Expanding the Way We Screen for Cancer: A Path to a 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 cancer 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 across more than 50 types of cancer and predicted cancer signal origin with approximately 90% accuracy[7,8]
- PATHFINDER (NCT04241796) 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

OBJECTIVE

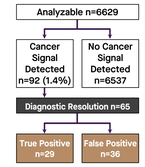
- Primary objective: assess the extent and types of diagnostic testing required to achieve diagnostic resolution following an MCED test result
- Secondary objectives, evaluate:
  - MCED test performance, including the positive predictive value (PPV) and the accuracy of cancer signal origin prediction
  - Participant-Reported Outcomes, including satisfaction with the MCED test and likelihood of future adherence to recommended cancer screening

A NOVEL BLOOD-BASED MULTI-CANCER EARLY DETECTION TEST DIRECTED DIAGNOSTIC FOLLOW UP, SUPPORTING ITS USE AS COMPLEMENT TO CURRENT RECOMMENDED SCREENING TESTS

Primary Analysis: Extent of Diagnostic Testing With MCED-E (Test Results Returned)

- A total of 1.4% (92/6629) of analyzable participants had a cancer signal detected. To date, 65/92 (71%) have achieved diagnostic resolution; 63 of these are included in the primary analysis (**Figure 2**)
- In the evaluation of extent of diagnostic testing required to reach diagnostic resolution:
  - 90.5% (57/63) had ≥1 imaging test
  - Median number of imaging tests was 1.0 (IQR 1.0-2.0), invasive procedures 0.0 (IQR 0.0-1.0), laboratory tests 3.0 (IQR 1.0-6.0), laboratory visits 1.0 (IQR 1.0-2.0) and clinic visits 0.0 (IQR 0.0-1.0; **Figure 2**)
    - Invasive diagnostic procedures were performed in 78% (21/27) of those ultimately confirmed to have cancer (true positives) versus 25% (9/36) of those who did not (false positives)
  - Median observed time to diagnostic resolution was 50 days (IQR 27.0-76.5) for the 27 individuals with a cancer diagnosis and 49 days (IQR 30.2-153.8) days for the 36 participants who did not receive a cancer diagnosis (**Figure 2**)
    - Across 90 MCED-E positive participants, median time to diagnostic resolution was estimated at 83.5 days (95% CI 60, 163) using Kaplan-Meier methods

Figure 2. Extent of Diagnostic Testing (Primary Analysis)



Median (Q1, Q3)	True Positives (n=27[a])	False Positives (n=36)	Total (n=63[a])
All Imaging Test/Invasive Procedures	2.0 (1.5, 3.0)	1.5 (1.0, 2.2)	2.0 (1.0, 3.0)
All Imaging Test	1.0 (1.1, 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)

[a]Two participants with 'signal detected' MCED test result (true positives) were excluded from the diagnostic workup analysis because diagnostic testing was initiated before MCED 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/sigmoidoscopy, endobronchial ultrasound-guided bronchoscopy, cystoscopy, hysteroscopy, fine needle aspiration of the thyroid gland, liver biopsy, thoracentesis, pulmonary arterio-venous malformation embolization. [e]A surgical procedures were performed, 2 in true positive, 1 in false positive set.
CT, computerized tomography; MCED-E, multi-cancer early detection, early test version; MRI, magnetic resonance imaging; PET, positron emission tomography; Q1, first quartile; Q3, third quartile.
Clinical database lock: Mar 2021.

Test Performance: MCED-E

- Nearly half of those achieving diagnostic resolution had a confirmed cancer; the positive predictive value was 44.6% (30.7-60.2%; **Table 1**)
- Cancer signal origin was predicted with 96.3% accuracy based on the first or second cancer signal origin prediction in participants with confirmed cancer (**Table 1**)

Table 1. Test Performance with MCED-E Overall and by Enrollment Cohort

	With Additional Risk	Without Additional Risk	Total
Cancer Signal Detection	n=3695	n=2934	N=6629
Detected, n (%)	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, n (%)	3639 (98.5)	2898 (98.8)	6537 (98.6)
PPV for Cancer Signal Detection	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	n=19[a]	n=8[b]	n=27[c]
First CSO[d] % (95% CI)	82.2 (62.4–94.5)	87.5 (52.9–99.4)	85.2 (67.5–94.1)
First or Second CSO[c] % (95% CI)	100.0 (83.2–100.0)	87.5 (52.9–99.4)	96.3 (81.7–99.8)

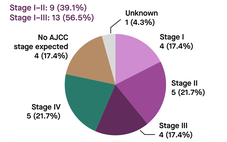
[a]Excludes 1 participant with unknown cancer type and 1 with indeterminate CSO from the true positive set. [b]Proportion of correctly predicted first CSO among true positive participants with determinate CSO. [c]Proportion of correctly predicted first or second CSO among true positive participants with determinate CSO.
CI, confidence interval; CSO, cancer signal origin; MCED-E, multi-cancer early detection, early test version; PPV, positive predictive value.
Clinical database lock: Mar 2021.

- Of true positive participants with information at time of analysis, 23/28 (82.1%) had a new cancer, and 5/28 (17.9%) had a recurrence. Of those with new cancer diagnoses, 13/23 (56.5%) were stage I-III, including 9 participants with stage I-II, and 4/23 (17.4%) were non-staged hematologic malignancies (**Figure 3**)

Figure 3. Cancer Characteristics of True Positive Set (MCED-E)

Cancer Type (n=29)	
n=8 (27.6%)	• Lymphoma (Hodgkin and Non-Hodgkin)
n=4 (13.8%)	• Breast (all recurrent [metastatic])
n=2 each (6.9%)	• Colon or rectum • Head and neck[a] • Liver or Bile-duct • Lymphoid leukemia[b] • Prostate (1 recurrent [local])
n=1 each (3.4%)	• Lung • Ovary, peritoneum or fallopian tube • Pancreas • Plasma cell neoplasm[c] • Small intestine • Waldenstrom macroglobulinemia • Unknown (at time of database lock)

New Cancers (n=23)[d]



Recurrent Cancers (n=5)

- 1 local recurrence (prostate)
- 4 metastatic recurrences (breast)

[a]Including oral cavity, pharynx, larynx, nasal cavity, major salivary glands. [b]Including chronic lymphocytic leukemia, hairy cell leukemia, B-ALL, T-ALL. [c]Including multiple myeloma. [d]Information not available for cancer type/stage/recurrence for one true positive participant.
AJCC, American Joint Committee on Cancer; ALL, acute lymphoblastic leukemia; MCED-E, multi-cancer early detection, early test version.
Clinical database lock: Mar 2021.

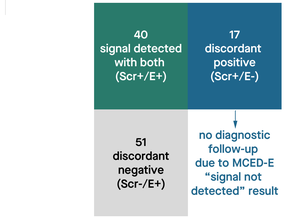
Test Performance: MCED-Scr

- The MCED-Scr test detected cancer signal in 0.9% (57/6516) of analyzable participants
- Among 57 with a signal detected with MCED-Scr, 40 also had a signal detected by MCED-E (including 19 with confirmed cancer), and 17 did not have a signal detected with MCED-E (termed "discordant positives") (**Figure 4**)
- The minimal conservative PPV estimated for MCED-Scr was 40.4% (27.6-54.7%) , based on 30 participants who reached diagnostic resolution (including 19 with cancer) and 17 discordant positives which were assumed to have no cancer
- The top (or first) cancer signal origin prediction was accurate for 17/19 or 89.5% (68.6-97.1%) of participants with confirmed cancer diagnoses
- Most true positives with MCED-E (66%) were also positive with MCED-Scr, whereas
- fewer false positives with MCED-E (31%) were positive with MCED-Scr
  - 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)

Figure 4. Concordance Between MCED-Scr and MCED-E for Signal Detection

	MCED-E signal detected (+)	MCED-E signal not detected (–)	Total
MCED-Scr signal detected (+)	40[a]	17	57
MCED-Scr signal not detected (–)	51	6405	6456
Total	91	6422	6513[b]

Percent Agreement Estimate (95% CI)	
Positive % (40/91)	44.0 (34.2–54.2)
Negative % (6405/6422)	99.7 (99.6–99.8)
Overall % (6445/6513)	99.0 (98.7–99.2)
Cohen's kappa: 0.54 (0.44–0.63)	



[a]Includes 19 with confirmed cancer, 11 without cancer diagnosis and 10 still undergoing diagnostic evaluation; 17 did not have a signal detected with MCED-E (termed "discordant positives").
[b]Includes participants with analyzable results for MCED-E and MCED-Scr; three participants did not have analyzable results by both MCED tests.
MCED, multi-cancer early detection (-E, early test version; -Scr, test further refined for screening).
Clinical database lock: Mar 2021.

CONCLUSIONS

- In this interim analysis, a blood-based MCED test was safely administered and detected signal from a broad range of cancers
- Overall performance metrics were consistent between MCED-E and MCED-Scr with similar PPV and high accuracy of cancer signal origin prediction
  - MCED-Scr became available for use in May 2021 (Galleri™)
- Participants reported high satisfaction scores with MCED test use, as well as a negligible impact on attitudes about future compliance with established screening regimens
- Follow-up 12 months from MCED testing will allow for a final assessment of the diagnostic work-up and MCED test performance for both versions of the test

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Disclosures

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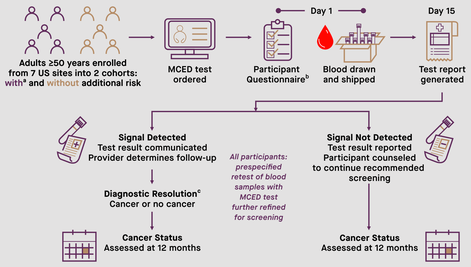
METHODS

Study Design

- 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 (**Figure 1**)

Figure 1. PATHFINDER STUDY DESIGN



[a]Previous history of cancer, smoking, and genetic risk; [b]Also collected at other timepoints during the study; [c]Defined as date when study team determines to end diagnostic evaluation triggered by a "signal detected" test result.
MCED, multi-cancer early detection.

- 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
  - Without Additional Risk: all other participants
- Cancer histories and staging were defined based on the American Joint Committee on Cancer (AJCC) Staging Manual version 8
- All blood samples were initially analyzed, reported, and results returned using an early version of the test (MCED-E)
  - MCED-E test results were returned to physicians and communicated to participants within approximately 30 days of blood draw
  - Participants with MCED-E 'cancer signal detected' result also received a cancer signal origin prediction and underwent diagnostic testing as directed by their medical team
- To optimize test performance, the study sponsor developed a refined version of the MCED test (MCED-Scr) based on data from other studies. Remaining blood specimens were reanalyzed with MCED-Scr; results were not returned with this test version

Primary Outcome: Extent of Diagnostic Testing

- Extent of testing required to achieve diagnostic resolution following a 'cancer signal detected' by MCED-E result is evaluated using the following 'per participant' endpoints for those who achieved diagnostic resolution:
  - Number of imaging tests, invasive tests, lab tests, clinical lab visits, clinic visits
  - Time required to achieve diagnostic resolution (number of days from when the test result is returned through the reporting portal to the date of diagnostic resolution)

Secondary Outcome: Test Performance Measures and Participant-Reported Outcomes

- Test performance measures for both MCED-E and MCED-Scr included:
  - Cancer signal detection rate
  - Positive predictive value [PPV] for cancer signal detection (proportion of participants with a cancer diagnosis among those with 'signal detected' results)
  - Accuracy of cancer signal origin prediction
- Assessment of participant satisfaction with MCED-E included a 3-item questionnaire
- Evaluation of participant's response to how likely they are to follow their healthcare provider's cancer screening recommendations

Analysis

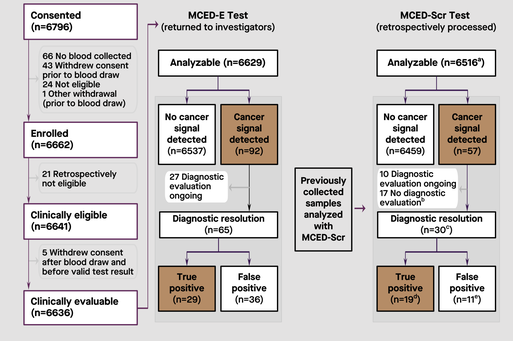
- Interim results are reported here, and follow-up for clinical diagnosis of cancer continues for 12 months after the blood draw
  - Additional participants may reach diagnostic resolution, and some currently categorized as not having cancer (false positive) may be found to have cancer
  - Final results will likely have higher number and types of tests, and time to diagnostic resolution
- Multiple calculations for PPV and accuracy of cancer signal origin prediction were performed
  - MCED-E: Included a calculation of overall PPV for cancer signal detection
  - MCED-Scr: Included a minimal PPV estimate for cancer signal detection assuming that all discordant positives (MCED-Scr positive/MCED-E negative) do not have cancer
  - Participants undergoing diagnostic evaluation who had not achieved resolution were excluded from PPV calculations
- Accuracy of signal origin prediction was assessed on participants with cancer diagnosis; participants with MCED-E 'indeterminate' signal origin or missing cancer type were excluded
- For participant-reported outcomes:
  - Total satisfaction score (ranging from 0 to 100 with higher scores representing higher satisfaction) was calculated across all questions. Descriptive statistics were provided for a total satisfaction score and individual question ratings
  - Attitude towards future cancer screening (pre- and post-test) was summarized descriptively by MCED test result. The proportion of MCED negative participants who changed their responses was reported

SUPPORTING DATA

Participant Disposition

- PATHFINDER consented 6796 participants between Dec 12, 2019 and December 4, 2020
- A total of 6662 were enrolled, and 6641 clinically evaluable participants were included in the interim analysis (63.5% female, 91.7% white, 24.7% with prior cancer); **Figure 5**
- Four study-related adverse events (3 anxiety and 1 bruise at venipuncture site, all mild severity) were reported

Figure 5. Trial Consort Diagram

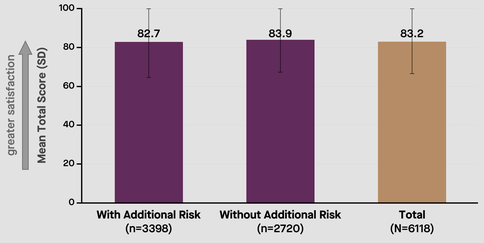


Blood samples were retrospectively processed with MCED-Scr. [a]120 assay results were not evaluable for MCED-Scr. [b]Due to "no cancer signal detected" MCED-E result. [c]Diagnostic resolution achieved based upon MCED-E test result. [d]Participants who had a cancer signal detected by MCED-E that was confirmed upon diagnostic resolution. [e]Participants who had a cancer signal detected by MCED-E that was not confirmed upon diagnostic resolution.
MCED, multi-cancer early detection (-E, early test version; -Scr, test further refined for screening).

Participant-Reported Outcomes

- Participants reported high test satisfaction (mean of 83.2 of 100-point scale; **Figure 6**)
- 96% of participants with "cancer signal not detected" were likely or very likely to follow their healthcare provider cancer screening recommendations both before and after MCED test; few participants (6%) changed their responses after the test result

Figure 6. Participant-Reported Outcomes With MCED-E: Total Satisfaction Questionnaire Score by Cohort (Secondary Endpoint)



Possible scores on the questionnaire ranged from 0 to 100, with higher scores indicating greater satisfaction. Satisfaction questionnaire was administered after diagnostic resolution for "Signal Detected" participants and post-test for "Signal Not Detected" participants. Excludes missing scores from 81 participants who did not complete a questionnaire.
MCED-E, multi-cancer early detection, early test version; SD, standard deviation. Clinical database lock: Mar 2021.