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National Cancer Policy Forum: Opportunities and Challenges for the Development and Adoption of MCD Tests

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Multi-Cancer Early Detection

Early detection and screening have helped contribute to a steady reduction in cancer mortality[1]

Yet…

Only **14%**

of cancers are detected through screening[2*]

*Limitations: Based on modeling data derived from numerous sources including self-reported surveys. Includes assumptions on detectability of certain cancer types. Does not include all cancer types or screening methods.

References: 1. Siegel RL, et al. Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12-49. 2. NORC at the University of Chicago. New Research Highlights Just One In Seven Diagnosed Cancers Found By A Recommended Screening Test. Accessed July 12, 2024. https://www.norc.org/content/dam/norc-org/pdfs/State-Specific%20PCDSs%20chart%201213.pdf?_sm_nck=

Multi-cancer early detection (MCED) testing has the potential to transform early cancer detection

We are developing a multi-cancer early detection test designed to be used alongside standard-of-care screening, with the following development goals:

Designing a test powered by the **additive sensitivity of multiple biomarker classes**

Detecting **multiple cancers** including those with the **biggest impac**t to public health

Delivering a high sensitivity test to detect more early-stage cancers when there is a greater chance for **curative intervention**

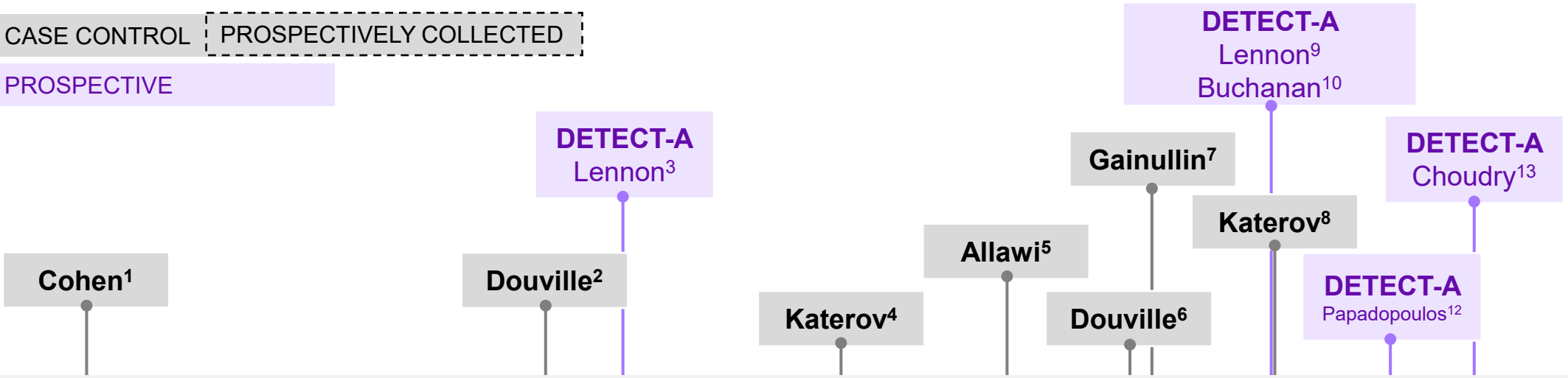
Providing high specificity to help **minimize false positive results**

Utilizing a **streamlined and standardized imaging-based diagnostic resolution pathway** that results in fewer procedures

Exact Sciences evolution of a rigorous and ongoing multi-biomarker class test development program

CASE CONTROL | PROSPECTIVELY COLLECTED

PROSPECTIVE



FEASIBILITY STUDIES

2018	2019	2020	2021	2022	2023	2024	2025

DEVELOPMENT STUDIES

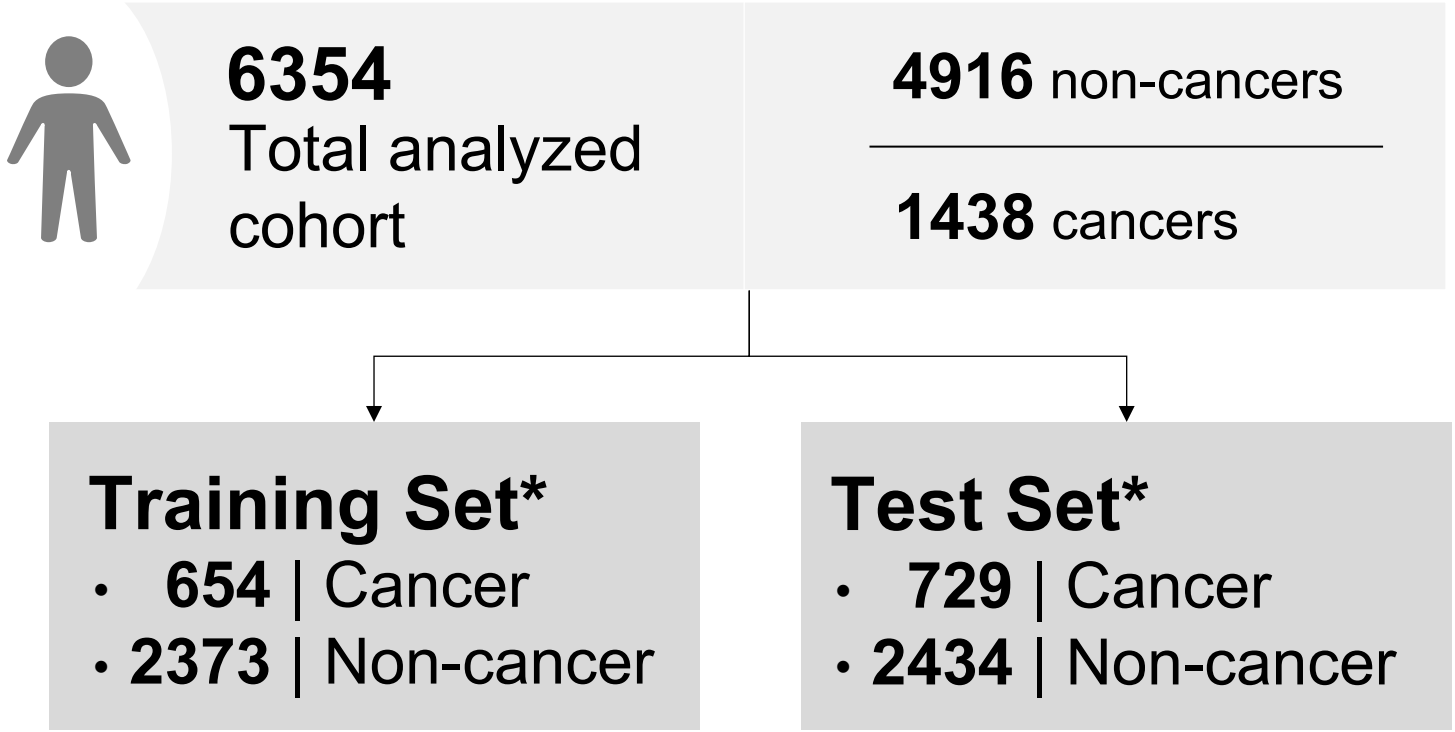
Douville[11]

Gainullin[14]

Reference: 1. Cohen et al. *Science* 23 Feb 2018: Vol. 359, Issue 6378, pp. 926-930. 2. Douville et al. *Proc Natl Acad Sci U S A*. 2020 Mar 3;117(9):4858-4863. Epub 2020 Feb 19. 3. Lennon AM, et al. *Science*. 2020;369(6499). 4. Katerov et al. *Cancer Res* July 1, 2021 (81) (13 Supplement) 111. 5. Allawi, et al. AACR 2022 presentation. https://aacrjournals.org/cancerres/article/82/12_Supplement/631/699551. Accessed July 12, 2024. 6. Douville C, et al. Presented at ESMO Congress in Paris, France on September 10, 2022. 7. Gainullin V, et al. Presented at AACR Special Conference: Precision, Prevention, Early Detection, and Interception of Cancer in Austin, TX on November 18, 2022. 8. Katerov, et al. Presented at the ASCO Annual Meeting in Chicago, IL on June 3, 2023. 9. Lennon, et al. *Cancer Prev Res*. 2024. doi: 10.1158/1940-6207.CAPR-23-045. 10. Buchanan, et al. *Cancer Prev Res*. 2024. doi: 10.1158/1940-6207.CAPR-24-0107. 11. Douville, et al. Presented at the ESMO Congress in Madrid, Spain on October 21, 2023. 12 Papadopoulos, et al. Presented at the ESMO Congress in Madrid, Spain on October 21, 2023. 13. Choudry, et al. Presented at the AACR Conference in San Diego, CA on April 8, 2024. 14. Gainullin, et al. Presented at the AACR Conference in San Diego, CA on April 8, 2024.

First analysis from the ASCEND 2 study assessed a Methylation + Protein test design

Sample allocation to Training and Test sets (after exclusions)



*Totals after exclusions.

Reference: Gainullin V, et al. Presented at the AACR Conference, San Diego, CA on April 8, 2024.

Results demonstrate the potential value of a multi-biomarker class test design for MCED testing

Sensitivities @ 98.5% Specificity (CI 97.9-98.9%)

ALL Cancers n=729	**Excluding** Breast & Prostate* (n=590)	**Cancers without Recommended Screening**** n=489	**6 Most Lethal Cancers†** n=292
50.9%	**56.8%**	**54.8%**	**63.7%**
95% CI: 47.3-54.5%	**95% CI:** 52.8-60.7%	**95% CI:** 50.4-59.2%	**95% CI:** 58-69%

* Excluding 88 breast and 51 prostate cancers.

**Excluded Breast (n=88), Cervical (n=13), Colorectal (n=88), Prostate (n=51) (USPSTF Grade C recommendation). Lung remains in the calculation even though there is SOC screening for those at high-risk.

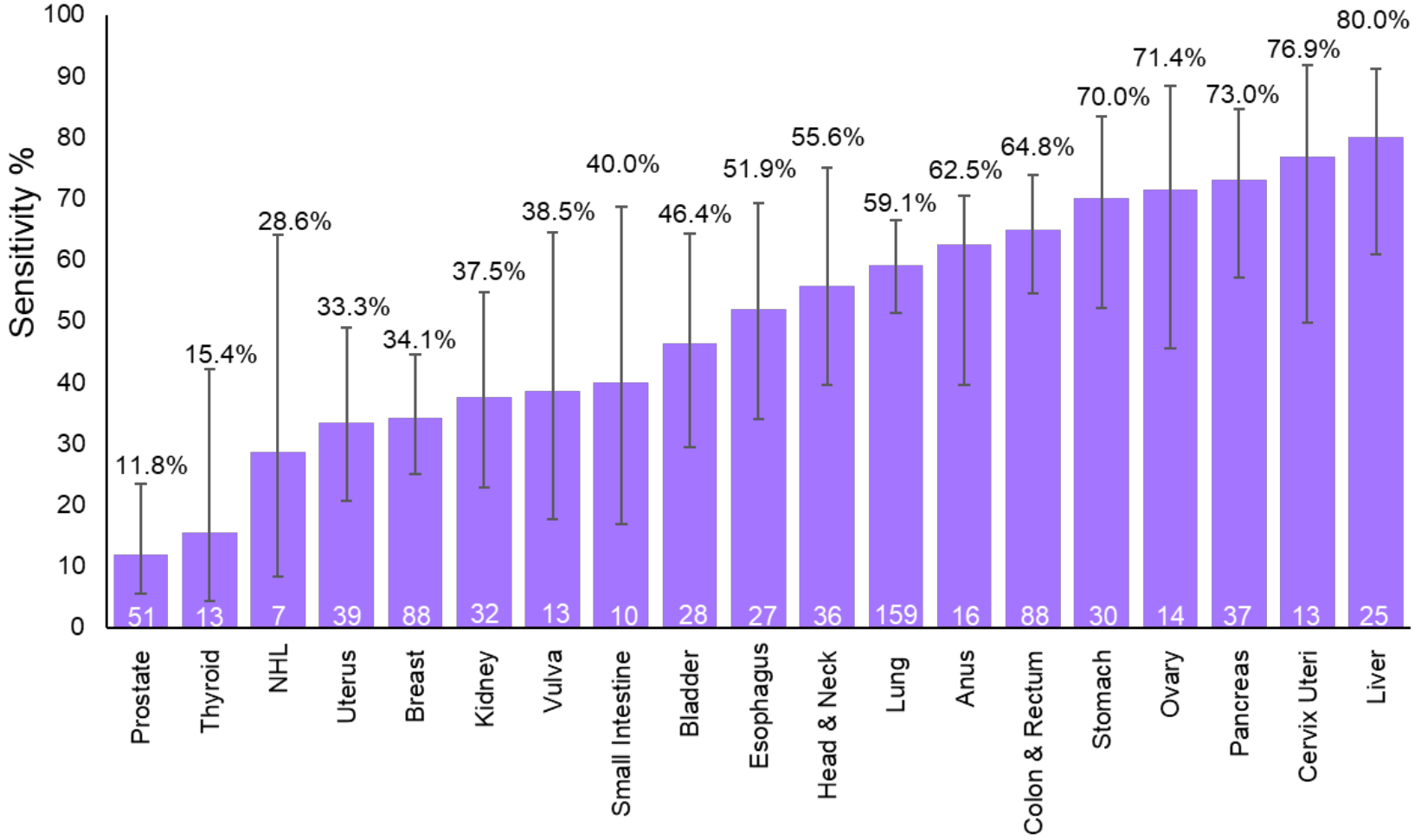
†Refers to those cancers with the shortest 5-year survival rates: Esophagus, Liver & Bile Duct, Lung & Bronchus, Ovarian, Pancreatic, Stomach.

Reference: Douville C, et al. Presented at the ESMO Conference, Barcelona Spain, September 16, 2024.

Results: Performance by organ type

Observed specificity:
98.5%

Excludes cancers with an n ≤2



NHL, Non-Hodgkin Lymphoma.

Reference: Douville C, et al. Presented at the ESMO Conference, Barcelona Spain, September 13-17, 2024.

Where we are headed next…

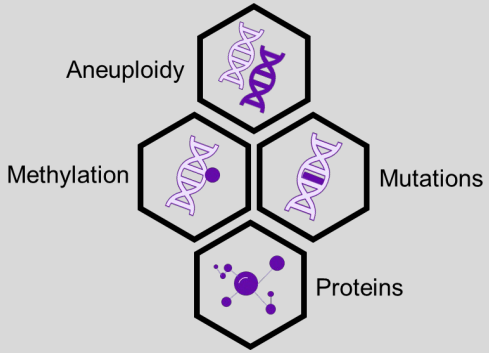
The Falcon Registry Study

New study underway to evaluate the clinical care for patients undergoing MCED testing[1]

- Two health systems
- Up to 25,000 patients enrolled
- Will continue for up to 7 years
- Utilizing a test that has been granted an Investigational Device Designation (IDE) from FDA

Ongoing analysis of ASCEND 2 data

Defining the final design for the Cancerguard™ test



Clinical Validity

Initiate pivotal study

1. Reference: ClinicalTrials.gov ID: NCT06589310

Cancer-specific mortality considered the "gold standard" to evaluate cancer screening effectiveness

Advantages:

- Absence of bias
- Definitive measure of health benefit

Disadvantages

- Time
  - Urgency of the problem
  - Rapid evolution of technologies
  - Contamination
  - Changes in practice
  - Evolving health priorities
- Cost
- Study size
- Barriers to entry

Reference: 1. Kumar SH. Alternative endpoints to mortality in cancer screening trials. *Mol Oncol*. 2024 Aug;18(8):1817-1820.

The PLCO Trial

Enrollment	Final Data	Costs*	Technologies became§
8 yrs	19+ yrs	$454 M	Obsolete

Mortality benefit varied by cancers

Prostate:	Lung:	Colorectal:	Ovarian:
No evidence of a mortality benefit for organized annual screening compared with opportunistic screening	Annual screening with **chest radiographs** over a 4-year period **did not significantly decrease** lung cancer mortality compared with usual care	Screening with **flexible sigmoidoscopy** was associated with a **significant decrease in colorectal-cancer incidence**† and **mortality**†	Simultaneous screening with **CA-125 and transvaginal ultrasound** compared with usual care **did not reduce ovarian cancer mortality**

PLCO Trial - The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

*Costs were in 2011 dollars, which equated to $562 million in 2022

§Chest x-ray (lung), Sigmoidoscopy (CRC)

†Incidence decreased in both the distal and proximal colon and mortality decreased in the distal colon only

Reference: 1. National Cancer Institute. Cancer Data Access System: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. https://cdas.cancer.gov/learn/plco/trial-summary/. Accessed on August 30, 2024

Alternative approaches for evaluation of MCD tests

Test positive population is the only population that obtains a clinical benefit from curative treatment—including deaths among those who test negative dilutes any effect on cancer-related mortality endpoint[1]

Nested mortality analysis: Less enrollment per arm | Avoids dilution effect[2]

Intermediate Endpoints

- Reduction in stage III/IV
- Recurrence-updated stage shift
- Mortality reduction based on stage shift

Reduction in absolute burden of metastatic disease

- Cancer- and treatment-related symptoms
- Functional decline
- Economic and social burdens

Quality of Life

- Nested analysis for Quality of Life?

Reduction in consequence of advanced cancer

- Pain, fatigue neuropathy
- Functional loss
- Economic and social burdens

Reference: 1. Klein EA, et al. *Cancer Epidemiol Biomarkers Prev*. 2023 Aug 1;32(8):1003-1010. 2. Hackshaw A, et al. *The Lancet: Oncology*. 2021; 22(10): 1360-1362.

Association Between Reduction of Late-stage Cancers and Reduction of Cancer-specific Mortality

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Dai J et al.: J Med Screen. 2024 May 26 (epub ahead of print)

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Thank You