3070

A Prespecified Interim Analysis of the PATHFINDER Study: Performance of a Multi-Cancer Early Detection Test in Support of Clinical Implementation

American Society of Clinical Oncology (ASCO)
June 4-8, 2021

Tomasz M. Beer,[1] Charles H. McDonnell, III,[2] Lincoln Nadauld,[3] Minetta C. Liu,[4] Eric A. Klein,[5] Robert Reid,[6] Catherine R. Marinac,[7] Karen Chung,[8] Margarita Lopatin,[8] Eric T. Fung,[8] Deborah Schrag[7]
[1]OHSU Knight Cancer Institute, Portland, OR; [2]Sutter Health, Sacramento, CA; [3]Intermountain Healthcare, St. George, UT; [4]Mayo Clinic, Rochester, MN; [5]Cleveland Clinic, Cleveland, OH; [6]US Oncology Research, VA Cancer Specialists, Merrifield, VA
[7]Dana-Farber Cancer Institute, Boston, MA; [8]GRAIL, Inc., Menlo Park, CA.

INTRODUCTION

- A blood-based multi-cancer early detection (MCED) test utilizing cell-free DNA (cfDNA) sequencing in combination with machine learning detected cancer signals signals across >50 cancer types and predicted cancer signal origin with high accuracy[1]
- PATHFINDER (NCT04241796) is a prospective study that returns results from an early version of the MCED test[2] (MCED-E) in a clinical setting (see Poster 3010)
- Specific adjustments were made to MCED-E based on earlier findings[2] to further refine it for use as a screening tool (MCED-Scr):
  - Increased specificity threshold for hematological signals to reduce false positives due to cancer-like signals from non-malignant hematological conditions
  - Removal of 'indeterminate' as a cancer signal origin, such that a prediction is returned for all test positive samples
  - Test report with a maximum of two predicted cancer signal origins
- The MCED-Scr test has been validated in a large case-controlled substudy of the Circulating Cell-free Genome Atlas study[1] and was evaluated using blood samples from PATHFINDER participants
- The goal is to develop an MCED test with performance characteristics that make it a valuable cancer screening tool in clinical practice

OBJECTIVE

To evaluate performance of the MCED-Scr test and compare its performance to that of the MCED-E test in a prespecified interim analysis of PATHFINDER study participants

A MULTI-CANCER EARLY DETECTION TEST REFINED FOR SCREENING DETECTS A BROAD RANGE OF EARLY AND ADVANCED STAGE CANCERS

MCED-Scr Test Performance

Table 1. MCED-Scr Test Performance

	≥50 y With Additional Risk	≥50 y Without Additional Risk	Total
Cancer Signal Detection, No.	n=3625	n=2891	N=6516
Detected, No. (%)	40 (1.1)	17 (0.6)	57 (0.9)
True Positive	15 (0.4)	4 (0.1)	19 (0.3)
False Positive	8 (0.2)	3 (0.1)	11 (0.2)
No Current Diagnostic Resolution	8 (0.2)	2 (0.1)	10 (0.2)
No Diagnostic Testing Initiated due to MCED-E (-) Result[a]	9 (0.2)	8 (0.3)	17 (0.3)
Not Detected	3585 (98.9)	2874 (99.4)	6459 (99.1)
Minimal PPV for Cancer Signal Detection,[b] No.	n=32	n=15	n=47
% (95% CI)	46.9 (30.9-63.6)	26.7 (10.9-52.0)	40.4 (27.6-54.7)
CSO Prediction Accuracy, No.	n=15	n=4	n=19
First CSO,[c] % (95% CI)	93.3 (70.2-99.7)	75.0 (30.1-98.7)	89.5 (68.6-97.1)
First or Second CSO,[d] % (95% CI)	93.3 (70.2-99.7)	75.0 (30.1-98.7)	89.5 (68.6-97.1)

Abbreviations: CI, confidence interval; CSO, cancer signal origin; PPV, positive predictive value
[a]Participants who had a signal detected with MCED-Scr but not with MCED-E had no diagnostic work up performed and are labeled as discordant positives.
[b]Minimal PPV is a conservative estimate which assumes that all discordant (MCED-Scr positive, MCED-E negative) positives will be false positives. Participants with no current diagnostic resolution are excluded.
[c]Proportion of correctly predicted first CSO among true positive participants.
[d]Proportion of correctly predicted first or second CSO among true positive participants.

- The MCED-Scr detection rate was 0.9% (57/6516), with a higher percentage observed in the cohort with additional risk (1.1% vs 0.6%; **Table 1**)
- Minimal PPV was conservatively estimated at 40.4%
  - It conservatively assumes all discordant positives (signal detected with MCED-Scr but not MCED-E) are false positives
  - Minimal PPV was 46.9% in the cohort with additional risk versus 26.7% in the cohort without additional risk (**Table 1**)
  - The study was not designed to compare performance between two cohorts
- The predicted cancer signal origin accuracy was high, though sample sizes were limited (**Table 1**)

MCED-E and MCED-Scr Comparison

Table 2. MCED-Scr and MCED-E Test Concordance

No.	MCED-E (+)	MCED-E (-)	Total
MCED-Scr (+)	40	17[a]	57
MCED-Scr (-)	51	6405	6456
Total	91	6422	6513[b]
Percent Agreement (95% CI)	Positive 44.0% (40/91) (34.2-54.2)	Negative 99.7% (6405/6422) (99.6-99.8)	Overall 99.0% (6445/6513) (98.7-99.2)

[a]17 Discordant Positives had no diagnostic evaluation based on negative MCED-E test results.
[b]Includes participants with analyzable results for MCED-E and MCED-Scr; three participants did not have analyzable results by both MCED tests.

- Negative and positive percent agreement, respectively, between MCED-E and MCED-Scr were 99.7% (99.6-99.8%) and 44.0% (34.2-54.2%) (**Table 2**)
- 17 of 57 were discordant positives (cancer signal detected with MCED-Scr but not MCED-E; **Table 2**)
  - All with solid cancer CSO predictions
  - Cancer status assessment was not available at the time of this interim analysis as only MCED-E test results were returned to investigators and triggered diagnostic follow up
  - Cancer status assessed for all participants at 12 month follow up will be included in the final analysis
- 51 were discordant negatives (cancer signal detected on MCED-E but not MCED-Scr; **Table 2**)
  - Most discordant negatives (42/51, 82%) had hematological MCED-E cancer signal origin prediction
- Most (66%) true positives and fewer (31%) false positives had cancer signal detected by MCED-Scr (**Table 3**)
  - Cancers identified by MCED-E but not by MCED-Scr tended to be of hematologic origin (7/10) and most did not require immediate therapy (8/10), as determined by investigators

Table 3. Summary of MCED-Scr Status for Participants with MCED-E Positive Results[a]

No.	MCED-E (+) Cancer (True Positives)	MCED-E (+) No Cancer (False Positives)	MCED-E (+) Diagnostic Evaluation Ongoing
MCED-Scr (+)	19	11	10
MCED-Scr (-)	10	24	17
Total	29	35	27
% MCED-Scr (+)	65.5% (19/29)	31.4% (11/35)	37.0% (10/27)

[a]One false positive participant with MCED-E "cancer signal detected" had no analyzable MCED-Scr result and hence is not included in this table.

Figure 1. Distribution of Predicted Cancer Classes With MCED-Scr (n=57 with MCED-Scr (+) Result)

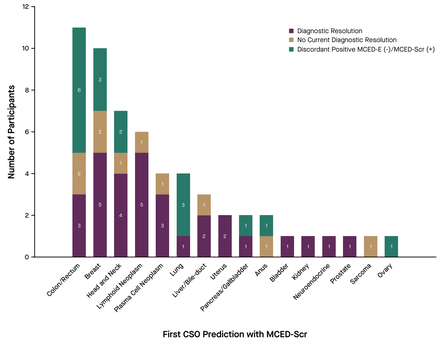


Table 4. Characteristics of Detected Cancers with MCED-Scr (n=19 True Positives)

Cancer Type Diagnosed	Clinical AJCC Stage[a] of New Cancers I	II	III	IV	Other	Extent of Recurrent Cancers Local	Distant	First Predicted Cancer Signal Origin
Colon or rectum				1	1 Unknown[b]			Colon/Rectum
Head and Neck		1		1				Head and Neck
Liver, bile duct	1		1					Liver, bile-duct
Lung			1					Lung
Lymphoid leukemia					1 NA[c]			Lymphoid Neoplasm
Lymphoma		1	1	1				Lymphoid Neoplasm
Ovary, peritoneum or fallopian tube			1					Uterus
Pancreas		1						Pancreas/Gallbladder
Plasma cell neoplasm					1 NA[c]			Plasma Cell Neoplasm
Small intestine	1							Colon/Rectum
Breast cancer							4	Breast
Total	2	3	4	3	3	0	4	

Abbreviations: AJCC, the American Joint Committee on Cancer; NA, Not applicable
[a]AJCC version 8.
[b]Unknown stage at time of analysis.
[c]No AJCC stage expected.

- MCED-Scr (+) participants had cancer signal origin distributed across 16 cancer classes (**Figure 1**), with colon/rectum, breast, head and neck, and lymphoid neoplasm appearing most frequently
- A total of 67% (38/57) had 2 predicted cancer signal origins
- Among true positives with a signal detected result with MCED-Scr, 15/19 (78.9%) of cancers diagnosed were de novo and 4/19 (21.1%) were recurrent (Table 4)
  - 11 different cancer types were detected

CONCLUSIONS

- MCED-Scr is a multi-cancer early detection test refined for use as a screening tool
  - In this prespecified interim analysis of the PATHFINDER study, MCED-Scr[1] detected cancer signals with 40% PPV and maintained a high accuracy of cancer signal origin prediction relative to the earlier version of the test (MCED-E)[2]
  - Similar to the earlier version of the test,[2] MCED-Scr detected a broad range of early and advanced stage cancers
  - The refinements implemented for the MCED-Scr test in comparison to the MCED-E test, reduced the number of hematologic cancer signal origin predictions, particularly false positives, and streamlined the test report to include no more than two cancer signal origins
  - Updated results and the specificity and negative predictive value of MCED-Scr and MCED-E will be reported after all PATHFINDER participants have been observed for 12 months

References

1. Klein, E. et al. Clinical Validation of a Targeted Methylation-Based Multi-Cancer Early Detection Test. Presented at the annual meeting of the American Association for Cancer Research. April 10-15, 2021. www.aacr.org/aacr2021. Abstract #LB103 (2021).
2. Liu MC, Oxnard GR, Klein EA, et al. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol*. 2020;31(6):745-759. doi:10.1016/j.annonc.2020.02.011

Disclosures

Study funded by GRAIL, Inc. KC, ML, and ETF are current or former employees of GRAIL, Inc. with equity in the company. All financial relationships disclosed at abstract submission. In addition to consulting with GRAIL, Inc (TMB, MCL, EAK), financial disclosures related to stock ownership are: TMB (Arvinas Salarius, Pharmaceuticals), CHM (Sutter Medical Group), LN (Citizen Corporation, Clarifi, Guidance Genomics), DS (Merck, family member).

Acknowledgements

Funded by GRAIL, Inc. Writing and editorial assistance provided by Prescott Medical Communications Group (Chicago, IL)

METHODS

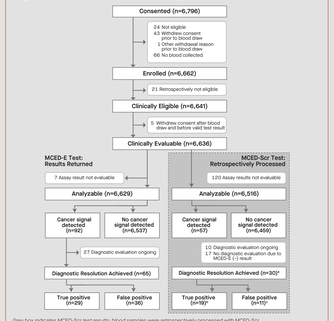
- PATHFINDER (NCT04241796) is a prospective, longitudinal, multi-center clinical study that enrolled 6662 participants from 7 clinical institutions in the United States between Dec 2019 and Dec 2020
- Participants consented to the MCED-E blood test with return of results to their physician
- Participants were ≥50 years old and recruited into two cohorts:
  - With Additional Risk: a history of smoking, prior cancer with treatment completed more than 3 years ago (excluding adjuvant hormone therapy), or known genetic cancer predisposition
  - Without Additional Risk: all other participants
- In this prespecified interim analysis, samples were retrospectively processed with the MCED-Scr; only MCED-E test results (detection and cancer signal origin prediction) were returned to the physician who facilitated informed consent
  - PATHFINDER results did not inform the refinements made to MCED-Scr
- The test performance characteristics of the MCED-Scr test, including the rate of cancer signal detection, PPV, and cancer signal origin prediction were evaluated and compared to the performance for the MCED-E test

SUPPORTING DATA

Participant Disposition

- A total of 6516 participants were analyzable: this includes clinically eligible participants with evaluable MCED-Scr test results (**Figure 2**)

Figure 2. Participant Flow Diagram



Grey box indicates MCED-Scr test results; blood samples were retrospectively processed with MCED-Scr.
[a]Diagnostic resolution achieved based upon MCED-E test result.
[b]Participants who had a cancer signal detected by MCED-E that was confirmed upon diagnostic resolution.
[c]Participants who had a cancer signal detected by MCED-E that was not confirmed upon diagnostic resolution.

Participant Demographics and Baseline Characteristics

- Demographics and baseline characteristics of the analyzable participants are shown in Table 5

Table 5. Participant Demographics and Baseline Characteristics (MCED-Scr Test Version)[a]

		MCED-Scr Test (Retrospectively Processed) ≥50 y With Additional Risk (n=3625)	≥50 y Without Additional Risk (n=2891)	Total (N=6516)
Age[b], Median (Q1, Q3), y		64.0 (58.0, 71.0)	60.0 (55.0, 67.0)	63.0 (56.0, 70.0)
Female, n (%)		2365 (65.2)	1786 (61.8)	4151 (63.7)
Non-Hispanic white, n (%)		3388 (93.5)	2583 (89.3)	5971 (91.6)
Age Group, n (%), y	50-64	1826 (50.4)	1909 (66.0)	3735 (57.3)
	65-79	1613 (44.5)	908 (31.4)	2521 (38.7)
	≥80	186 (5.1)	74 (2.6)	260 (4.0)
BMI Category, n (%)	Underweight	31 (0.9)	18 (0.6)	49 (0.8)
	Normal	1028 (28.4)	937 (32.4)	1965 (30.2)
	Overweight	1270 (35.0)	1019 (35.2)	2289 (35.1)
	Obese	1252 (34.5)	876 (30.3)	2128 (32.7)
	Other/Missing	44 (1.2)	41 (1.4)	85 (1.3)
Smoking Status, n (%)	Current Smoker	258 (7.1)	0	258 (4.0)
	Former Smoker	2189 (60.4)	0	2189 (33.6)
	Non-smoker	1178 (32.5)	2891 (100)	4069 (62.4)
Eligible for Lung Cancer Screening,[c] n (%)		218 (6.0)	0	218 (3.3)
Prior Cancer History, n (%)		1612 (44.5)	0	1612 (24.7)
Genetic Cancer Predisposition, n (%)		422 (11.6)	0	422 (6.5)

Abbreviations: BMI, body-mass index; LDCT, low-dose computed tomography; USPSTF, United States Preventive Services Task Force, y, years.
[a]Blood samples collected at the start of the trial were first tested by MCED-E, and the remaining samples from these same participants were then evaluated by MCED-Scr.
[b]Age was truncated at 85 years to protect confidentiality.
[c]Satisfy approved USPSTF criteria for lung cancer screening using LDCT.