Multi-Cancer Detection Tests and NCI's Vanguard Study

Elyse LeeVan, MD, MPH
Program Officer
Division of Cancer Prevention, NCI

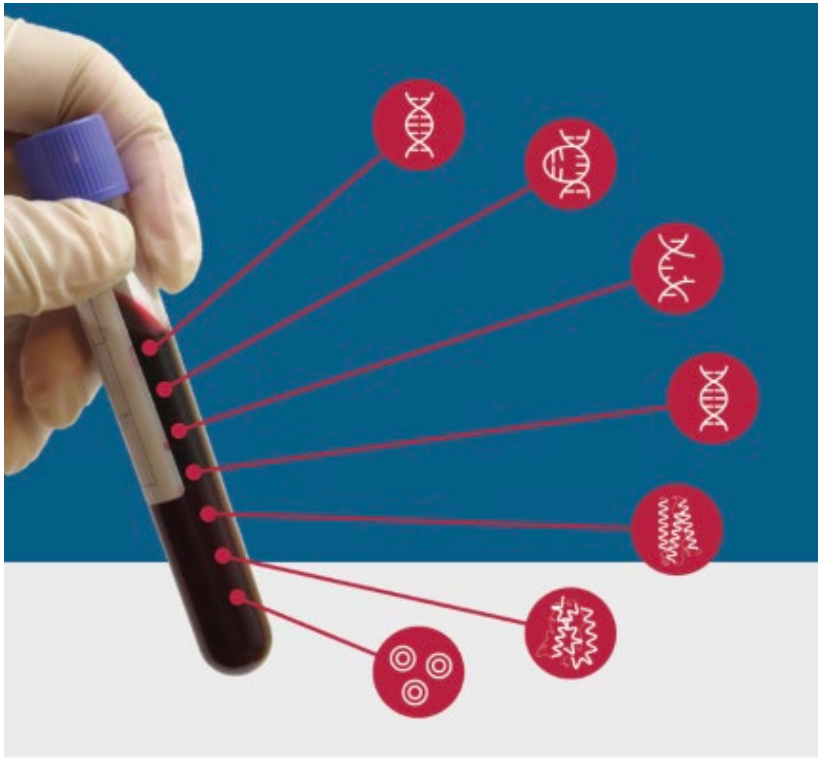
NIH NATIONAL CANCER INSTITUTE

Value in Cancer Care Summit
November 15, 2024

What are Multi-Cancer Detection (MCD) Assays?

Multi-Cancer Detection Assays

- A new type of cancer screening test that evaluates molecular signatures from tumors in readily accessible body fluids to predict the presence of cancer in individuals without known cancer

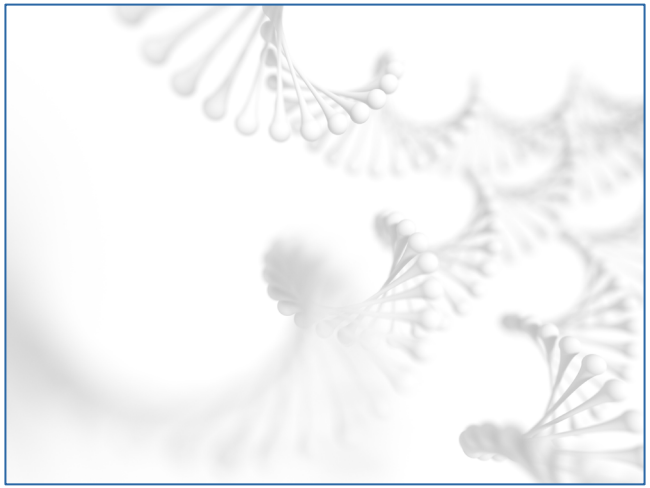


Analytes and Technologies Used to Develop MCDs

- MCD assays use circulating tumor DNA (ctDNA) and other biomarkers analyzed by variable technologies.

Examples of other biomarkers include:

- Cell-free RNA, proteins, metabolites, and glycans.
- Circulating tumor cells.
- Tumor-educated platelets (platelets changed by tumors).
- Cancer stem cells in blood and other biospecimens.



Facets of Multi-Cancer Detection Assays

- Developed to screen for cancers from different organ sites using a single test
    - Each test has a different ‘menu’ of organ sites
- Each test contains two components:
    - Biologic measurement of the specific signals
    - Algorithm for determining what is a positive test

Tissue of Origin

Many MCD Assays provide a likely “Tissue of Origin” if a cancer signal is detected

- Primary, Secondary, Tertiary
- This may guide the diagnostic work-up

How Could MCD Assays Improve Cancer Screening?

Possible Benefits to Cancer Screening

- Screening for cancer at organ sites currently without screening test.
- MCD tests *may* detect cancers which are hard to identify at an early stage.
- MCD tests can potentially identify cancers from many different organ sites with only a single test.
- MCD tests rely on a blood draw, which may be more acceptable to patients than other forms of cancer screening tests.

MCD Results and Next Steps

What Does an MCD Test Result Mean?

A positive MCD test means that there *may* be cancer.

- An MCD test does not diagnose cancer
- All positive tests need a follow up diagnostic work-up

A negative MCD test means there's no identified signal.

- A small percentage of people with a negative test will still have cancer
- There is not enough biochemical signal for a particular test to be positive
- A person may have a cancer that the MCD test does not detect

.

What Happens After a Positive Test Result?

All positive tests need a follow up diagnostic work-up

- Clinicians must make decisions what diagnostic work-up to pursue
- No current guidelines for work up
- Access to follow up tests will affect the equity of benefit of this technology
- Clinicians must also decide when to stop looking if follow up tests do not reveal cancer
  - Only 40% of people with a + MCD test result are found to have cancer

MCDs Represent a Paradigm Shift

- Cancers vary dramatically by histology and organ site.
- MCD technologies use a wide range of biologic markers.
- MCD technologies encompass biological signals and AI algorithms.

What Unknowns Remain Regarding MCDs?

Unknowns: Screening for Cancer with MCD Assays

- What kind/how many diagnostic tests are needed to make a cancer diagnosis?
  - How many people will be subjected to unnecessary invasive procedures and suffer from various complications of those procedures?
- What happens if following a positive MCD test, you do not find a cancer?
- Will a blood test make screening more accessible or exacerbate disparities?
- Will people stop standard of care screening if they get a negative MCD test?
- Will these assays lead to overdiagnosis* of indolent cancers?

What Do We Know about MCD Performance?

Clinical Chemistry 70:1
90–101 (2024)

Review

Predictive Performance of Cell-Free Nucleic Acid-Based Multi-Cancer Early Detection Tests: A Systematic Review

Elyse LeeVan[a] and Paul Pinsky [a,*]

"To date, relatively few published studies have assessed the clinical validity of MCD tests.

Most used cancer cases assessed at diagnosis, with generally high specificity and variable sensitivity depending on cancer type and stage.

The next steps should be testing in the intended-use population, i.e., asymptomatic persons."

Table 2. Sensitivity, specificity, and AUC.

Author/reference	Validation	Model[a]	Sample size[b] (cases |controls)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC (95% CI)
Chen (9) (Phase 2)	Independent	PanSEER	113|207	88 (80–93)	96.1 (92.5–98.3)	97
Chen (9) (Phase 3)	Independent	PanSEER	98|207	95 (89–98)	Same as above	99
Cohen (10)	Cross	CancerSEEK	1005| 812	62 (56–68)	99[c]	91 (90–92)
Constâncio (11)	Cross	PanCancer	223|136	64	69.8	
Cristiano (12)	Cross	DELFI	236|245	73 (67–79)	98[c]	94 (92–96)
Douville (13)	Cross	Aneu + Mut + Proteins [7]	883|812	75 (72–78)	99[c]	94
Gao (14)	Independent	MCEDBT-1 [2]	473 | 473	69 (65–73)	98.9 (97.6–99.7)	—
Haldavnekar (15)	Independent	—	36|6	95 (88–99)	83	—
In' t Veld (16)	Independent	ThromboSeq	1096|146	64 (61–66)	99 (95–100)	91 (89–92)
Jamshidi (17)	Independent	Pan-feature [10]	464|362	36 (31–40)	98	
Kandimalla (18)	Cross	Pan-GI/Git-BS	254|46	—	—	88 (82–94)
Klein (19)	Independent	Galleri	1346|1254	76 (74–79)[d]	99.5 (99–99.8)	—
Lennon (21)	Independent	CancerSEEK Blood test[c]	96| 9815	27 (19–37)	98.9 (98.7–99.1)	—
Liu (22)	Independent	—	68|25	84 (74–91)	100	—
Liu (23)	Independent	—	356|610	76 (73–81)[d]	99.3 (98.3–99.8)	—
Ris (24)	Training	DEEPGEN	260|415	43 (37–49)	99[c]	90 (88–92)
Stackpole (25)	Cross	cfMethyl-Seq	217	81 (69–91)	97.9	97.4 (92.6–99.8)
Sundquist (26)	N/A	n(DNA)	66|136	72 (61–83)	71	78 (70–86)
Zhou (27)	Independent	—	43| 24	—	—	91.2 (83.7–98.7)
Zhou (28) (Phase 2)	Cross	SRFD-Bayes [4]	2000|400	92 (81–97)	99.5[c]	97.6 (97.2–98.0)
Zhou (28) (Phase 3)	Independent	SRFD-Bayes [2]	191| 207	38 (31–44)	95[c]	

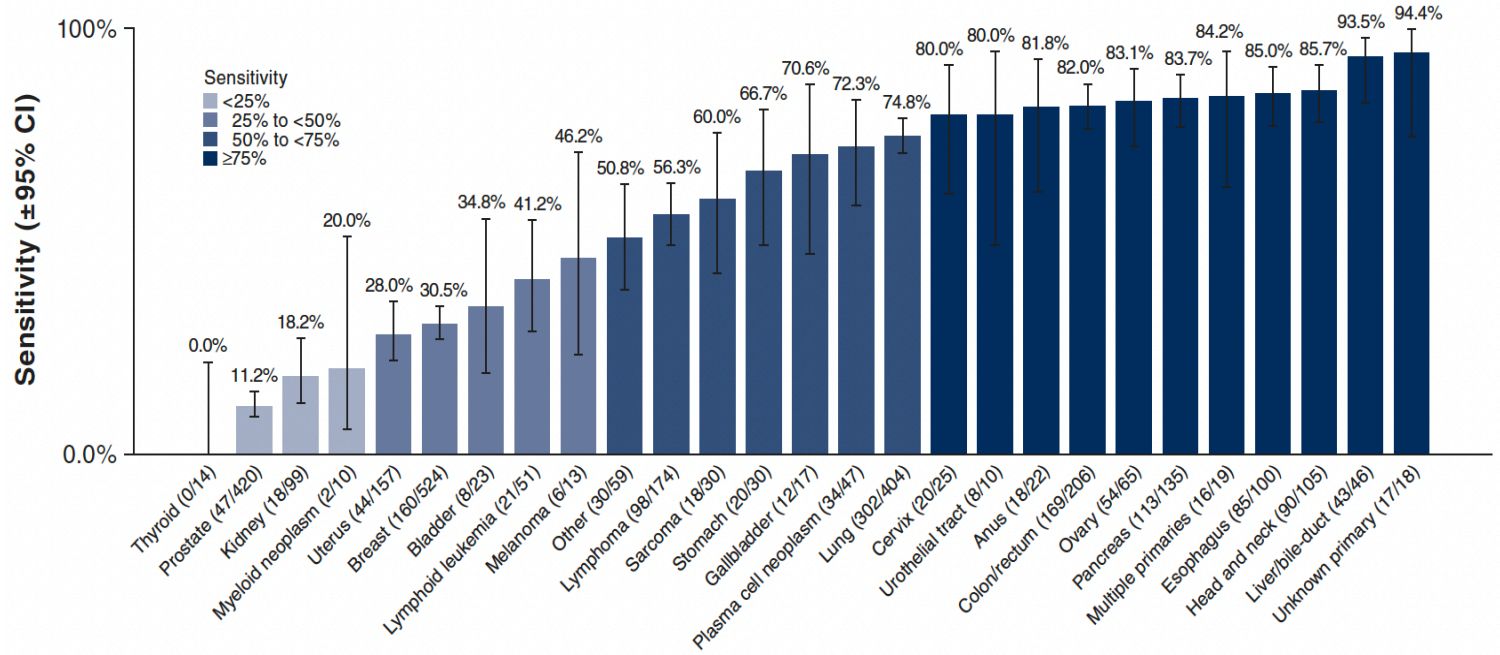
[a]Number in brackets indicates total number of models reported on, if >1.
[b]For independent validation, sample size is number in validation set; for cross-validation, sample size is number is total number used is the cross-validation process.
[c]Specificity fixed at the indicated level.
[d]Sensitivity based on 12 pre-specified cancer types, as shown in Table 2.

Diagnostic Performance of MCD Tests

- **Sensitivity and Specificity**
- Average overall Sensitivity of MCD tests: 27% - 95%, at Specificities of 95% - 99%
  - Early-stage cancer (e.g., Stage I) Sensitivity: 27% - 62%
  - Late-stage cancer (e.g., Stage III) Sensitivity: 60% - 87%

- **Tissue-of-Origin (TOO) Prediction**
- Most MCD tests provide a primary and secondary predictions for possible TOO of a positive MCD signal to help guide the diagnostic workup
- Average accuracy of TOO prediction is ~77% with a range of 68% - 86%

Performance by Cancer Type for One MCD Test



Klein EA, Richards D, Cohn A, *et al*. Ann Oncol. 2021 Sep;32(9):1167-1177. doi: 10.1016/j.annonc.2021.05.806. Epub 2021 Jun 24. PMID: 34176681.

What Do We Know about MCD Cost?

Costs of MCD Tests

Current costs of available tests:

- Galleri: $949,
- OneTest/premium $199/$355
- EPISEEK $699

Who Will Get These tests?

- 115,000,000 people in the US over 50
- About 1%-2% of people will have a positive test

What Happens Next?

- PET-CT 61%, CT 39%, MRI 21%, Ultrasound 10%, Mammography, Endoscopy 13%

NCI Efforts:

Cancer Screening Research Network and the Vanguard Study

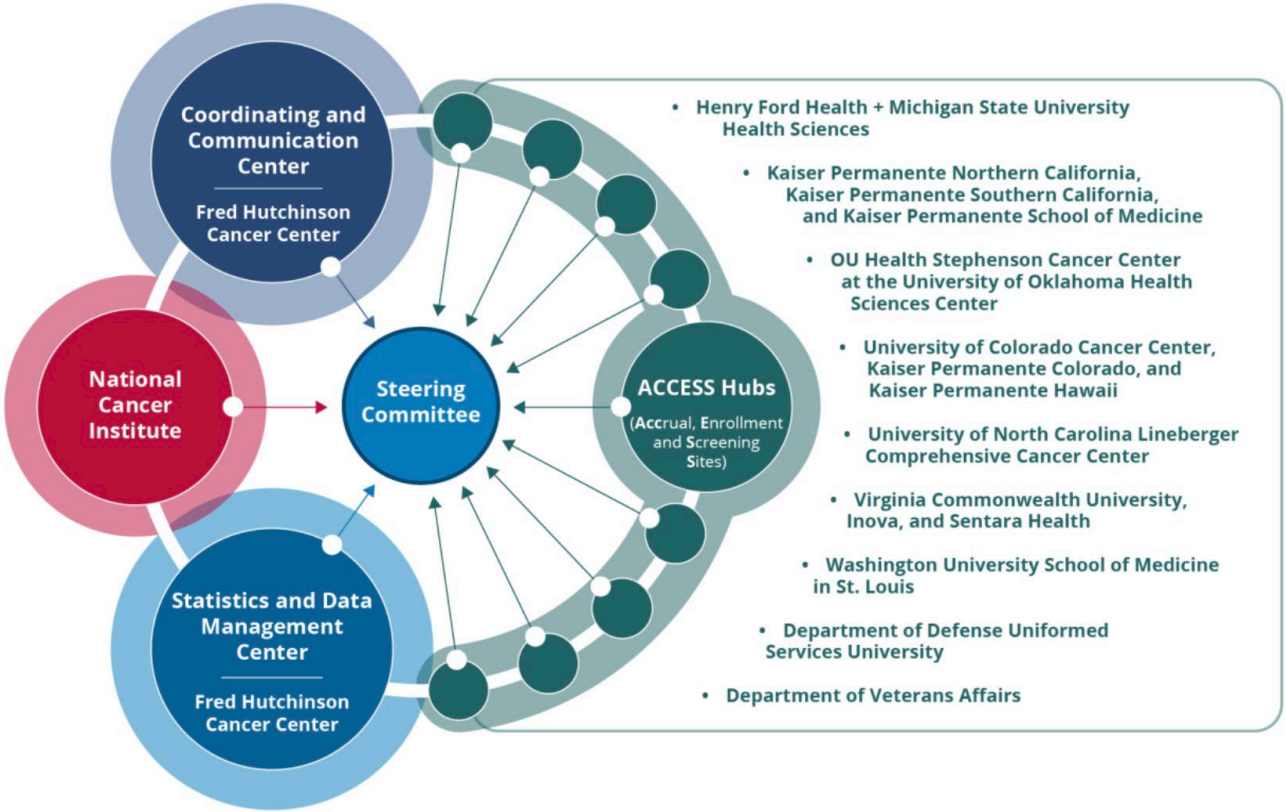
CSRN Objectives

Establish the organizational infrastructure for all necessary components to implement cancer screening clinical studies

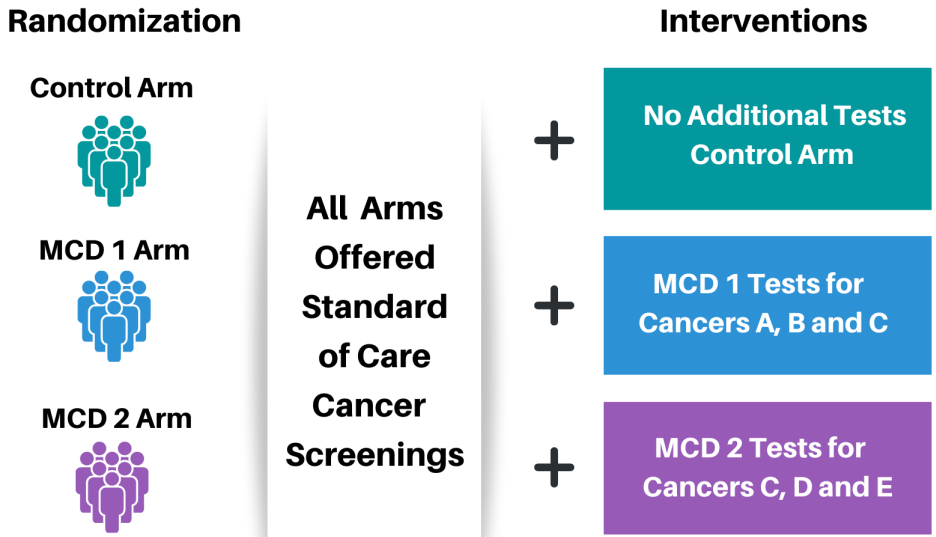
- Develop cancer screening trials to evaluate emerging technologies
- Assess the clinical utility of cancer screening programs or biomarkers of detection including downstream interventions and health outcomes
- Apply precision medicine approaches to screening using novel risk assessment tools to individualize screening protocols
- Evaluate the effectiveness, feasibility and scalability of screening strategies
- Conduct surveillance of cancer screening in diverse populations

NATIONAL CANCER INSTITUTE

CANCER SCREENING RESEARCH NETWORK



The Vanguard Study



Estimated sample size for the Vanguard is 6,000- 8,000 persons per arm

Multi-cancer detection (MCD) tests are a new type of blood test designed to detect cancers from different organ types.

Clinical trials are needed to provide the evidence that using these tests to screen persons for cancer will save lives.

Thank you!

www.cancer.gov

www.cancer.gov/espanol

Questions?

NCI Resources for Multi-Cancer Detection Tests

- MCD Research (landing page)
  - https://prevention.cancer.gov/major-programs/multi-cancer-detection-mcd-research
  - or search for “NCI” + “MCD” or “MCED”
    - See Questions and Answers about MCD Tests
- Our mailbox:
  - NCIMCED@mail.nih.gov
- LeeVan E, Pinsky, P. Predictive performance of cell-free nucleic acid-based multi-cancer early detection tests: A systematic review. Clinical Chemistry. 2023;, hvad134
  - https://pubmed.ncbi.nlm.nih.gov/37791504/
- Rubinstein WS, Patriotis C, Dickherber A, Han PKJ, Katki HA, LeeVan E, Pinsky PF, Prorok PC, Skarlupka AL, Temkin SM, Castle PE, Minasian LM. Cancer screening with multicancer detection tests: A translational science review. CA Cancer J Clin. 2024 Jul-Aug;74(4):368-382.
  - https://pubmed.ncbi.nlm.nih.gov/38517462/