Expanding the Way We Screen for Cancer: A Path to a Multi-Cancer Early Detection Test

Academy of Oncology Nurse & Patient Navigators (AONN) Navigation & Survivorship Conference
November 17-21, 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; [7]Dana-Farber Cancer Institute, Boston, MA; [8]GRAIL, Inc., Menlo Park, CA

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

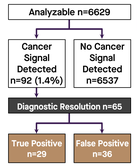
- Primary objective: assess the extent and types of diagnostic testing required to achieve diagnostic resolution following an MCED test result
- Secondary objectives, evaluate:
  - MCED test performance, including the positive predictive value (PPV) and the accuracy of cancer signal origin prediction
  - 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[b])
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[c]	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-MR, bone scan. [c]Anatomic imaging includes CT, MRI, ultrasound, mammography, plain film X-ray (including skeletal survey). [d]For the statistical analysis plan, minimally invasive describes procedures such as endoscopy, bone marrow biopsy, core biopsy, fine-needle aspiration, fiberoptic exam, pap smear and paracentesis. [e]Surgical procedures were performed, 0 in true positives, 1 in false positive set.
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[c] % (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.
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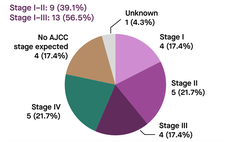
- Of true positive participants with information at time of analysis, 23/28 (82.1%) had a new cancer, and 5/28 (17.9%) had a recurrence. Of those with new cancer diagnoses, 13/23 (56.5%) were stage I-III, including 9 participants with stage I-II, and 4/23 (17.4%) were non-staged hematologic malignancies (**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)



[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.

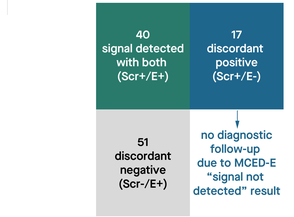
Test Performance: MCED-Scr

- 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 June 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

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 relationships 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

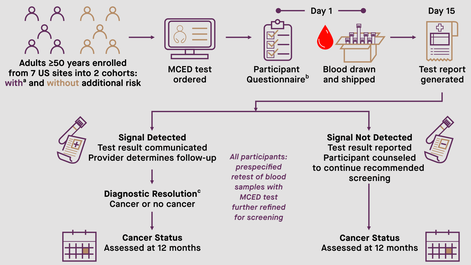
Funded by GRAIL, Inc. Writing and editorial assistance provided by Prescott Medical Communications Group (Chicago, IL).

METHODS

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

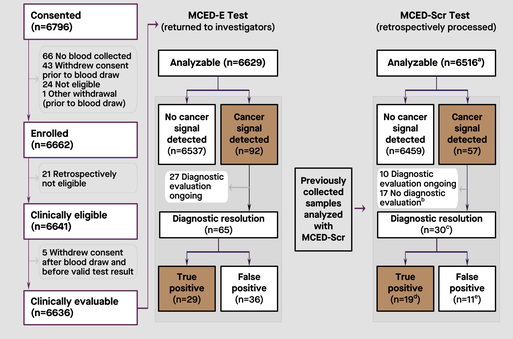
- Interim results are reported here, and follow-up for clinical diagnosis of cancer continues for 12 months after the blood draw
  - Additional participants may reach diagnostic resolution, and some currently categorized as not having cancer (false positive) may be found to have cancer
  - Final results 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

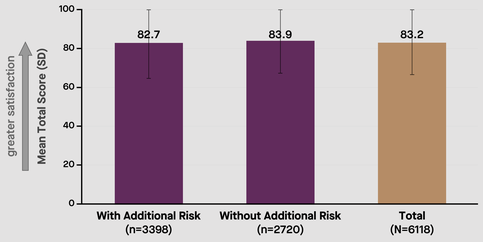


Blood samples were retrospectively processed with MCED-Scr. [a]120 assay results were not evaluable for MCED-Scr. [b]Due to "no cancer signal detected" MCED-E result. [c]Diagnostic resolution achieved based upon MCED-E test result.
[d]Participants who had a cancer signal detected by MCED-E that was confirmed 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.