NASEM-National Cancer Policy Forum

Strategies for Implementing MCD Tests into Clinical Practice

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MCD Testing in Primary Care

A patient had a positive MCD result and a predicted cancer signal of origin (CSO) work up was negative. The PCP is concerned about missing a cancer diagnosis but unclear what further workup is needed or whether the MCD should be repeated

- Why did the practice sign up to offer MCD?
- How did the patient hear about the test?
  - *Communication from the practice*
- What is the role of patient values and preferences in the absence of evidence?‡
- What is the workup for a positive result with/without information on CSO/TOO?
  - How is false positive determined?
- What do primary care clinicians and patients need to know about MCDs?

Promoting MCD "tests for use before valid and rigorous evaluations are performed is similar to marketing a drug without first showing that it is safe and effective."*

*Doubeni CA, Castle PE. AFP. 2023 Mar;107(3):224-225A. ‡Crossnohere, et al. Cancer Control. 2024

How might MCD be used in primary care?

Potential Uses of Novel Tests	Definition	Example in Cancer Screening
As sole screening test	No preexisting test	Detecting preclinical pancreatic or ovarian cancer
Replacement	Replaces an existing test	Fecal immunochemical test (FIT) replacing guaiac-based fecal occult blood test
Parallel use or cotesting	Used together with an existing test; both results are used for patient management	High-risk human papillomavirus (HPV) (new test) done at the same time as cytology for cervical cancer screening
Triage and risk stratification	A novel test used before the existing test or testing pathway	FIT followed by colonoscopy
Reflex or add-on test	Individuals with either positive or negative existing test results will receive the add-on test	Cytology followed by high-risk HPV test for cytology with ASCUS

The Web and AI Can and Promote Misinformation and Commercial Interests over Scientific Evidence

Multicancer early detection (MCED) tests are designed to detect multiple types of cancer from a single blood sample [1]. In primary care, these tests could be used as a **screening tool** to identify cancers at an early stage, even before symptoms appear [2]. This could potentially improve early diagnosis and treatment outcomes [2].

However, it's important to note that the use of MCED tests in primary care is still under research [3]. Current guidelines suggest that these tests should be used in the context of well-designed clinical research studies and not as a replacement for established screening methods [3].

Would you like to know more about how these tests work or their current status in clinical research?

[1] www.cancer.org [2] www.mdanderson.org [3] www.aafp.org

AI Overview

Multi-cancer early detection (MCED) tests can be used in primary care to help identify cancer at an early stage, which can lead to better outcomes for patients:

Detect multiple cancers

MCED tests can detect many types of cancer from a single blood sample. This can help identify cancers that are not currently screened for, such as those of the pancreas, ovary, liver, uterus, small intestine, oropharyngeal, bone, thyroid, and hematologic malignancies.

Improve screening efficiency

MCED tests can improve screening efficiency by detecting multiple cancers at once, instead of using individual, organ-specific tests.

Reduce the need for costly treatments

Early detection can reduce the need for costly advance-stage treatments.

Improve patient outcomes

Cancers that are found early are often easier to treat and tend to have better outcomes.

Doubeni CA, Lau YK, Lin JS, Pennello GA, Carlson RW. Development and evaluation of safety and effectiveness of novel cancer screening tests... Cancer. 2022

Current State of Cancer Screening in Primary Care

- Screening is critical for cancer control and an essential of primary care.*
- Improved screening and timely follow-up can accelerate progress on cutting the cancer death rate by 50%.
- Abnormal screening results may require invasive procedures
- There are no effective screening tests for all but 4 cancers
  - Highly lethal cancers (e.g., ovarian) lack effective screening
  - Value of screening in indolent or very rare cancers is uncertain
- The accuracy of current screening tests is suboptimal:
  - Missed detection, interval cancers or harms from false-positive results
- Multiple encounters and separate procedures for screening.

Cancer Deaths in 2022, (SEER)	
Total cancer	608,366
Lung cancer	131,888
Colorectal cancer	52,967
Breast cancer	42,211
Cervical cancer	593

*Doubeni CA, Castle PE. Multicancer Early Detection: A Promise Yet to Be Proven. AFP. 2023 Mar;107(3):224-225A. PMID: 36920808.

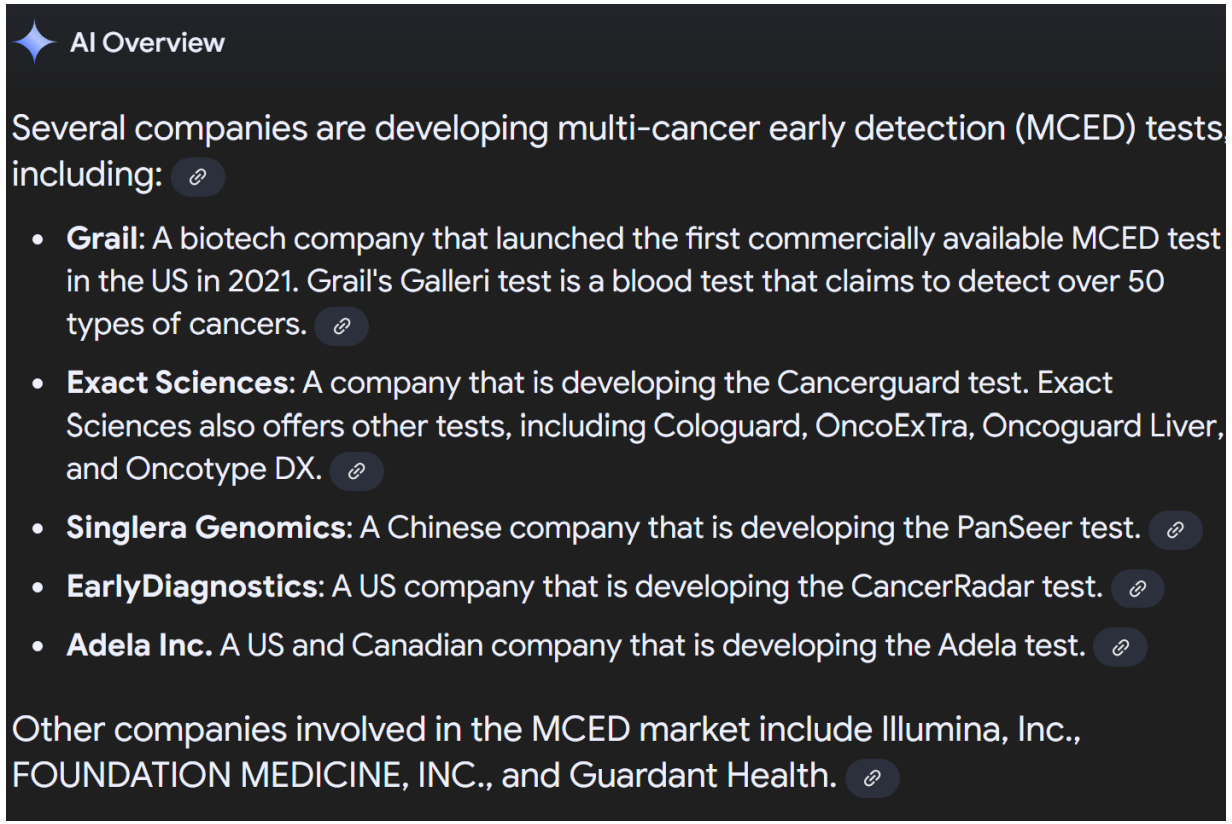
Current State of Multicancer Detection Tests

- **Sensitivity** and **specificity** and harms in asymptomatic people who would be screened in primary care are **not unknown**
- MCD are primarily tests for **detecting more advanced disease**
  - Poor sensitivity for precursor lesions
  - Low sensitivity for early, more treatable cancers.
- **Diagnostic pathway is unclear**, even when TOO/CSO are suggested
- The implications of a negative result or a positive result with negative **follow-up testing are unclear**.
- Follow-up screening interval is unknown but may need to annually
  - MCDs have low sensitivity for precursors and early cancers.

*Doubeni CA, Castle PE. Multicancer Early Detection: A Promise Yet to Be Proven. AFP. 2023 Mar;107(3):224-225A. PMID: 36920808.

How Do Patients and Clinicians Learn about MCED?

Who is developing MCD tests?



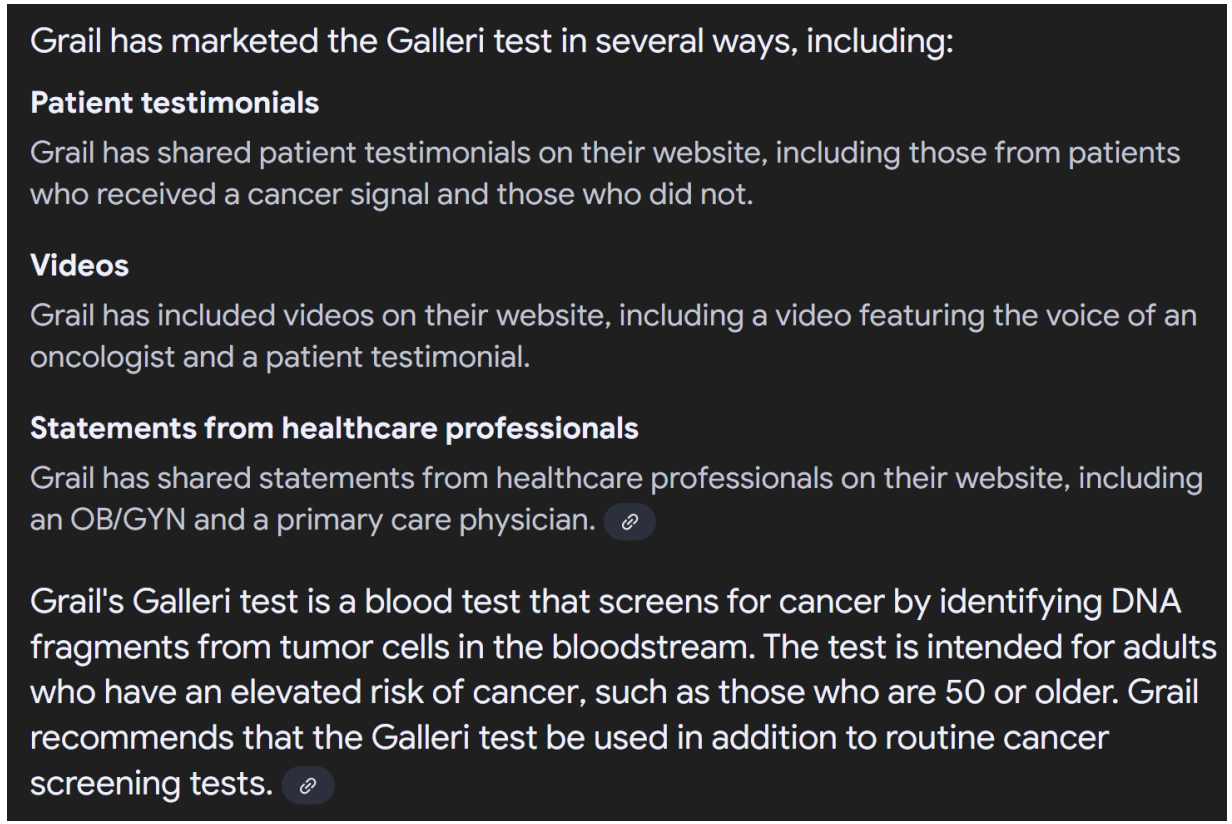
AI Overview

Several companies are developing multi-cancer early detection (MCED) tests, including:

- **Grail**: A biotech company that launched the first commercially available MCED test in the US in 2021. Grail's Galleri test is a blood test that claims to detect over 50 types of cancers.
- **Exact Sciences**: A company that is developing the Cancerguard test. Exact Sciences also offers other tests, including Cologuard, OncoExTra, Oncoguard Liver, and Oncotype DX.
- **Singlera Genomics**: A Chinese company that is developing the PanSeer test.
- **EarlyDiagnostics**: A US company that is developing the CancerRadar test.
- **Adela Inc.** A US and Canadian company that is developing the Adela test.

Other companies involved in the MCED market include Illumina, Inc., FOUNDATION MEDICINE, INC., and Guardant Health.

How has Grail marketed Galleri?



Grail has marketed the Galleri test in several ways, including:

Patient testimonials

Grail has shared patient testimonials on their website, including those from patients who received a cancer signal and those who did not.

Videos

Grail has included videos on their website, including a video featuring the voice of an oncologist and a patient testimonial.

Statements from healthcare professionals

Grail has shared statements from healthcare professionals on their website, including an OB/GYN and a primary care physician.

Grail's Galleri test is a blood test that screens for cancer by identifying DNA fragments from tumor cells in the bloodstream. The test is intended for adults who have an elevated risk of cancer, such as those who are 50 or older. Grail recommends that the Galleri test be used in addition to routine cancer screening tests.

Public Perspectives on Multi-Cancer Early Detection

(Crossnohere…[Doubeni]…. Cancer Control. 2024)

- Purposive sample of American Population Panel (n=27, age 48–70 years old)
- Watched 3-minute video followed → Semi-structured interview (11/2023 – 02/2024)

Perceptions About MCEDs

- Positive – 85%
- Easy concept to understand – 88%
- Convenient – 30%
- Screens for multiple cancers – 70%
- Detect cancer early – 33%

Concerns:

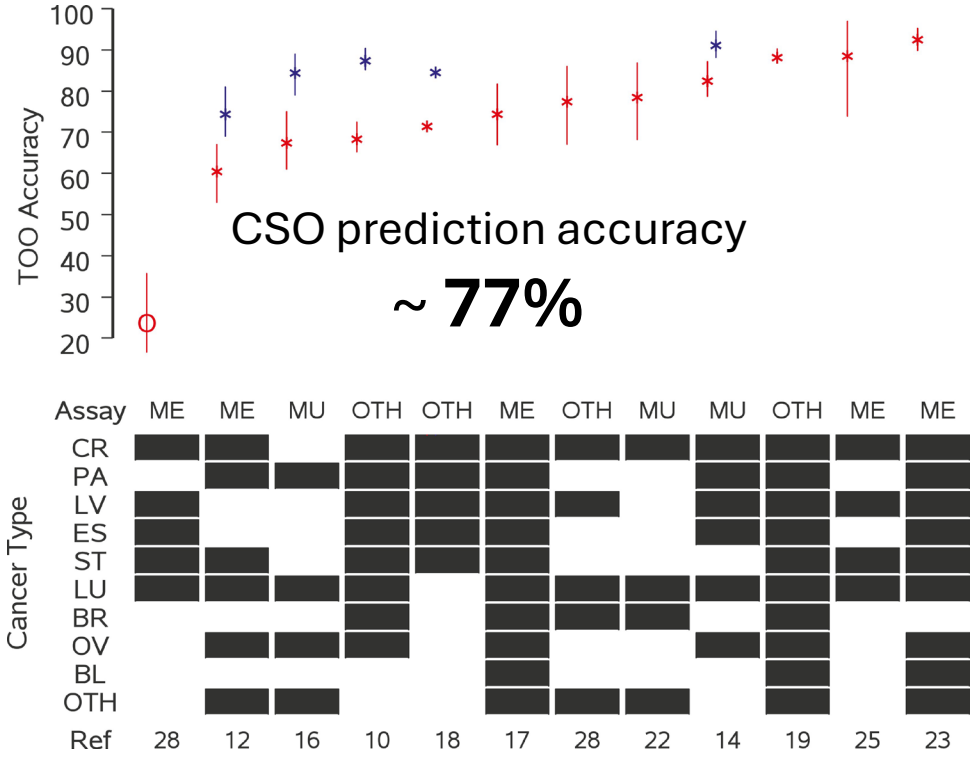
- Inaccuracy - 96%
- Cost – 92%
- Test-related anxiety – 56%
- Lack of evidence on effectiveness – 22%

Gaps: Need to improve public and clinician knowledge of MCD to support informed decision-making; research to guide inclusion of patient values and preferences in screening uncertainty

Considerations for follow-up after cfDNA test

A negative workup for a positive cfDNA test may need to expanded beyond the predicted target tissue or cancer signal of origin (TOO/CSO) adding to cost and strained healthcare (e.g., radiology) resources

***Clin Chem*, 70(1); 90–101 (Sys Review of cfDNA assays)**



JCO 40, 2022;Suppl.10553 (abstract)

302 controls vs. 598 cases (8 cancer types*)

- 114 true positives (predicted CSO)
- Top 1 most probable – 75.4%
  - **71.1% in stage I-III**
  - **84.0% in stage IV**
- Top 2 most probable – 84.2%.
  - **82.2% in stage I-III**
  - **90.0% in stage IV.**

***Lancet* 2023; 402: 1251–60**

	Top 1	**Top 2**
PATHFINDER (average risk)	82% (52.3-94.9)	91% (62.3-99.5)

*colorectal, lung, liver, pancreatic, gastric, esophagus, breast and ovarian

Considerations on using MCDs in Primary Care

Considerations for Screening in Primary Care	Conventional	MCD	Consideration on MCD and Care
Safety and Effectiveness	Evidence-based (USPSTF)	Undetermined	Use USPSTF-recommended preventive services; Support MCD studies
Detect cancer early	Yes	Limited	May influence potential benefit
Detect precursor	Yes (CRC. Cervical)	No (~13% sensitivity in CRC)	Unlikely to prevent cancer
Regulatory approval	FDA approval	Not FDA approved	FDA approval is a minimum criterion for using a screening test
Health Insurance Coverage	CMS Legislated mandate	Not covered; High cost Added downstream cost	Avoid legislation that undermine the scientific process
Delivery/Convenience	Varies; non-visit, self-collection options	Requires a visit (no self-collection)	Does not address key drivers of disparities
Care pathway well-defined	Yes	No; CSO accuracy ~77% Testing interval is unclear	MCD use may lead to diagnostic gray areas/odyssey/pan-imaging
Quality Metric and Incentives	HEDIS, CMS/Payer	No	MCD use does not contribute to quality

Concluding Comments

- Improved cancer prevention and screening technologies are needed to accelerate decreases in the US cancer death rate
- USPSTF evidence-based recommended tests remain the standard of care
- We should not supplant scientific evidence with anecdotes or patient stories
- MCD may be an option when their role and effectiveness is determined
  - Use MCED in the context of clinical studies paired with SOC tests.
  - Current decisions to use should be based on informed decision-making
- Educate the public, patients, clinicians, and health systems
  - Negative MCED may mean the absence of advanced cancer but provide no reassurance about early stage cancers or precancers.
  - Diagnostic evaluation of a positive screen:
    - Comprehensive history and physical examination plus guided laboratory testing
    - Performed predicted CSO-guided work-up
    - If CSO work-up is negative or not provided, CT and PET scanning may be needed