Session 3: Overview of MCDs in Development and Clinical Practice

National Cancer Policy Forum Workshop at NASEM

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Review

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

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

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.

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REVIEW ARTICLE

Cancer screening with multicancer detection tests: A translational science review

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Rubinstein, Patriotis et al. CA A Cancer J Clinicians, March 2024 DOI: (10.3322/caac.21833)

Clinically available multicancer detection tests in the U.S.

No mandatory, comprehensive resource for laboratory-developed tests (LDTs)*

- LDTs we are aware of:
  - Galleri | Grail
  - OneTest | 20/20 GeneSystems
  - EPISEEK (was Sentinel-10) | Precision Epigenomics
- Currently, no FDA-authorized MCD tests

Volume of MCD testing

- Galleri | Grail 185,000 commercial tests as of March 2024 (U.S.)
- Others unknown

*The FDA's final rule on LDTs, published April 29, 2024, requires that LDTs be registered and listed as medical devices. The FDA expects laboratories to comply by May 6, 2026.

Role of Federal Regulations

Under federal regulations, MCD tests may be used in clinical care as laboratory-developed tests (LDTs) without FDA review.

- LDTs are in vitro diagnostic products intended for clinical use that are designed, manufactured, and used within a single clinical laboratory.
  - They cannot be distributed for use in other laboratories.

- Laboratories offering LDTs are required to show that they measure what they say they can measure.
- MCD tests that are now available as LDTs are not required to show clinical validity (accurately predict the presence of cancer at early or advanced stages) or to show that the tests can be safely used without prompting unnecessary or harmful diagnostic evaluations.

Regulatory Standards Applied by FDA and CLIA

	FDA-reviewed in vitro diagnostics	Laboratory-developed tests overseen by CLIA
Demonstration of analytical performance (accurate and reproducible detection of the analytes of interest) for new tests	Yes	Yes
Demonstration of clinical validity (accuracy of identifying, measuring, or predicting a clinical condition, such as the presence of cancer at early or advanced stages)	Yes	No
External review of moderate-risk and high-risk tests before use on patients	Yes	No
Public reporting of adverse events (e.g., false results leading to unnecessary diagnostic workups)	Yes	No
Review and approval of product labeling to ensure comprehensiveness and accuracy	Yes	No
Review and approval of marketing claims based on supporting evidence	Yes	No
Registration of tests in a public database	Yes	No
Oversight that can recall faulty tests	Yes	No
Evaluation of a test's clinical utility, such as an effect of a test on reducing mortality	No	No

Table 1: Rubinstein, Patriotis et al. CA A Cancer J Clinicians, March 2024 DOI: (10.3322/caac.21833)

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.

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Analytes and technologies used to develop MCDs

Analyte	Subanalyte	Measurement technology	Extracted cancer-related features
Cell-free DNA, circulating tumor DNA	DNA sequence	Whole-genome sequencing	Somatic copy number alterations of the DNA sequence, fragment end points, fragment length, allelic imbalance (Jamshidi 2022,[22,a] Wan 2019[23,b])
		Whole-genome sequencing followed by targeted next-generation sequencing (Keller 2021[24,c])	Short and long fragment coverage characteristics, chromosomal arm copy number changes, mitochondrial copy numbers (Cristiano 2019[25,a]), small somatic variants (Jamshidi 2022[22,a])
		Targeted quantitative real-time polymerase chain reaction	Single nucleotide variants/small insertions and deletions (Cohen 2018,[26,a] Stackpole 2022[27,a])
	Methylation of the analyte	Whole-genome bisulfite sequencing	Cancer-specific hypomethylation and hypermethylation and tissue-specific hypomethylation and hypermethylation (Stackpole 2022[28,a]), whole-genome methylation pattern (Jamshidi 2022[22,a])
		Reduced representation bisulfite sequencing followed by next-generation sequencing	Sequenced methylation profile and copy number profile (Van Paemel 2021[29,a])
		Sodium bisulfite treatment followed by quantitative real-time polymerase chain reaction	DNA methylation signal (Vrba 2022[30,a])
		Targeted sodium bisulfite treatment enrichment followed by next-generation sequencing	Methylation block score (Liang 2021[31,a])
			Hypomethylation and/or hypermethylation states for cancer and/or tissue-specific methylation patterns (Liu 2020[32,a])
			Methylation fraction (Liang 2021,[31,a] Oxnard 2019,[33,a] Chen 2020[34,a])
		Immunoprecipitation enrichment followed by quantitative real-time polymerase chain reaction or next-generation sequencing	Methylated fragment sequence (Song 2017,[35,a] Shen 2018[36,a])
	DNA copy number aberrations	Next-generation sequencing	Copy number variants (Chan 2013,[37,a] Keller 2021[24,c])

Table 2: Rubinstein, Patriotis et al. CA A Cancer J Clinicians, March 2024 DOI: (10.3322/caac.21833)

Analytes and technologies used to develop MCDs

Analyte	Subanalyte	Measurement technology	Extracted cancer-related features
Cell-free RNA	miRNA	Quantitative real-time polymerase chain reaction with a gene panel	Gene expression (Vykoukal 2022[38,b])
Protein	Plasma proteins	Immunoassays with a protein panel	Quantity of protein (Cohen 2018,[26,a] Lennon 2020,[27,a] Fahrmann 2019[39,a])
	Serum proteins	Immunoassays with a protein panel	Quantity of protein (Wen 2015,[40,a] Wang 2018[41,a])
Metabolites		Ultra performance liquid chromatography, quadrupole time-of-flight mass spectrometry	Feature annotation based on custom libraries of standards (Fahrmann 2019[39,a])
Glycans	Glycosaminoglycans	Capillary electrophoresis with laser-induced fluorescence (Gatto 2018[42,b]) ultra high-performance liquid chromatography—tandem mass spectrometry (Bratulic 2022[43,a])	GAGome features
Extracellular vesicles (EVs)	Total EV RNA	Quantitative real-time polymerase chain reaction	Gene expression (Alen 2023[44,a])
	miRNA	Quantitative real-time polymerase chain reaction	Gene expression (Tengda 2018[45,b])
	Proteins	Aptamer-based proteomics	Protein expression level (Fahrmann 2020[46,a])
		Immunoassay for targeted protein	Quantity of protein (Hinestrosa 2022[47,a]), quantification of protein (Hinestrosa 2022[47,a])
	Proteins of serum EVs	Flow cytometry on isolated exosomes for presence of targeted protein	Count of EVs with target protein (Melo 2015[48,b])
	mRNA	Targeted nanoString nCounter (nanoString Technologies, Inc.)	Gene expression (Fortunato 2022[49,b])

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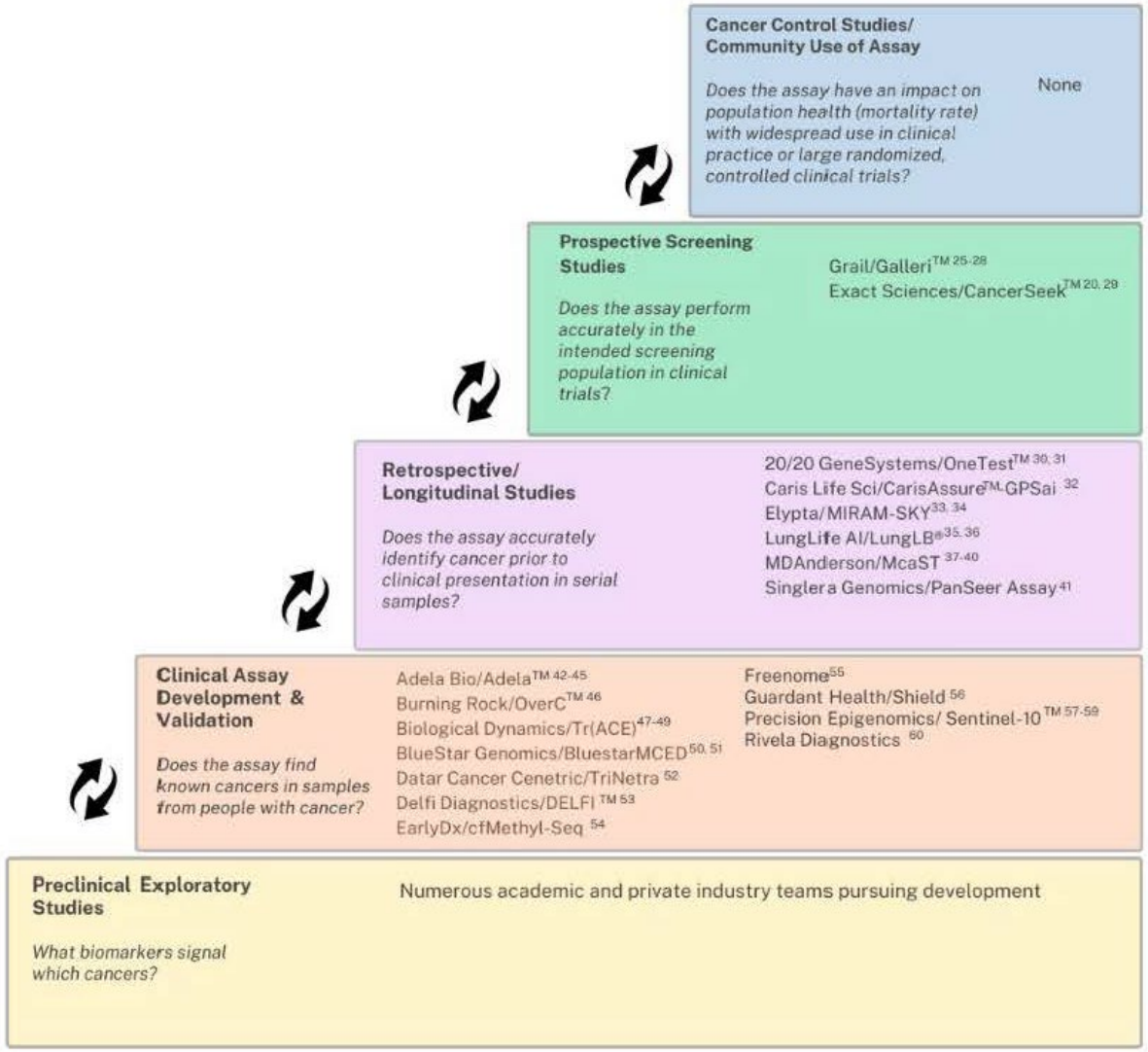
Analytes and technologies used to develop MCDs

Analyte	Subanalyte	Measurement technology	Extracted cancer-related features
Tumor-educated platelets	mRNA	Next-generation sequencing	Differential level of expression (Best 2018[50,a])
Cancer stem cells	mRNA	Quantitative real-time polymerase chain reaction	Gene expression (Tripathi 2021[51,a])
Circulating tumor cells	Chromosomal aberrations	Locus-targeted fluorescence in situ hybridization assay	Circulating tumor cells and total number of abnormality quantities (Katz 2020[52,b])

Table 2: Rubinstein, Patriotis et al. CA A Cancer J Clinicians, March 2024 DOI: (10.3322/caac.21833)

Stage of Biomarker Development of MCD Tests Using Early Detection Research Network 5-phase Framework



Phase 4: Test Sensitivity drops further due to imperfect downstream diagnostic procedure; Specificity of test may drop.

Phase 3: Test Sensitivity drops due to presence of earlier stage disease in presymptomatic, pre-clinical specimens

Phase 2: Test clinical diagnostic performance is most optimistic

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Diagnostic Performance of MCD Tests

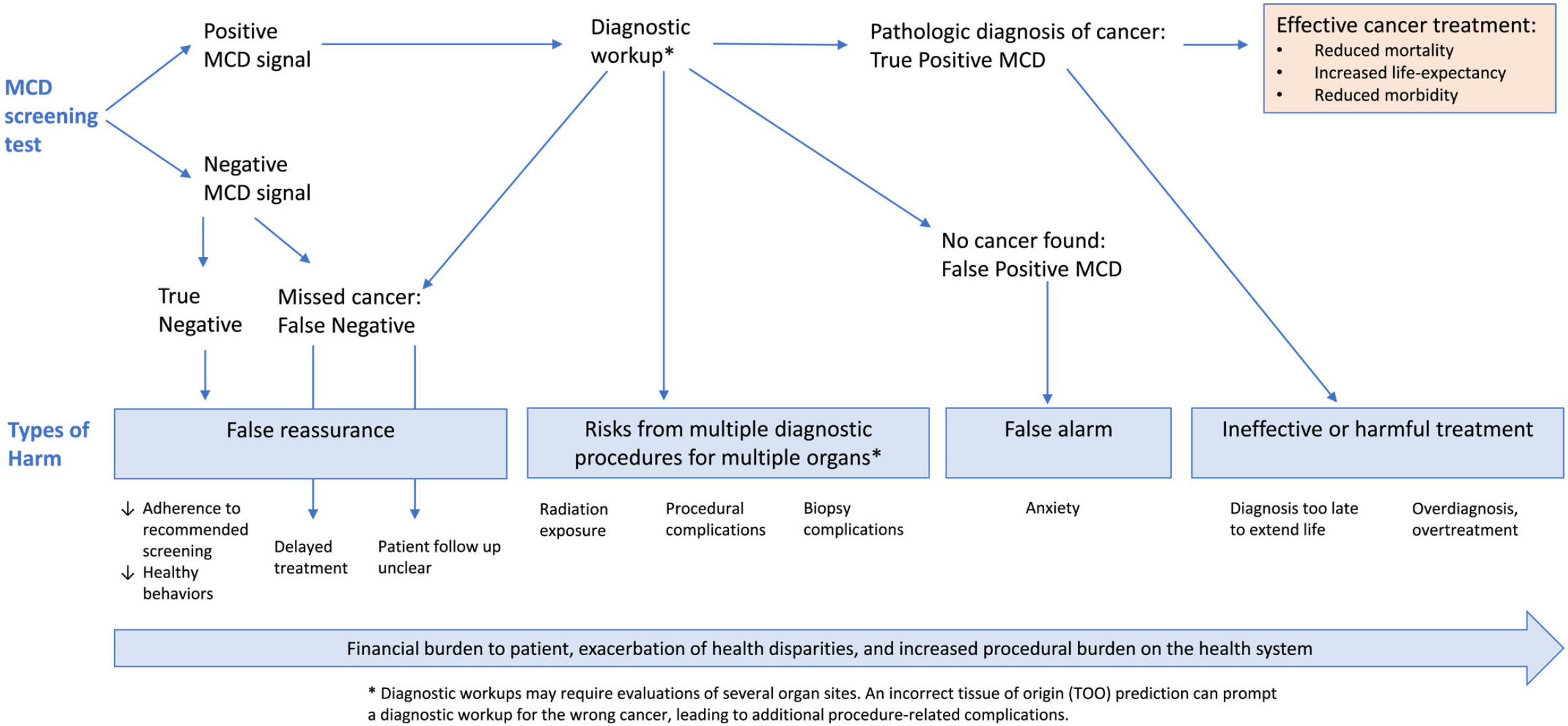
- **Sensitivity and Specificity**
- Average overall Sensitivity of MCD tests: 27% - 95%, at Specificities of 95% - 99%
  - Early-stage cancer (e.g., Stage I) Sensitivity: 27% - 62%
  - Late-stage cancer (e.g., Stage III) Sensitivity: 60% - 87%

- **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%

Unique Challenges of MCDs

- Defining a meaningful endpoint(s) for clinical trials of MCDs.
  - Cancer mortality has been the benchmark for a meaningful endpoint
  - Stage shift has not been proven as a surrogate endpoint for cancer mortality
- Potential Harms:
  - False reassurance
  - Risks from multiple procedures
  - False alarms
  - Ineffective or harmful treatment

Possible Outcomes from an MCD Screening Test



* Diagnostic workups may require evaluations of several organ sites. An incorrect tissue of origin (TOO) prediction can prompt a diagnostic workup for the wrong cancer, leading to additional procedure-related complications.

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Patient perceptions

- Patient testimonials
- Anxiety scales in research studies
- Emerging literature on perceptions of patients and clinicians
  - Samimi et al. Primary care physicians and laypersons' perceptions of multicancer detection clinical trial designs.
    JNCI Cancer Spectr. 2024 Sep 2;8(5):pkae084. doi: 10.1093/jncics/pkae084.
  - Roybal et al. Perceptions of multi-cancer early detection tests among communities facing barriers to health care.
    Health Affairs Scholar, 2(9), 2024, qxae102, https://doi.org/10.1093/haschl/qxae102
  - Stay tuned for publications from CSRN investigators

Patient perceptions

Subtheme	Quote
Simple and less invasive is good	“You’re not cutting someone open and opening up the body and spreading things, so if this is something that's out there, that going to be useful for us.”
One-stop shop to detect multiple cancers is convenient	“I like the idea of sort of one and done. One test sounds like it's pretty easy. You get results and then proceed from there.”
A chance to treat it and beat it	“Early is important to me because the theory is the earlier you catch it, the better the results.”
Comprehensive information about MCEDs	“And I would want to know how long this has been tested. How long has it been out there? What have been the results?”

Roybal et al. Perceptions of multi-cancer early detection tests among communities facing barriers to health care. Health Affairs Scholar, 2(9) 2024, qxae102, https://doi.org/10.1093/haschl/qxae102

Patient perceptions

Subtheme	Quote
Fear of screening outcomes	“You do have the psychological aspect. ‘Oh my God, I can't sleep at night. Do I have cancer? Am I gonna die tomorrow?’”
Lack of information on procedural aspects of screenings	“A lot of it is just not knowing what the procedure actually is and what's going to happen to you. If you're well informed, it does help.”
Untrustworthy biomedical research and technology	“Right now, honestly, people don't trust science and so, to tell someone we have a test out here that's gonna cure and you're gonna know everything…it's not believable. It's almost like, almost far-fetched.”
Lack of provider communication about and advocacy for screening	“My doctor didn't even tell me that there's screenings.”

Roybal et al. Perceptions of multi-cancer early detection tests among communities facing barriers to health care. Health Affairs Scholar, Volume 2, Issue 9, September 2024, qxae102, https://doi.org/10.1093/haschl/qxae102

NCPF Workshop Topics

- Examples of current and emerging MCD tests.
- Challenges and opportunities to validate MCD tests and determine their clinical utility for detecting cancer and reducing cancer-specific mortality.
- Strategies for cancer care downstream of MCD testing, such as follow-up diagnostic testing and treatment decision-making.
- Limitations of MCD tests, including the burden on patients and health care systems from false-positive test results, overdiagnosis, and overtreatment.
- Research and policy gaps for assessing MCD tests and their impact on cancer care and outcomes and health equity.

Thank You