3010

Interim Results of PATHFINDER, a Clinical Use Study Using a Methylation-Based Multi-Cancer Early Detection Test

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INTRODUCTION

- More than 2/3 of lethal cancers have no recommended screening options[1]
- Early detection of cancers may reduce cancer-related morbidity and mortality[2–4]
- Circulating cell-free DNA (cfDNA) sequencing allows for early detection of multiple cancers simultaneously using a single blood test[5,6]
- A large case-control study that did not return results to patients demonstrated that a multi-cancer early detection (MCED) test using targeted methylation-based cfDNA technology detected cancer signal in more than 50 types of cancer and predicted cancer signal origin with over 90% accuracy[7]
- PATHFINDER (NCT04241796; see also poster 3070) is a prospective study in adults ≥50 years of age that returns results of a MCED test and evaluates the diagnostic steps clinicians and patients undertake when the test indicates the presence of cancer

OBJECTIVES

- Primary objective: among individuals who have achieved diagnostic resolution, assess the extent and types of diagnostic testing required to achieve diagnostic resolution following a MCED test result indicating the potential presence of malignancy
- Secondary objectives, evaluate:
  - MCED test performance, including the positive predictive value (PPV) and the accuracy of cancer signal origin prediction
  - Satisfaction with MCED screening reported by study participants
- Exploratory objective: participant attitude toward future screening
- Safety analyses: study-related adverse events

METHODS

- PATHFINDER (NCT04241796) is a prospective, multi-center study that enrolled 6662 participants from 7 clinical institutions in the United States between Dec 2019 and Dec 2020
- Participants were adults ≥50 years and recruited into two cohorts:
  - With Additional Risk: a history of smoking, prior cancer treatment completed more than 3 years ago (excluding adjuvant hormone therapy), or genetic cancer predisposition (including hereditary cancer syndrome or meeting criteria for germline testing based on NCCN guidelines)[12]
  - Without Additional Risk: all other participants
- Participants were ineligible if they had a current clinical suspicion for cancer or history of/treatment for invasive/hematologic malignancy within 3 years
- Blood samples were analyzed using the MCED test and results including a binary signal indicating the presence or absence of signal for cancer detection and a prediction of the cancer signal origin (CSO) were returned to the physician who facilitated informed consent
  - Participants with "cancer signal detected" test result underwent diagnostic tests, as determined by the treating physician informed by standard practice guidelines,[8–11] until diagnostic resolution based on the diagnosis of an invasive cancer (true positive) or no cancer (false positive) was reached
- These are interim results and follow-up for clinical diagnosis of cancer among participants with and without cancer signal detected on the MCED test continues for 12 months from the date of testing
- With longer follow-up, additional participants may reach diagnostic resolution and some currently categorized as not having cancer (false positives) may be found to have cancer. Final results are expected to reveal more testing and longer time required for diagnostic resolution
- Participants satisfaction with and attitudes towards the MCED test were collected as detailed below; additional patient-reported outcomes will be returned at study end
  - "Satisfaction with the MCED test" consists of three questions with a total score between 0-100, with higher scores indicating higher satisfaction. It was administered post-test for participants with cancer signal not detected and at diagnostic resolution for those with cancer signal detected
  - "Attitude towards adherence to guideline-recommended screening" was a single question administered for all participants before MCED test and for participants with cancer signal not detected after MCED test

MCED TEST DETECTED BROAD RANGE OF CANCER SIGNALS, INFORMING DIAGNOSTIC WORKUP, WITH 45% PPV

Diagnostic Workup

Table 1. Diagnostic Workup Procedures Per Participant with Diagnostic Resolution

	Median (Q1, Q3)		
	True Positive (n = 27[a])	False Positive (n = 36)	Total (n = 63)[a]
All Imaging Tests/Invasive Procedures	2.0 (1.5, 3.0)	1.5 (1.0, 2.2)	2.0 (1.0, 3.0)
All Imaging Tests	1.0 (1.0, 1.5)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Functional[b]	1.0 (0, 1.0)	1.0 (0, 1.0)	1.0 (0, 1.0)
Anatomic[c]	1.0 (0, 1.0)	1.0 (0, 1.0)	1.0 (0, 1.0)
All Invasive Procedures	1.0 (1.0, 1.0)	0 (0, 0.2)	0 (0, 1.0)
Minimally Invasive[d]	1.0 (0.5, 1.0)	0	0 (0, 1.0)
Surgical[e]	0	0	0
Clinical Lab Tests	3.0 (1.0, 5.5)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
Days to Diagnostic Resolution	50.0 (27.0, 76.5)	49.0 (30.2, 153.8)	50.0 (28.0, 91.0)

Abbreviations: CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; Q1, first quartile; Q3, third quartile.
[a]2 participants with "signal detected" MCED test result (true positives) were excluded from the diagnostic workup analysis. because diagnostic testing was initiated before MCED test results were returned.
[b]Functional imaging includes PET-CT, PET-MRI, bone scan.
[c]Anatomic Imaging includes CT, MRI, ultrasound, mammography, plain film X-ray (including skeletal survey).
[d]Minimally invasive procedures include esophagogastroduodenoscopy, colonoscopy, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, bronchoscopy, cystoscopy, hysteroscopy, fine needle aspiration of the thyroid gland, liver biopsy, thoracentesis, pulmonary arterio-venous malformation embolization.
[e]4 surgical procedures were performed, 3 in true positive, 1 in false positive set.

- Most participants with diagnostic resolution (57/63, 90.5%) had at least 1 imaging test
  - Median number of imaging tests per participant was the same in true and false positive groups (**Table 1**)
- Most invasive procedures were minimally invasive (28/32 procedures, 87.5%)
  - 26/30 (86.6%) participants had only minimally invasive procedures
  - 2/30 (6.7%) participants had both minimally invasive and surgical procedures
  - 2/30 (6.7%) participants had only surgical procedures
- Invasive procedures were more common in true positive participants (**Table 1**)
  - 21/27 (77.8%) of true positive and 9/36 (25.0%) of false positive participants had at least 1 invasive procedure
  - 21/30 (70.0%) of participants with invasive procedures had cancer diagnosis
- Median time to diagnostic resolution, estimated using Kaplan-Meier methods, was 83.5 days (95% CI: 60-163); 66% of the 90 participants with "cancer signal detected" were estimated to reach diagnostic resolution within 6 months
- There were 4 reports of study-related adverse events; 3 of anxiety and 1 bruise at venipuncture site, all were of mild severity

Test Performance

Table 2. MCED Test Performance

	≥50 y With Additional Risk	≥50 y Without Additional Risk	Total
Cancer Signal Detection, No.	n=3695	n=2934	N=6629
Detected, No. (%)	56 (1.5)	36 (1.2)	92 (1.4)
True Positive	20 (0.5)	9 (0.3)	29 (0.4)
False Positive	15 (0.4)	21 (0.7)	36 (0.5)
No Current Diagnostic Resolution	21 (0.6)	6 (0.2)	27 (0.4)
Not Detected	3639 (98.5)	2898 (98.8)	6537 (98.6)
PPV for Cancer Signal Detection, No.	n=35	n=30	n=65
% (95% CI)	57.1 (40.9-72.0)	30.0 (16.7-47.9)	44.6 (33.2-56.7)
CSO Prediction Accuracy, No.	n=19[a]	n=8[a]	n=27[a]
First CSO,[b] % (95% CI)	84.2 (62.4-94.5)	87.5 (52.9-99.4)	85.2 (67.5-94.1)
First or Second CSO,[c] % (95% CI)	100 (83.2-100)	87.5 (52.9-99.4)	96.3 (81.7-99.8)

Abbreviations: CI, confidence interval, CSO, cancer signal origin, PPV, positive predictive value.
[a]Excludes 1 participant with unknown cancer type and 1 with indeterminate CSO from the true positive set.
[b]Proportion of correctly predicted first CSO among true positive participants with determinate CSO.
[c]Proportion of correctly predicted first or second CSO among true positive participants with determinate CSO.

- Of the 6629 analyzable participants, the MCED test detected cancer signal in 92 (1.4%); 1.5% of participants with additional risk and 1.2% without (**Table 2**)
- The PPV of the MCED test for participants with cancer signal detected who achieved diagnostic resolution was 44.6% (**Table 2**)
  - PPV was 57.1% in the "additional risk" vs 30.0% in the "without additional risk" cohort
- The accuracy of cancer signal origin prediction among true positives was 85.2% for the first cancer signal origin and 96.3% for the first and second cancer signal origins (**Table 2**)
  - Accuracy of the first or second cancer signal origin was 100% for the "additional risk" and 87.5% for "without additional risk" cohort

Table 3. Cancer Stage at Diagnosis Following a Positive MCED Result (n=28[a] True Positives)

Cancer Type Diagnosed	Clinical AJCC Stage[b] of New Cancers					Extent of Recurrent Cancers		First Predicted Cancer Signal Origin
	I	II	III	IV	Other	Local	Distant	
Colon or rectum				1	1 Unknown[c]			Upper GI Tract (stage IV pt) Colon/Rectum (unk pt)
Head and Neck		1		1				Head and Neck
Liver, bile duct	1		1					Liver, bile-duct
Lung			1					Lung
Lymphoid leukemia					2 NA[d]			Lymphoid Neoplasm
Lymphoma	2	3	1	2				Lymphoid Neoplasm
Ovary, peritoneum or fallopian tube			1					Uterus (ovary second CSO)
Pancreas		1						Pancreas/Gallbladder
Plasma cell neoplasm					1 NA[d]			Plasma Cell Neoplasm
Prostate				1				Indeterminate
Small intestine	1							Colon/Rectum (upper GI second CSO)
Waldenstrom macroglobulinemia					1 NA[d]			Lymphoid Neoplasm
Breast							4	3 cases Breast 1 case Breast (first CSO), lymphoid (second)
Prostate						1		Lymphoid (first CSO), prostate (second)
Total	**4**	**5**	**4**	**5**	**5**	**1**	**4**	

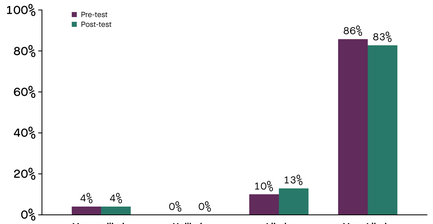
Abbreviations: AJCC, the American Joint Committee on Cancer; CSO, cancer signal origin; GI, gastrointestinal.
[a]Information not available for cancer type/stage/recurrence for one true positive participant at time of analysis.
[b]AJCC version 8.
[c]Unknown stage at time of analysis.
[d]No AJCC stage expected.

- 82.1% (23/28) of cancers diagnosed were de novo and 17.9% (5/28) were recurrent among participants with a history of the cancer and no evidence of recurrence for at least the 3 preceding years (**Table 3**)
- 13 different cancer types were diagnosed (**Table 3**)
  - Of the 23 participants with new cancer diagnoses, 39% were stage I/II, 17% were stage III, 22% were stage IV; 17% were hematologic (AJCC stage not expected) and 4% had unknown stage at time of analysis
  - Of the 5 participants with recurrence of an earlier cancer, 80% were metastatic and 20% localized

Participant Satisfaction with MCED and Attitude Towards Future Screening

- Among the 6118 participants who completed the questionnaire either following a "cancer signal not detected" result or upon diagnostic resolution for those with a "cancer signal detected":
  - Total mean satisfaction score was 83.2/100
  - 83% were extremely/very confident "that this MCED test is a good thing for you"
  - 90% were extremely/very certain "that the good things about the MCED test outweigh the bad things"
  - 97% were extremely/very/satisfied with the MCED test

Figure 1. Attitude Towards Future Screening Among Participants with "Cancer Signal Not Detected" MCED Test Result



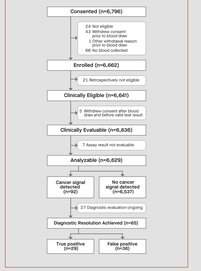
- Among participants with "cancer signal not detected" MCED test result who completed a questionnaire about their attitudes toward future screening:
  - **Before the MCED test**, 6159/6425 (96%) indicated they were likely or very likely to undergo future cancer screening recommended by their physician (**Figure 1**)
  - **After the MCED test**, the same percentage (5829/6070, 96%) indicated they were likely or very likely to undergo future cancer screening recommended by their physician (**Figure 1**)
- For participants with "cancer signal detected", this questionnaire was only administered before the MCED test; 83/89 (93%) answered that they were likely/very likely to undergo future cancer screening recommended by their physician

SUPPORTING DATA

Participant Disposition

- A total of 6796 participants provided informed consent, 6662 were enrolled and 6629 were analyzable (clinically eligible with an evaluable MCED test result)
- Of these 6629, 92 (1.4%) had cancer signal detected and 65 (1.0%) achieved diagnostic resolution as of March 2021 (**Figure 2**)

FIGURE 2. Participant Flow Diagram



Participant Demographics and Baseline Characteristics

Table 5. Participant Demographics and Baseline Characteristics

		≥50 y With Additional Risk n=3695	≥50 y Without Additional Risk n=2934	Total n=6629
Age,[a] Median (Q1, Q3), y		64.0 (58.0, 71.0)	60.0 (55.0, 67.0)	63.0 (56.0, 70.0)
Female, n (%)		2402 (65.0)	1807 (61.6)	4209 (63.5)
Non-Hispanic White, n (%)		3455 (93.5)	2624 (89.4)	6079 (91.7)
Age Group, n (%), y	50-64	1863 (50.4)	1934 (65.9)	3797 (57.3)
	65-79	1645 (44.5)	925 (31.5)	2570 (38.8)
	≥80	187 (5.1)	75 (2.6)	262 (4.0)
BMI Category, n (%)	Underweight	32 (0.9)	19 (0.6)	51 (0.8)
	Normal	1051 (28.4)	952 (32.4)	2003 (30.2)
	Overweight	1301 (35.2)	1036 (35.3)	2337 (35.3)
	Obese	1267 (34.3)	885 (30.2)	2152 (32.5)
Smoking Status, n (%)	Current Smoker	268 (7.3)	0	268 (4.0)
	Former Smoker	1637 (60.4)	0	2232 (33.7)
Eligible for Lung Cancer Screening,[b] n (%)		223 (6.0)	0	223 (3.4)
Known Prior Cancer History, n (%)		1637 (44.3)	0	1637 (24.7)
Genetic Cancer Predisposition, n (%)		428 (11.6)	0	428 (6.5)

Abbreviations: BMI, body mass index; LDCT, low-dose computed tomography; USPSTF, United States Preventive Services Task Force.
[a]Age truncated at 85 years.
[b]Satisfy approved USPSTF criteria for lung cancer screening using LDCT.

CONCLUSIONS

- In this prespecified interim analysis, the MCED test detected cancer signal in a broad range of cancer types, consistent with previous findings,[7] and was safely administered
- More than half of new cancers were detected at early stages (clinical stages I-III)
- Follow-up of PATHFINDER participants continues and will identify the incidence of cancer diagnoses for all participants within 12 months of their initial blood draw, at which time the specificity and negative predictive value of the MCED test will be evaluated

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