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PATHFINDER: A Prospective Study of a Multi-Cancer Early Detection Blood Test

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On behalf of PATHFINDER study investigators

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DECLARATION OF INTERESTS

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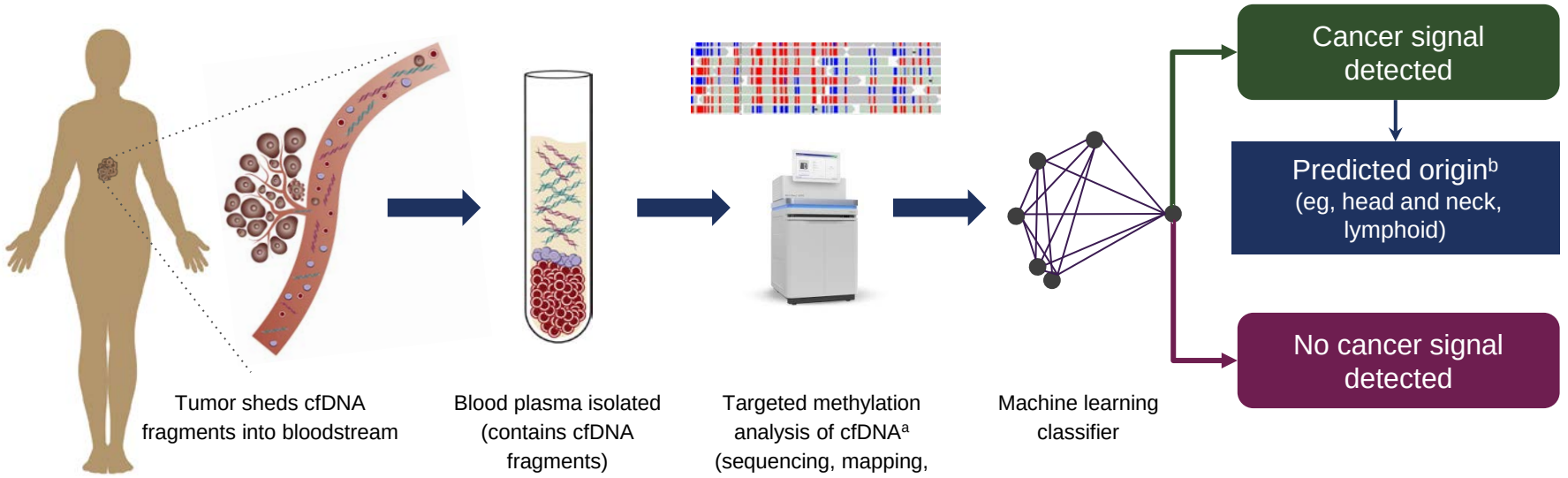
*GRAIL, LLC, is currently held separate from Illumina Inc. under the terms of the Interim Measures Order of the European Commission dated 29 October 2021

Background: Multi-Cancer Early Detection (MCED) Blood Assays

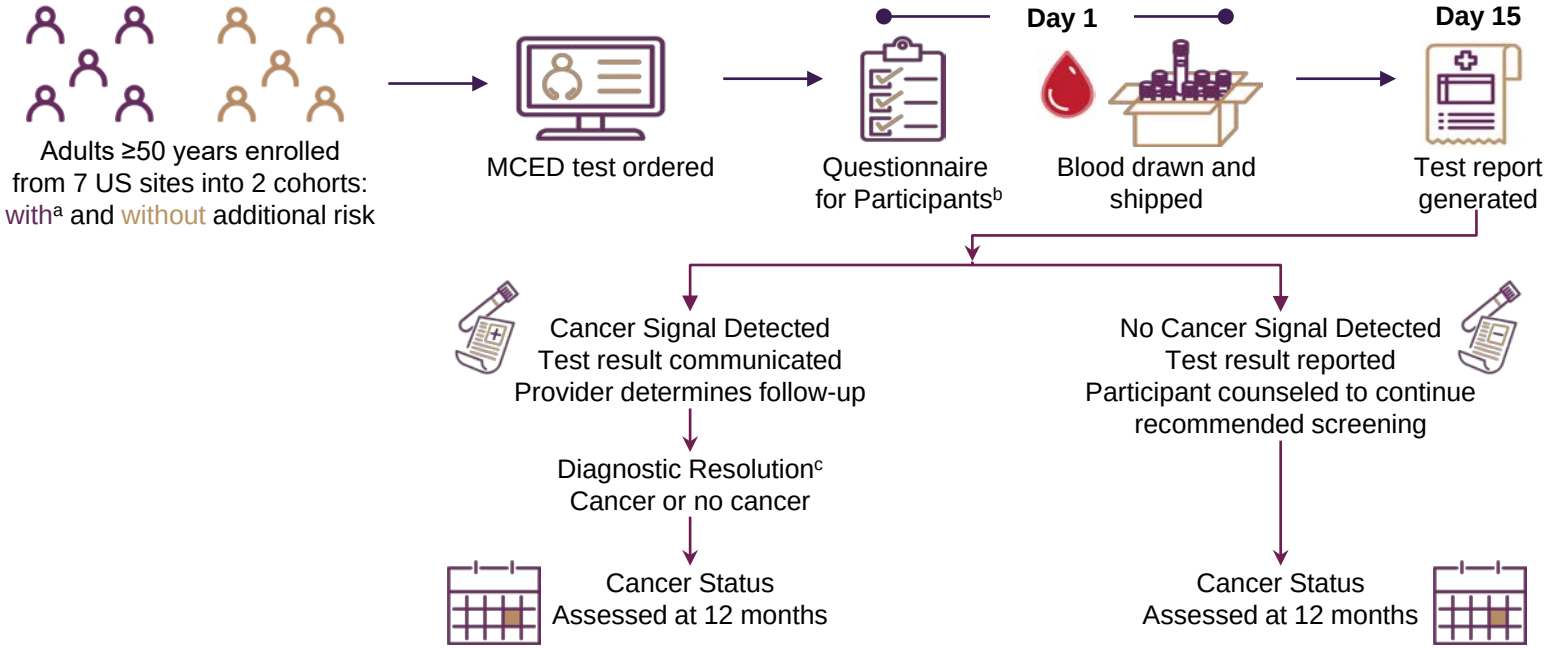
MCED testing uses a targeted methylation, next-generation sequencing (NGS)-based assay to:

- Detect and analyze cfDNA in the bloodstream
- Deploy machine learning to detect a cancer signal
- Predict the likely cancer signal origin (CSO)



cfDNA, cell-free DNA. [a]Bisulfite treatment; targeted probes pull out fragments matching regions of interest. [b]For a detected signal, the MCED test predicts 1-2 cancer signal origins (CSO) that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid). Adapted from Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759. PMID: 33506766

PATHFINDER: A Prospective Cohort Study to Return the Results of MCED Tests to Participants



MCED, multi-cancer early detection. [a]Previous history of cancer, smoking, and genetic risk; [b]Also collected at other time points during the study; [c]Defined as date when study team determines to end diagnostic evaluation triggered by a "signal detected" test result. Adapted from Nadauld LD, et al. *Cancers (Basel).* 2021;13(14):3501. PMID: 34298717.

Study Motivation

Understand the Clinical Experience of MCED Testing

- Understand the diagnostic evaluations precipitated by receipt of a “signal detected” MCED test
- Evaluate MCED test performance characteristics
- Understand levels of participant anxiety and distress associated with MCED testing

PATHFINDER: NCT04241796

Participants were enrolled from **December 2019 to December 2020**
in the ambulatory care practices at 7 US health care systems

Participants were followed for one year from the date of MCED testing (**through December 2021**)

PATHFINDER Study Objectives

Primary Objective

- Assess extent of diagnostic testing required to achieve diagnostic resolution following a “signal detected” test result
  - Time to diagnostic resolution
    - Diagnostic resolution was ascertained by the MD who ordered and disclosed the MCED test result
  - Number and types of diagnostic tests

Secondary Objectives

- Evaluate test performance
  - Specificity
  - Positive Predictive Value (PPV)
  - Negative Predictive Value (NPV)
  - Number Needed to Screen (NNS), Yield
  - Cancer Signal Origin[a] (ie, Predicted Origin) Accuracy
- Evaluate participant reported anxiety, distress, satisfaction (presented in poster #908P)

[a]For a detected signal, the MCED test predicts 1-2 cancer signal origins (CSO) that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid).

PATHFINDER Eligibility Criteria

Inclusion:

- **Adults ≥50 years** who were eligible for either:
  - **With Additional Risk Cohort**
  - **Without Additional Risk Cohort**
- **Eligibility for With Additional Risk Cohort:**
  - **Lifetime history of smoking at least 100 cigarettes**
  - **Hereditary cancer predisposition[a]**
  - **A history of cancer with no treatment for >3 years[b]**
- **Eligibility for Without Additional Risk Cohort:**
  - **None of the above risk factors**

Exclusion:

- **Clinical suspicion of malignancy**
- **Undergoing diagnostic evaluation for malignancy**
- **History of invasive or hematologic malignancy diagnosed <3 years before enrollment**
- **Definitive treatment for invasive or hematologic malignancy <3 years before enrollment[b]**

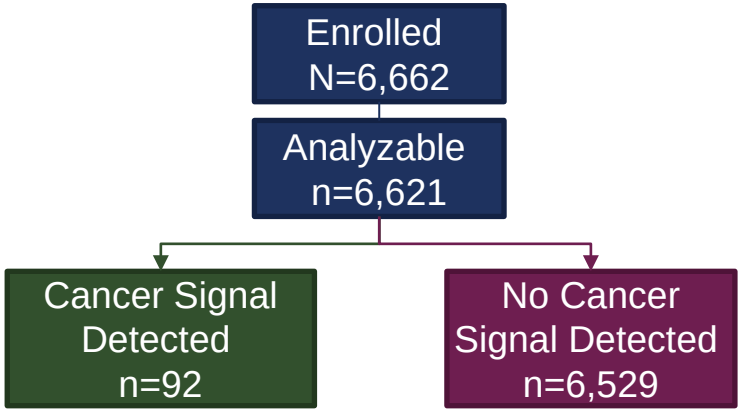
[a]Genetic cancer predisposition, hereditary cancer syndrome, or meeting criteria for germline testing based on NCCN guidelines.
[b]Personal history of invasive or hematologic malignancy, with definitive treatment completed >3 years prior to enrollment. Adjuvant hormone therapy for breast cancer was permissible.

Participant Characteristics

	With Additional Risk[a] n = 3,681	Without Additional Risk n = 2,940	Total N = 6,621
Age[b], in years, mean (SD)	64.7 (8.7)	61.6 (8.1)	63.4 (8.6)
Female	65%	62%	63%
White, Non-Hispanic	93%	89%	92%
College Degree or Higher	59%	71%	65%
Up to Date With Standard Cancer Screening Prior to MCED Testing			
Colorectal Cancer[c]	91%	92%	92%
Breast Cancer[d]	78%	83%	80%

[a]Previous history of cancer, smoking, and hereditary risk.
[b]Participants >85 were eligible to participate, but to protect confidentiality, 85 years was the maximum age recorded and used in calculations for participants ≥85 years of age.
[c]Participants ≤75 years old, up to date with USPSTF colorectal cancer screening recommendations (n=4888 total eligible with complete information).
[d]Women 50-74 years old up to date with breast cancer screening recommendations (USPSTF, MRI, or ultrasound; n=3547 total eligible with complete information).

Cancer Signal Detection



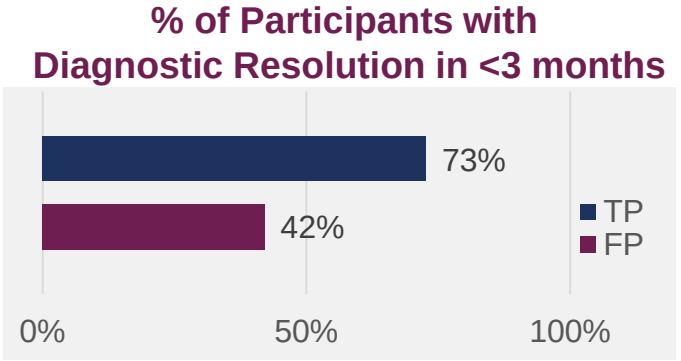
	With Additional Risk[a] n = 3,681	Without Additional Risk n = 2,940	Total N = 6,621
Signal Detected	1.5%	1.2%	**1.4%**
No Signal Detected	98.5%	98.8%	98.6%

[a]Previous history of cancer, smoking, and genetic risk.

Primary Objective: Time to Achieve Diagnostic Resolution

Time to Diagnostic Resolution for Participants with MCED Signal Detected
(N=90; not calculable for 2 participants who began diagnostic evaluation before test results returned)

	TP 33	FP 57[a]	Total 90
Median # of Days to Diagnostic Resolution (Interquartile Range)	57 (33, 143)	162 (44, 248)	79 (37, 219)



- Median time to diagnostic resolution was longer for FPs than TPs
- Most TPs reached resolution in <3 months

TP, true positive; FP, false positive.
[a]Includes 1 participant without diagnostic resolution who was conservatively assumed to be FP.

Primary Objective: Extent of Diagnostic Evaluation

Extent and Types of Diagnostic Evaluation for Participants with MCED Signal Detected (N=90)			
% of participants	**TP N=33[a]**	**FP N=57[b]**	**Total N=90[a]**
Any imaging procedure, %	**91**	**93**	**92**
Any advanced imaging (CT, PET, MRI)	**88**	**89**	**89**
Any invasive procedure, %	**82**	**30**	**49**
Non-surgical invasive procedure (endoscopy, FNA, core biopsy)	**79**	**28**	**47**
Surgical invasive procedure	**9**	**2**	**4**

TP, true positive; FNA, fine needle aspiration; FP, false positive.
[a]Two participants with 'signal detected' MCED test result (TPs) were excluded from the diagnostic workup analysis because diagnostic testing was initiated before MCED results were returned.
[b]Includes 1 participant without diagnostic resolution who was conservatively assumed to be FP.

Safety

- There were no serious, study-related adverse events reported as **a result of MCED testing**
- There were no serious, study-related adverse events **due to diagnostic workup** prompted by receipt of a “signal detected” MCED test result

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Secondary Objective: Accuracy of Predicted Cancer Origin

Test Performance: Ability to Predict Origin of Malignancy

	TP	FP	Total
Participants, n	35	57	92
Determinate predicted origin	**34**	53	87
Indeterminate predicted origin	1	4	5

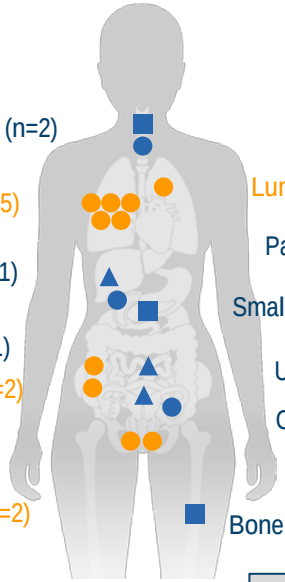
Predicted Origin Accuracy	
First Predicted Origin,[a] n	29/34[b]
% (95% CI)	**85.3** (69.9-93.6)
First or Second Predicted Origin,[a,c] n	33/34[b]
% (95% CI)	**97.1** (85.1-99.8)

- **The predicted origin helped to direct diagnostic workups**

CI, confidence interval.
[a]For a detected signal, the MCED test predicts cancer signal origins (CSO) that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid).
[b]Excludes 1 participant with indeterminate origin prediction from the true positive per study protocol.
[c]Proportion of first or second origin correctly predicted among true positive participants.

Cancers Diagnosed After a True Positive MCED Signal

19 Solid Tumors



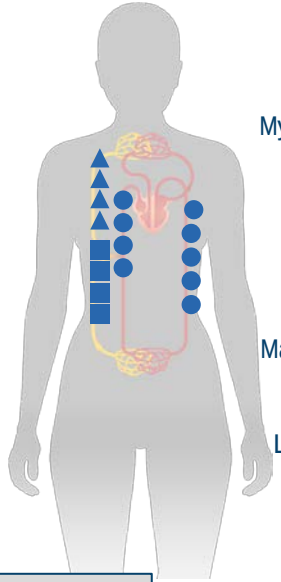
Oropharyngeal (n=2)
Breast ♀ (n=5)
Liver (n=1)
Intrahepatic Bile Ducts (n=1)
Colon/Rectum (n=2)
Prostate ♂ (n=2)
Lung (n=1)
Pancreas (n=1)
Small Intestine (n=1)
Uterus ♀ (n=1)
Ovary ♀ (n=1)
Bone (n=1)

35 people were diagnosed with 36 cancers

- 24 in high-risk cohort
- 11 in not-high-risk cohort

- 7 recurrent cancers
- 14 early-stage cancers
- 26 cancers lacking standard screening

17 Hematologic Cancers



Plasma Cell Myeloma/Disorders (n=1)
Lymphoid Leukemia (n=2)
Waldenstrom Macroglobulinemia (n=2)
Lymphoma (n=12)

AJCC Staging: ▲ Stage I ■ Stage II ● Stage III/IV/No Stage/Recurrent

Available Screening: **USPSTF cancer screening** or **No standard screening**

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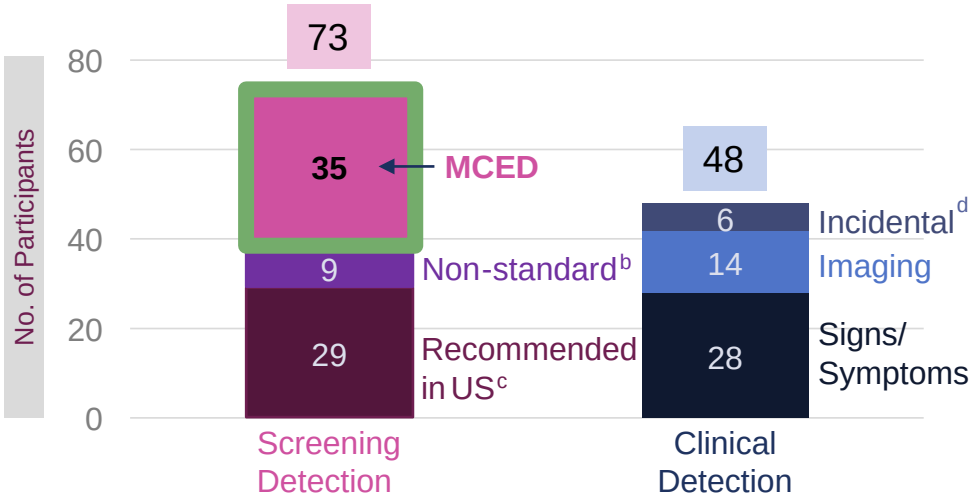
Cancers Identified Within One Year of MCED Testing

Participants with Cancers Detected by Either Screening or Clinical Findings

121 participants had a cancer diagnosis within 1 year



- 35/121 (29%) had cancer diagnosed and positive MCED
  - 2/35 had cancer detected by the MCED test but work-up began before results were disclosed

MCED, multi-cancer early detection.
[a]Based on participants with cancer status assessment at the end of the study.
[b]3 thyroid and 6 melanoma.
[c]Breast, cervical, colorectal, lung, and prostate cancer.
[d]1 incidental radiology finding, 1 incidental finding on routine physical exam, 2 changed lab values, 1 surveillance of prior cancer, 1 follow-up after MGUS diagnosis.

Secondary Objective: MCED Test Performance

Test Performance Metric	Result	Number
Cancer Signal Detected	1.4%	92/6621
Specificity[a]	99.1%	6253/6290
Positive Predictive Value (PPV)	38.0%	35/92
Negative Predictive Value (NPV)[a]	98.6%	6235/6321
Number needed to screen to detect one cancer	189	6621/35
Yield	0.5%	35/6621

MCED, multi-cancer early detection.
[a]Based on participants with cancer status assessment at the end of the study.

Secondary Objective: Performance of a Refined MCED Test

- The banked specimens were re-analyzed using a refined version of the MCED assay
- These results were not returned to participants or their physicians
- The refined MCED assay was intended to:
  - Reduce false positives with hematologic predictions
  - Improve prediction of the tumor origin

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Secondary Objective: Performance of a Refined MCED Test

Test Performance Metric	Refined Version of MCED Test (Results Not Returned to Participants or Providers)		MCED Test Results Returned
Cancer Signal Detected	0.9%	58/6578	1.4%
Specificity[a]	99.5%	6216/6249	99.1%
Positive Predictive Value PPV	43.1%	25/58	38.0%
Negative Predictive Value NPV[a]	98.5%	6216/6311	98.6%
Number needed to screen, No.	263	6578/25	189
Yield	0.38%	25/6578	0.53%
First Predicted Origin	84.0%	21/25	85.3%
First or Second Predicted Origin[b]	88.0%	22/25	97.1%

[a]Based on participants with cancer status assessment at the end of the study.
[b]Proportion of first or second origins correctly predicted among true positive participants.

Conclusions

- MCED screening was safely implemented for adults with and without additional cancer risk
- 1.4% of participants had a cancer signal detected
- 0.5% of participants were diagnosed with cancer due to MCED signal detection
- Median time to diagnostic resolution was 79 days
- High accuracy of predicted origin enabled targeted diagnostic evaluations
- Most diagnostic evaluations involved imaging, few required invasive procedures
- This study shows that it is feasible to detect cancers early using blood tests

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Limitations and Caveats

- It will be important for future clinical utility studies to evaluate whether MCED testing reduces mortality, the primary goal of all cancer screening
- Study cohort had limited diversity
- 12 month follow-up was incomplete for 3% of the cohort
- Further work is needed to understand the reasons underlying both false positive and false negative MCED test results
- Participation in current cancer screenings with established effectiveness must continue as MCED technologies are refined

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Future/Ongoing Work

- Evaluation of MCED screening in cohorts with greater socioeconomic, ethnic and racial diversity
- Optimization of test performance characteristics
- Ongoing PATHFINDER2 study is screening 20,000 individuals using the refined version of the MCED test
- NHS-Galleri (ISRCTN 91431511) will assess clinical utility of the refined MCED test in a randomized trial of 140,000 adults 50-77 in the UK's NHS. This pragmatic trial compares the incidence of advanced cancer diagnoses among participants who have annual MCED screening for 3 years to those who have usual care only

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Thank you to study participants who were recruited from:

- Dana Farber Cancer Institute
- Sutter Health
- OHSU Knight Cancer Institute
- US Oncology
- Intermountain Healthcare
- Cleveland Clinic
- Mayo Clinic

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PATHFINDER Secondary Objective:
Patient Reported Outcomes
Presented in poster #908P