# Ethical Considerations for Multi-Cancer Early Detection Testing

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# Presenter

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- Dr. Eric Blackstone has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
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# Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Summarize the current state of research regarding multi-cancer early detection (MCED) testing.
2. Identify current knowledge gaps and ethical issues raised.
3. Apply ethical principles to decisions about MCED testing.

# What is Multi-Cancer Early Detection?

- Blood test using cell-free DNA (cfDNA) to detect 50+ types of cancer
  - Includes likely tissue of origin
- Available direct-to-consumer
- Several cancer centers have established early detection clinics offering MCED

# Polling Question #1

How familiar are you with Multi-Cancer Early Detection (MCED)?

a. Not at all
b. Somewhat
c. Very

# MCED at Dana-Farber and My Role

- Disclaimer: I am not an expert in the science behind MCED!
- I am collaborating with Dana-Farber's MCED Clinic
- The MCED Clinic at Dana-Farber:
  - Provides counseling and testing
  - Diagnostic workup for those with positive results
  - Ongoing research evaluating MCED in various high-risk populations such as military veterans, people with familial or genetic risk factors, and patients with symptoms concerning for cancer

# MCED or MCD?

- Multi-Cancer Early Detection (MCED) vs. Multi-Cancer Detection (MCD)
- We currently lack data on whether cancers detected by these tests are found early enough to alter the course of the disease
- Often better at detecting late-stage cancers (more cfDNA in the blood) compared to early-stage, curable cancers

# Test Performance

**PATHFINDER (US):**

- Population: 6661 asymptomatic patients
- Sensitivity = 28.9%
- Specificity = 99.1%
- Positive Predictive Value (PPV) = 38%

**SYMPLIFY (UK):**

- **Population: 5461 patients with suspected malignancies**
- **Sensitivity = 66.3%**
- **Specificity = 98.4%**
- **Positive Predictive Value (PPV) = 75.5%**

(Cotner & O'Donnell, 2024)

# Sensitivity by Cancer Stage

- Stage I = 18%
- Stage II = 43%
- Stage III = 81%
- Stage IV = 93%

(Liu et al., 2020)

# PATHFINDER (1 of 4)

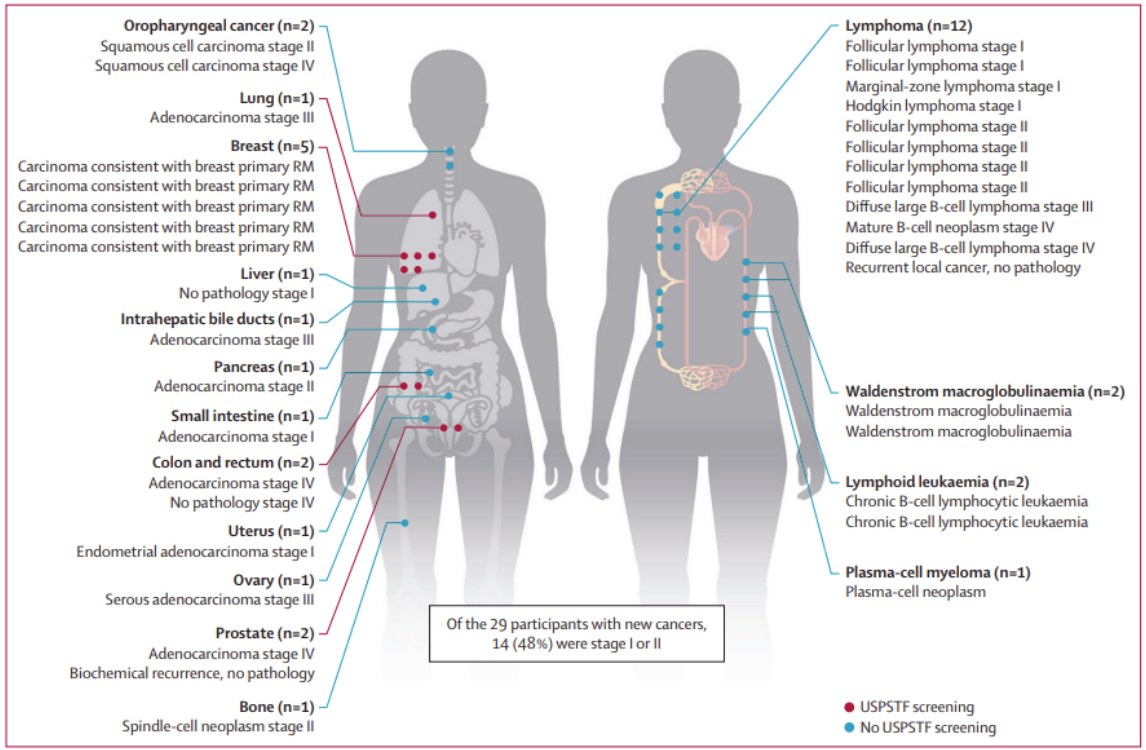
## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

*Deb Schrag, Tomasz M Beer, Charles H McDonnell III, Lincoln Nadauld, Christina A Dilaveri, Robert Reid, Catherine R Marinac, Karen C Chung, Margarita Lopatin, Eric T Fung, Eric A Klein*

- 6,662 participants from US oncology and primary care clinics
- 92 positive tests (1.4%)
- 35 diagnosed with cancer (38% of positive results)
- 57 false positives (62% of positive results)
- Median time to diagnostic resolution = 79 days

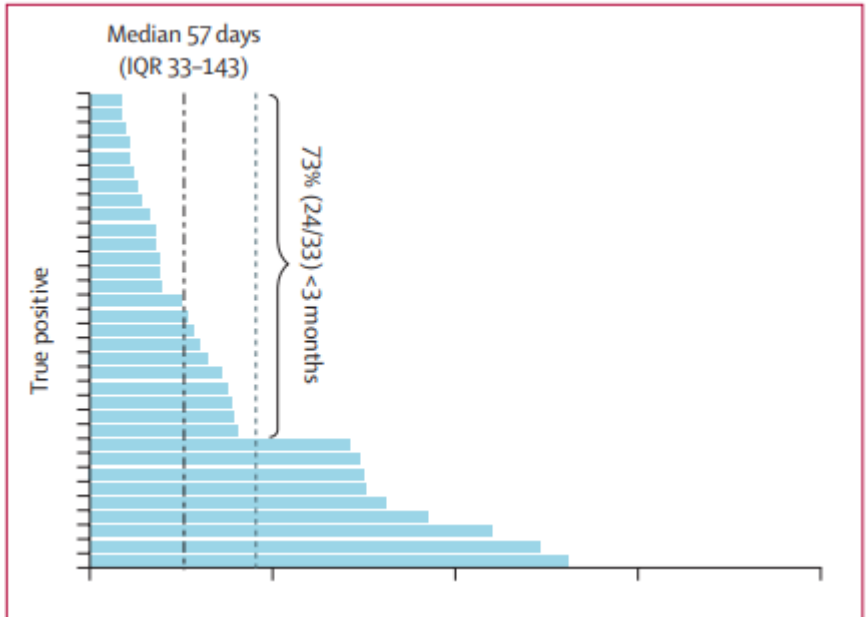
(Schrag et al., 2023)

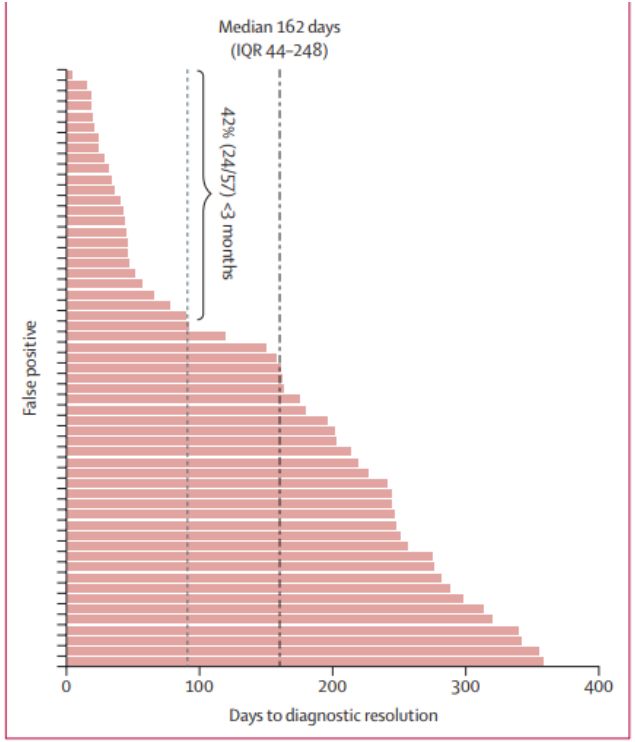
# PATHFINDER (2 of 4)




(Schrag et al., 2023)

# PATHFINDER (3 of 4)




(Schrag et al., 2023)

# PATHFINDER (4 of 4)

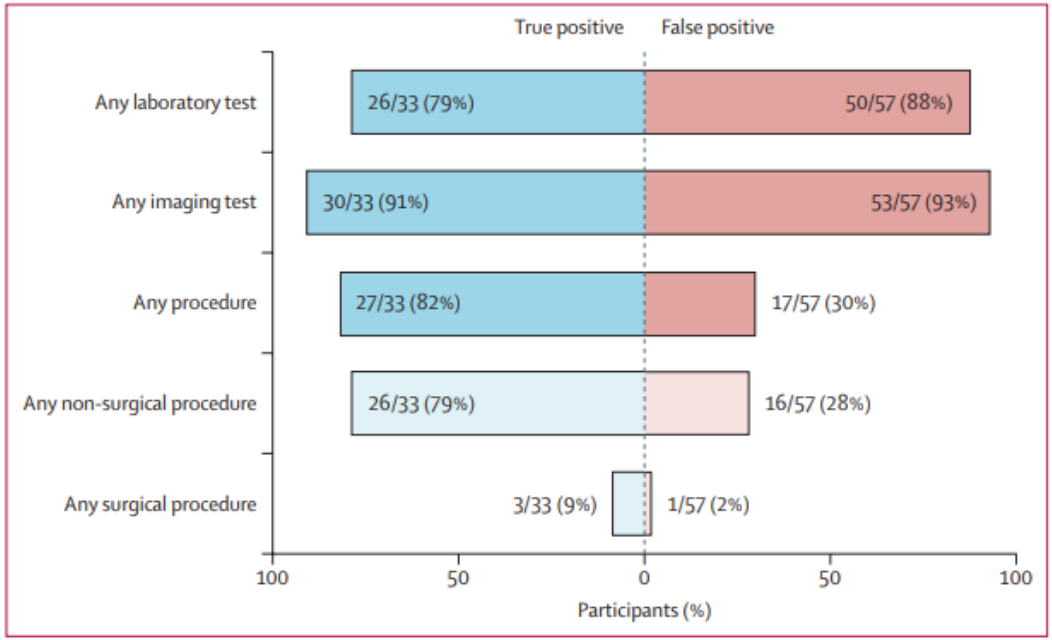



*Figure 3:* **Extent of diagnostic testing in participants with cancer signal detected (n=90)**

(Schrag et al., 2023)

# How Does MCED Compare to Other Screening Tests?

**Table 2.** Sensitivity and specificity of USPSTF-endorsed tests.

| Screening | USPSTF Screening Recommendation | Sensitivity | Specificity |
|---|---|---|---|
| Breast | Women aged 40–74 years [48] | | |
| | Biennial mammography [46,49] | 70–87% | 89–92% |
| Cervical | Women aged 21–65 years [50] | | |
| | Cytology-based screening [51] | 36–100% * | 96–98% * |
| | Cotesting with cytology and HPV [51] | 93.7–100% * | 90–94% * |
| Colorectal ** | Adults aged 45–75 years [52] | | |
| | Fecal immunochemical test (FIT) [52] | 64–83% | 93–96% |
| | Stool DNA-FIT test [52] | 87–100% | 84–86% |
| | CT colonography [52] | 86–100% | Not reported |
| Lung | Adults aged 50–80 years with a 20 pack-year smoking history currently smoking or who quit in last 15 years [53] | | |
| | Low-dose CT screening [47] | 91–96% | 73–74% |
| CancerSEEK | N/A | 23.5% | 98.9% |
| Galleri | N/A | 28.9% | 99.1% |

* Sensitivity and specificity of detecting cervical intraepithelial neoplasia 3 or greater. ** Colonoscopy serves as the reference group for sensitivities and specificities of listed colorectal cancer screening tests.

(Cotner & O'Donnell, 2024)

# MCED and Primary Care

- Why should primary care worry about MCED ethics?
- Cancer screening is often managed through primary care
- Multiple studies have been conducted to evaluate MCED knowledge and interest for primary care patients/clinicians

# Concerns for Primary Care

ORIGINAL ARTICLE

## Perspectives of primary care providers regarding multicancer early detection panels

Benjamin E. Ueberroth[1], Richard J. Presutti[2], Alyssa McGary[3], Mitesh J. Borad[4], Neera Agrwal[5]

- Limitations: small sample size (n=88) and low response rate (27%)

(Ueberroth et al., 2024)

**Table 2.** Potential concerns related to the use of multicancer early detection panels in primary care practice

| Potential concern | Median (IQR) |
|---|---|
| Liability/medicolegal | 6.0 (4.0-8.0) |
| Cost to patient | 6.0 (3.0-8.0) |
| False reassurance with a negative test | 5.5 (3.0-8.0) |
| Burden of documentation | 5.0 (3.0-8.0) |
| Impact on health equity (*i.e.*, access to a $979 test) | 5.0 (3.0-8.0) |
| Rate of false positives | 5.0 (3.0-7.0) |
| Cost to healthcare system (*e.g.*, downstream testing, referrals) | 5.0 (2.0-6.0) |
| Burden of counseling/integrating into a busy practice | 4.0 (3.0-7.0) |
| Patient anxiety with a positive result | 4.0 (2.0-6.0) |

# Primary Care Patient Interest

Journal of *Personalized Medicine*

MDPI

*Article*

**Primary Care Patient Interest in Multi-Cancer Early Detection for Cancer Screening**

Ronald E. Myers [1,*], Mie H. Hallman [1], Ayako Shimada [2], Melissa DiCarlo [1], Kaitlyn Davis [3], William T. Leach [3], Hattie Jackson [1], Amanda Indictor [1] and Christopher V. Chambers [3]

- Survey of primary care patients (n=159) in 2023
- 79% reported a high level of interest in MCED
- Positive association with: recommendation, convenience, ability to detect early-stage cancers

(Myers et al., 2023)

# Primary Care Receptivity

Journal of *Personalized Medicine*

MDPI

*Article*

## Primary Care Provider Receptivity to Multi-Cancer Early Detection Test Use in Cancer Screening

Christopher V. Chambers [1,*], William T. Leach [1], Kaitlyn Davis [1] and Ronald E. Myers [2]

- Survey of PCPs (n=351) in 2022
- High receptivity and perceived competence
- High awareness of challenges: false positives/negatives, time to explain, cost, insurance coverage, provider knowledge

(Chambers et al., 2023)

# Primary Care Barriers

Journal of *Personalized Medicine*

MDPI

*Article*

**Perspectives on Clinical Adoption Barriers to Blood-Based Multi-Cancer Early Detection Tests across Stakeholders**

Monica M. Schroll [1], Elissa Quinn [2], Daryl Pritchard [3], Allina Chang [1], Kristen Garner Amanti [1], Omar Perez [2], Arushi Agarwal [1,*] and Gary Gustavsen [1]

- Survey of 238 providers (159 PCPs and 79 OB-GYNs) in 2023
- Current barriers: lack of data, high out-of-pocket costs, and lack of insurance coverage

(Schroll et al., 2024)

# Public Attitudes

- Qualitative interviews with 27 US adults (ages 45-70)

| Themes | Illustrative Quotes |
|---|---|
| Public enthusiasm for MCEDs | As someone who has gone through a lot of cancer screenings…I think that they're just unpleasant. A blood test…it seems super easy. (Participant 15)<br>Get it done, you know. Don't wait. And peace of mind, too. I mean, if you get to test, and everything comes out fine. (Participant 21) |
| Balancing MCED benefits and harms | It'd be nice way to get some peace of mind. Then, you know, I'd have to struggle with saying, am I willing to shell out a thousand bucks to get that peace of mind? (Participant 2)<br>Even if you find [cancer] earlier, you know what I mean, and you go through chemo, that doesn't mean it's gonna save your life, either. (Participant 26) |
| MCED use in clinical care | With this particular product, with it being so new, I would like to hear [information about MCED] from my primary care. I would like for him to be well versed in the product and confident in it….and then [receive] material to take home. If I had any follow up questions, I could email my doctor's team. (Participant 27)<br>She would just have to tell me that it's fairly new. And it's not…a proven thing. (Participant 1) |

(Crossnohere et al., 2024)

# Controversy

*Cambridge Quarterly of Healthcare Ethics (2024), 1–14*
doi:10.1017/S0963180124000756

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## Multicancer Early Detection Screening Tools: Not Economically Efficient, Not Ethically Equitable, Marginally Medically Effective

Leonard M. Fleck

- Significant evidence gaps
- Harms of false positives
- Not approved by the Food and Drug Administration (FDA)
- Cost to patients (~$950) and to healthcare system

(Fleck, 2024)

# Evidence Gaps

- Comparison to standard of care
  - Stage shift
  - Survival and quality of life
- Limitations of studies assessing patient decision-making
  - Hypothetical tests and decisions
- Other ethically relevant questions
  - Appropriate populations to be offered testing
  - Ethical standards for informed consent
  - Best practices for results counseling

# Regulatory Status

- Not approved by the FDA - why?
- Laboratory-developed test (LDT)
  - Can be prescribed by a physician
  - Regulated by Centers for Medicare and Medicaid Services via Clinical Laboratory Improvement Amendments (CLIA)
  - Limited oversight over reliability and quality
  - Not routinely covered by insurers

# Current and Planned Studies

| Study Name | Sponsor | Study Type | Population | Size | Outcomes |
|---|---|---|---|---|---|
| NHS-Galleri (ISRCTN91431511) | NHS, GRAIL | Randomized controlled trial | Adults 50–77 years of age | 140,000 | Primary: cancer incidence and stage at diagnosis<br>Secondary: cancer mortality, number of follow-up procedures, number of complications and deaths from diagnostic procedures, radiation exposure, and psychologic impact of Galleri test |
| PATHFINDER 2 (NCT05155605) | GRAIL | Prospective cohort | Adults ≥50 years of age | 35,000 | Primary: test performance and number and type of invasive procedures performed in false positives<br>Secondary: participant-reported anxiety, perceptions of Galleri, and intention to follow standard-of-care cancer screenings, radiation exposure, and diagnostic evaluation |
| REFLECTION (NCT05205967) | GRAIL | Prospective cohort | Adults ≥22 years of age | 17,000 | Primary: describe signal and cancer detection<br>Secondary: assess the feasibility and acceptability of Galleri from the participant's perspective and patient-reported outcomes; to assess healthcare resource utilization associated with diagnostic workups when the test result is positive |
| VANGUARD [39,40] | NCI | Randomized controlled trial | Preliminarily 45–70 years | 24,000 | Outcomes are to be defined. The study will preliminarily have three groups and evaluate two MCD assays compared to a control group. The purpose of the trial is to inform a larger randomized trial. |

SUMMIT and STRIVE are additional ongoing studies seeking to evaluate Galleri in populations undergoing LDCT and mammography screening.

(Cotner & O'Donnell, 2024)

# Ethical Considerations

# Beneficence

## Advantages:

- Detects some cancers that currently have no screening strategy
- Earlier detection often means better outcomes

## Risks:

- Lead time bias: Diagnosing cancer sooner does not necessarily mean they live longer
- Direct-to-consumer testing from a company may dehumanize the process of cancer diagnosis

# Nonmaleficence

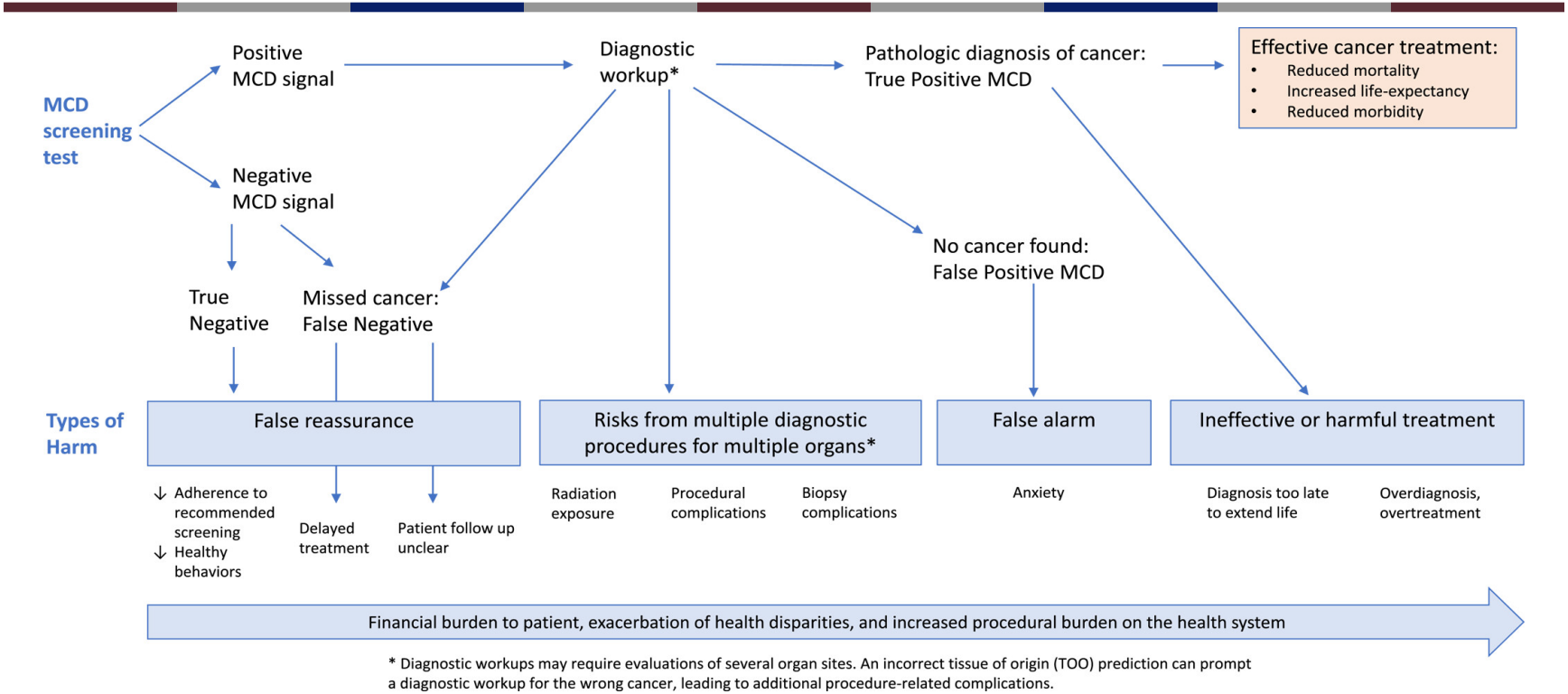
## Advantages:

- Less invasive and lower risk than other methods
- Less likely to detect indolent cancers, making overtreatment less of a concern

## Risks:

- False reassurance
- False positives
- Anxiety
- Costs of testing and follow-up diagnostic procedures
- Opportunity cost: limited bandwidth for health behaviors

# Potential Harms




(Rubinstein et al., 2024)

# Patient-Reported Outcomes from PATHFINDER

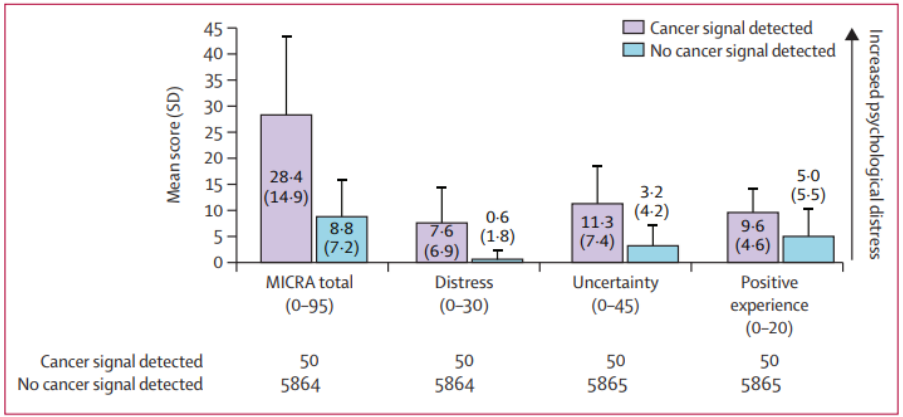



***Figure 2:*** **Impact of MCED test results by signal detection status (adapted MICRA) at results disclosure**
MICRA score range for each domain is indicated under each column (eg, total score range is 0–95). N values are given below each set of columns for those with and without a cancer signal detected. MCED=multicancer early detection. MICRA=Multidimensional Impact of Cancer Risk Assessment.

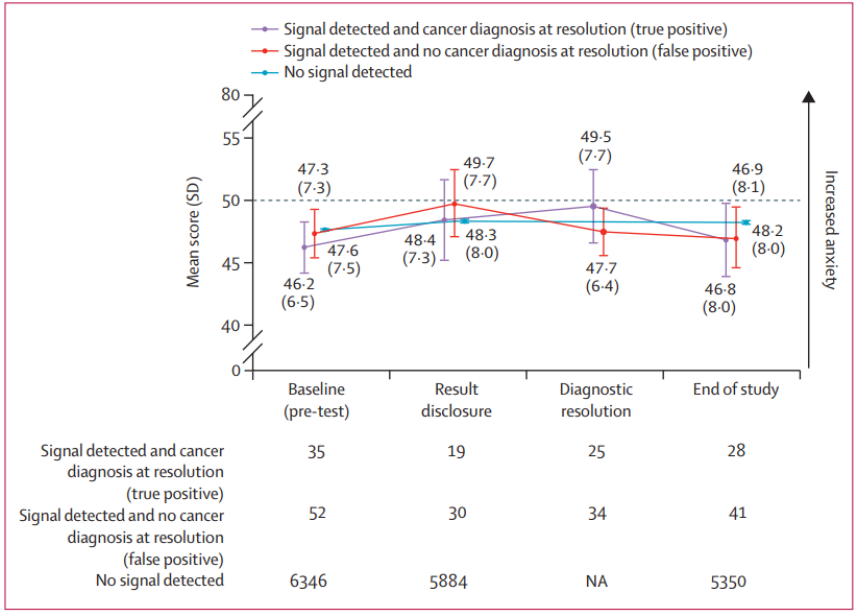



***Figure 3:*** **General anxiety symptom score by MCED test outcome (PROMIS Anxiety 4)**
Average score for the general population is indicated with a dashed grey line. Error bars indicate SD. N values for each group are given below the figure. FP=false positives. MCED=multicancer early detection. PROMIS=patient-reported outcome measurement information system. TP=true positives.

(Nadauld et al., 2025)

# Respect for Autonomy

**Advantages:**

- Health information can maximize autonomous decision-making if results are delivered with counseling and person-centered care

**Risks:**

- Direct-to-consumer advertising may oversell benefits
- True informed consent is difficult to obtain with lack of data
- “Let the patient decide” does not obviate duty to provide evidence-based care

# Justice

**Advantages:**

- Blood tests are easier to obtain than other screening methods, potentially increasing access

**Risks:**

- Specialized clinicians needed to counsel patients
- Currently expensive
- Research needs generalizable samples

# Health Maximization

**Advantages:**

- Early diagnosis for multiple cancers could improve overall public health

**Risks:**

- Societal opportunity cost
- Research has yet to show stage shift
- Uncertain improvement in overall survival and/or quality of life

# Efficiency

**Advantages:**

- Screens for 50 cancers at once
- Could make screening for rarer cancers cost-effective

**Risks:**

- We currently lack data to assess whether public health benefits justify the cost to the healthcare system

# Talking with Patients about MCED

- **What are the potential benefits?**
  - It is possible that the test would find cancer early, before symptoms are showing. We think that this could lead to a better outcome, but this has not been proven yet.
  - If the result is negative, it could be reassuring for you.
- **What are potential risks?**
  - No studies have proven that MCED testing is better than no testing.
  - Insurance may not cover testing or diagnostic workup.
  - So far, most positive results are false positives, which may cause anxiety, overtreatment, and added costs.

# Talking with Patients about MCED, continued

- How should I make this decision?
  - First, this should not replace standard screening recommendations. MCED is not currently recommended by any major organization.
  - Consider the costs and limitations of our current data. Are you going to take the test one time? Yearly?
  - You may want to wait until ongoing studies have been completed. You could consider participating in research if you are eligible and interested.

# Polling Question #2

Would you recommend MCED testing for your patients?

a. Yes
b. No
c. Unsure

# Key Takeaways

- While MCED tests show promise in detecting many cancers for which we currently lack screening, they have yet to prove that they lead to better outcomes.
- The current availability of MCED tests (and significant cost) despite this uncertainty raises concerns for informed consent, non-maleficence, and justice.
- Primary care providers should consider whether and under what circumstances they would recommend MCED given current limitations, and how best to communicate with patients.

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# Questions?

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Credits are awarded by session. To claim CE/CME credit or certificate of attendance for the session(s) you attend, you must register by 4:00 p.m. ET on June 6, and then you must complete the course evaluation and posttest for each session by 11:59 p.m. ET on Thursday, June 19, 2025.

1. Visit the main event page at https://www.dhaj7-cepo.com/content/2025-jun-ccss to register for the live event or to log in to your account if already registered.
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3. Under the “Get Started” tab, scroll down to a session you attended and select “Claim credit.”
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