are detected each year by a recommended preventive cancer screenings*

Siegel at al. (2022) Cancer statistics. *CA*. 72(1) 7-33.
And *https://cancerdetection.norc.org/

Current Preventative Screening Methods

- Breast cancer – mammography
- Colorectal cancer – stool-based tests and colonoscopy
- Cervical cancer – human papillomavirus (HPV) and PAP tests
- Lung cancer – low-dose computed tomography (CT scans)
- Prostate cancer – prostate specific antigen (PSA) tests (*USPSTF Grade C recommendation, men ages 55 to 69*)

FDA Review of Single Cancer Screening Tests

- **Intended Use /Indications for Use Statement**
  - What does the test measure (methylated DNA, fragmented DNA, protein, CTC, etc)
  - Specimen type
  - Technology (digital PCR, high throughput sequencing, etc)
  - Target population
  - Clinical indication (e.g., screening, early detection)
  - Contraindications for specific conditions as needed
- **Preanalytical and Analytical validation**
- **Clinical Validation**

Clinical Validation of Single Cancer Screening Tests

- Prospective, multi-center studies in the intended use population
  - Asymptomatic subjects, in the US
  - Prespecified inclusion/exclusion criteria
- Predefined "high-risk patients" based on consensus guidelines
- Appropriately sized study based on prevalence with enrichment strategies
- Prespecified how histopathological diagnoses will be considered (“positive” vs “negative” for analysis)
- Prespecified clinical decision point (cancer detected vs not detected)

FDA Review Single Cancer Detection Assays

- Appropriate statistical analyses that accounts for:
  - Sources of bias (e.g., missing data, imbalance in patient demographics and conditions)
  - Subset analyses by stage and histology
  - Subset analyses by key demographics
  - Evaluation of potentially confounding benign conditions and comorbidities related to the cancer (e.g., inflammatory bowel disease for CRC, emphysema for lung)

FDA Review Single Cancer Detection Assays

- Prespecified Statistical Analysis Plan that covers the intended use population
  - Sensitivity and specificity – probability that a test result is correct given that the patient does/does not have cancer
  - Positive predictive value (PPV) and negative predictive value (NPV) - probability that a patient does/does not have cancer based on the test result

	CLINICAL TRUTH		
	MALIGNANT	BENIGN	
MCD TEST POSITIVE	TRUE POSITIVES	FALSE POSITIVES	PPV
MCD TEST NEGATIVE	FALSE NEGATIVE	TRUE NEGATIVE	NPV
	SENSITIVITY	SPECIFICITY	

Clinical Validation of Single Cancer Screening Tests

- Benefits outweigh the risks
  - Magnitude of benefit
  - Magnitude of risks
  - Level of uncertainty
  - Risk mitigation measures (e.g., labeling, postmarket studies)

Example of Single Cancer Screening Test

Intended Use:

Cologuard is intended for the **qualitative detection of colorectal neoplasia** associated **DNA markers** and for the presence of **occult hemoglobin** in human stool. *Cologuard* is for use with the *Cologuard* collection kit and the following instruments: BioTek ELx808 Absorbance Microplate Reader; Applied Biosystems® 7500 Fast Dx Real-Time PCR; Hamilton Microlab® STARlet; and the Exact Sciences System Software with *Cologuard* Test Definition.

Indications for Use:

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A **positive result** may indicate the presence of **colorectal cancer** (CRC) or **advanced adenoma** (AA) and should be followed by **colonoscopy**. *Cologuard* is indicated to screen adults of either sex, 45 years or older, who are at typical **average-risk for CRC**. *Cologuard* is **not a replacement** for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.

Example of Single Cancer Screening Test

- *Cologuard* was not clinically evaluated for the following types of patients:
  - Patients with a history of CRC, adenomas, or other related cancers
  - Patients who have had a positive result from another CRC screening method ≤ 6 mo
  - Patients who have been diagnosed with a condition that is associated with high risk for CRC. These include but are not limited to:
    - Inflammatory bowel disease (IBD)
    - Chronic ulcerative colitis (CUC)
    - Crohn's disease
    - Familial adenomatous polyposis (FAP)
    - Family history of colorectal cancer
  - Patients who have been diagnosed with a relevant familial (hereditary) cancer syndrome

Example of Single Cancer Screening Test

- Prospective, cross-sectional, multi-center study ages 50-84 average risk for the development of colorectal cancer
  - 10,023 in primary analysis
  - 90 sites in the US and Canada, including colonoscopy centers and primary care sites
- *Cologuard* and the FIT test were compared to the results of colonoscopy, and histopathologic diagnosis for all significant lesions discovered during the colonoscopy
- Sensitivity for categories 1 and 2, specificity for categories 3-6

Table 8: Histopathological category definitions

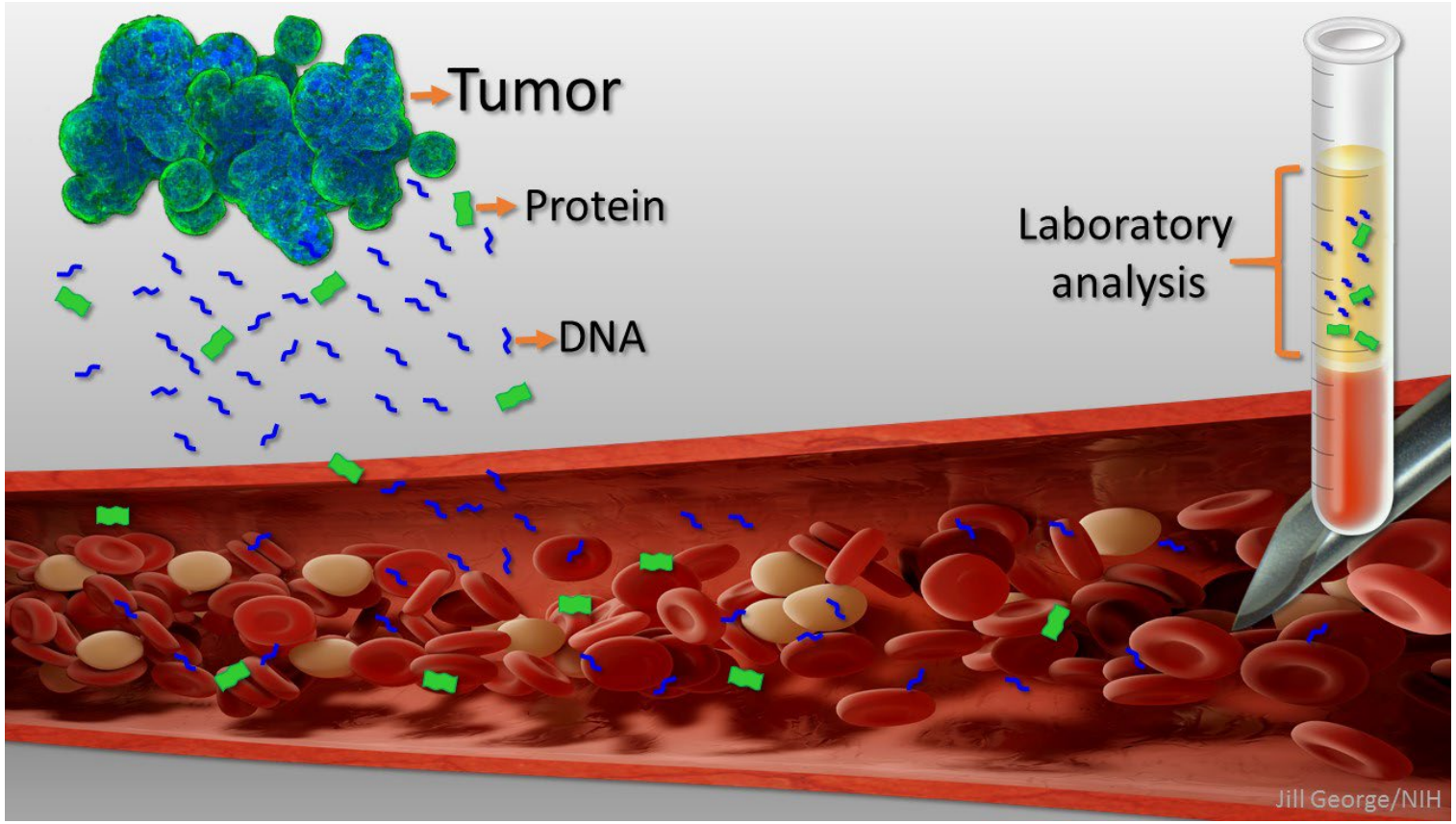
Category	Findings
1	CRC, all stages (I-IV)
2	Advance adenoma, including the following subcategories: 2.1 – Adenoma with carcinoma *in situ*/high grade dyplasia, any size 2.2 – Adenoma, villous growth pattern (≥25%), any size 2.3 – Adenoma ≥ 1.0 cm in size, or 2.4 – Serrated lesion, ≥ 1.0 cm in size
3	1 or 2 adenoma (s), >5 mm in size, or < 10 mm size, non-advanced
4	≥ 3 adenomas, <10mm, non-advanced
5	1 or 2 adenoma(s), ≤5 mm in size, non-advanced
6	Negative – No neoplastic findings 6.1 – negative upon histopathological review 6.2 – no findings on colonoscopy, no histopathological review

Example of Single Cancer Screening Test

- Primary Effectiveness Analyses
  - Cologuard for CRC:
    - Sensitivity (true positive fraction): 92.3% (60/65)
    - Specificity (true negative fraction): 86.6% (7967/9198)
  - FIT alone
    - Sensitivity for CRC (73.8%)
    - Specificity for CRC (93.4%)
    - Subgroup analysis by age, gender, race/ethnicity, histology, lesion size, lesion location

Cologuard	**CRC stages 1-4 Category 1**	**Advanced Adenoma Category 2**	**Non-advanced adenoma and negative colonoscopy Categories 3-6**
Negative	5 (7.7)	438 (57.6)	**7967 (86.6)**
Positive	**60 (92.3)**	322 (42.4)	1231 (13.4)

Multi-cancer Detection (MCD) Devices



Multi-Cancer Detection assays (MCDs) also referred to as **Multi-Cancer Early Detection assays (MCEDs),** measure biological substances that cancer cells may shed in blood and other body fluids– such as circulating tumor cells, tumor DNA, and other analytes – that may suggest the presence of cancer.

Benefits and Challenges for MCDs

New Opportunities:

- Potential to improve cancer screening
- Broaden the range of cancers detected with a single test
- Non-invasive may improve compliance
- Earlier detection enables early treatment and may lead to improved survival

New Challenges:

- Risks differ by cancer type
- Simultaneous multi-organ detection requires localization of cancer
- Level of evidence needed to determine benefit uncertain
- Potential harms and prolonged process from procedures needed to diagnose the cancer
- Potential for overtreatment and overdiagnosis

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.

Background – Topic 1

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

- Critical design considerations when planning an MCD clinical validation
- Evaluation per cancer
- Analysis of performance
- Performance expectations

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?

Background – 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

- Benefits and risks of various tumor of origin (TOO) methods
- Clinical truth for test positives and negatives

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 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)?

Background – Topic 3

Benefit/risk considerations,

including postmarket study considerations

- Evaluation of probable benefits
- Evaluation of probably risks
- Evaluation of stage shift and whether it is necessary for evaluation of benefit
- Use of real-world data and postmarket studies

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 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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