A Prospective Study of a Multi-Cancer Early Detection Blood Test in a Clinical Practice Setting

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INTRODUCTION

- Early detection of cancers may reduce cancer-related morbidity and mortality, though only a few cancers have recommended screening options[1–4]
- Multi-cancer early detection (MCED) testing provides an expanded approach to cancer screening that could complement established methods as well as provide options for cancers that currently lack effective screening[5]
- The MCED test described here uses a targeted methylation, next-generation sequencing-based assay to:
  - Detect and analyze cell-free DNA (cfDNA) in the bloodstream
  - Deploy machine learning to detect a shared cancer signal
  - Predict the likely cancer signal origin (CSO; ie, tissue type where the cancer originated)

OBJECTIVES

- The PATHFINDER study (NCT04241796) evaluated use of MCED testing in an outpatient setting, including characterization of diagnostic journeys after a cancer signal was detected and test performance metrics (**Figure S1**)
- A prespecified analysis also evaluated performance of a test version that was further refined for screening (see also **Methods**)
- Participant reported outcomes and perceptions were also collected, and results are reported in the EDCC 2022 Schrag et al poster

KEY RESULTS: DIAGNOSTIC EVALUATIONS FOLLOWING A BLOOD-BASED MULTI-CANCER EARLY DETECTION TEST WERE OFTEN RESOLVED WITHIN 3 MONTHS, SUPPORTING FEASIBILITY IN ROUTINE OUTPATIENT PRACTICE

Cancer Signal Detection

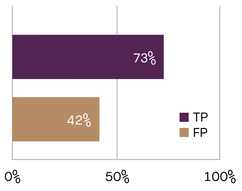
- Of 6621 participants with analyzable samples (99.9% of those with clinically evaluable samples), cancer signal was detected in 92 participants (1.4%), 91 reached diagnostic resolution, and 90 were evaluable for the primary outcome (**Figure S2**)

Extent of Diagnostic Testing (Time to Diagnostic Resolution, Number and Types of Procedures)

- Median observed time to diagnostic resolution was 79 days (IQR 37, 219; **Figure 1**)
  - True positives had a shorter median time to resolution (57 days) compared to false positives (162 days)
  - Most true positives (73%; 24/33) achieved resolution within 3 months
  - It is feasible that the time to diagnostic resolution may have been influenced by COVID-induced disruptions to healthcare access
- Most participants (92%; 83/90) had ≥1 imaging test
- Of the 90 participants with evaluation triggered by MCED testing, 49% (44/90) had ≥1 invasive procedure
  - Overall, 17/57 (30%) of false positives had invasive procedures; of those, 71% (12/17) had procedures prompted only by imaging/lab findings after the MCED test result or because of medical history risk
  - Only 4 surgical procedures were performed (3 in true positives; 1 in a false positive participant)

Figure 1. Time to 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)



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

Cancer Diagnoses in PATHFINDER

All Cancers Diagnosed Within One Year of MCED Testing

- **Table 1** summarizes characteristics of cancers diagnosed (in true positive and false negative participants)
  - A total of 121 participants were diagnosed with 122 cancers by the end of the study, including 36 cancers found via MCED testing

Table 1. Summary of Cancers Diagnosed

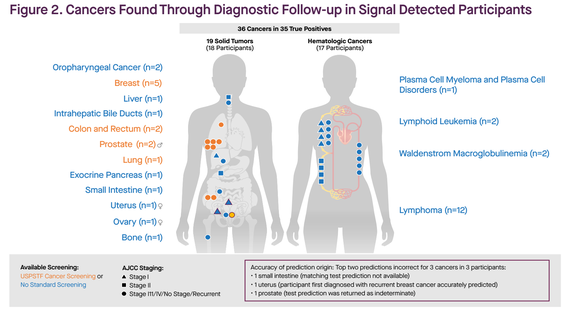
Cancer Type Diagnosed	Clinical AJCC Stage (New Cancers) I	II	III	IV	NA	Recurrent Cancers[a]	Total
No Cancer Signal Detected							
Solid Tumors	33	18	7	1	5	10	74
Hematologic Malignancies	3	1	0	1	6	1	12
Total	36	19	7	2	11	11	86
Cancer Signal Detected							
Solid Tumors	3	3	3	4	0	6	19b
Hematologic Malignancies	4	4	1	2	5	1	17
Total	7	7	4	6	5	7	36b

AJCC, the American Joint Committee on Cancer 8th edition Cancer Staging Manual; NA, not available or no AJCC stage expected.
[a]Local or metastatic.
[b]One participant was diagnosed with recurrent breast cancer and then with stage I uterine cancer.

Cancers Diagnosed After a True Positive MCED Signal

- 35 true positive participants were diagnosed with 36 cancers found by MCED testing (**Figure 2**)
  - 14 of 35 true positives (40%) had early-stage (Stage I or II) cancers
  - 26 of 36 diagnosed cancers (72%) lack standard screening

Figure 2. Cancers Found Through Diagnostic Follow-up in Signal Detected Participants



Test Performance

- MCED test performance is summarized in **Table 2** for both versions of the MCED test (version returned to physicians/participants and version further refined for use in a screening population that is commercially available [Galleri®])
  - Specificity was high, and positive predictive value was approximately 40% (**Table 2**)
  - Most true positive participants had an accurately predicted cancer signal origin (**Table 2**)

Table 2. Test Performance

	MCED Test Results Returned	Refined MCED Test Results Not Returned
PPV, n	35/92	25/58
% (95% CI)	38.0 (28.8-48.3)	43.1 (31.2-55.9)
NPV,[a] n	6235/6321	6216/6311
% (95% CI)	98.6 (98.3-98.9)	98.5 (98.2-98.8)
Specificity,[b] n	6235/6290	6216/6249
% (95% CI)	99.1 (98.9-99.3)	99.5 (99.3-99.6)
Yield, n	35/6621	25/6578
% (95% CI)	0.53 (0.36-0.71)	0.38 (0.23-0.53)
Number needed to screen, n	6621/35	6578/25
% (95% CI)	189 (140.87-275.88)	263.12 (187.94-438.53)
First Predicted Origin Correct,[c] n	29/34[d]	21/25
% (95% CI)	85.3 (69.9, 93.6)	84.0 (65.3, 93.6)
First or Second Predicted Origin Correct,[c,e] n	33/34 d	22/25
% (95% CI)	97.1 (85.1-99.8)	88.0 (70.0, 95.8)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value
[a]Denominators include all participants with no cancer signal detected and an end of study assessment.
[b]Denominators include all participants with no cancer diagnosis and an end of study assessment.
[c]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)
[d]Excludes 1 participant with indeterminate origin prediction from the true positive per study protocol.
[e]Proportion of first or second origin correctly predicted among true positive participants.

CONCLUSIONS

- A blood-based assay to screen for multiple cancer types prompted a diagnostic evaluation for 1.4% of adults and led to a cancer diagnosis for 0.5%. Specificity was high (99.1%), and positive predictive value was approximately 40%
- High accuracy of predicted origin enabled targeted diagnostic evaluations
- Most diagnostic evaluations involved imaging, few required invasive procedures
- Multi-cancer early detection was feasible in routine outpatient practice without significant adverse events

References

1. Search Results | United States Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/uspstf/search_results?searchterm=cancer.
2. DaCosta Byfield, S. et al. *J. Med. Econ.* 16, 1379–1386 (2013).
3. Croswell, J. M. et al. *Ann. Fam. Med.* 7, 212–222 (2009).
4. Ahlquist, D. A. *Npj Precis. Oncol.* 2, 23 (2018).
5. Clarke, C. A. et al. *Cancer Cell* 39, 447–448 (2021).

Disclosures

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

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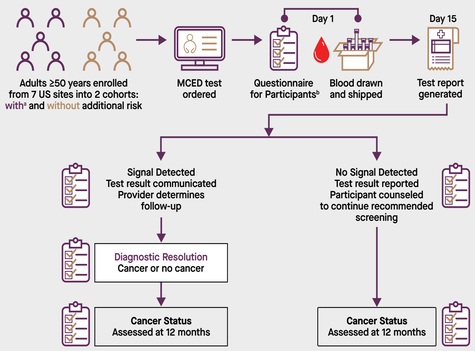
SUPPORTING INFORMATION

Methods

Study Design and Outcomes

- 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 S1**)
  - Participants were aged ≥50 y with or without additional cancer risk factors (smoking history, genetic predisposition, prior cancer diagnosis). cfDNA from blood samples was analyzed, and MCED test results were returned.
  - Cancer status was confirmed at 1 year from enrollment; those with a cancer signal detected and confirmed cancer were true positive, those without confirmed cancer were false positive. Participants without a cancer signal detected but with a cancer diagnosis were false negative
- The primary outcome was the extent of testing required to achieve diagnostic resolution following a 'cancer signal detected' result, including:
  - 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)
  - Number and types of imaging tests, invasive tests, lab tests, clinical lab visits, clinic visits
- Secondary measures included MCED test performance measures:
  - Cancer signal detection rate
  - Positive and negative predictive value (PPV, NPV) for cancer detection, specificity, yield rate, and number needed to screen (NNS)
  - Accuracy of CSO prediction (first or second CSO correctly identified)
- As part of the ongoing refinement of the MCED test, the study sponsor developed another version of the test further refined for screening. Banked specimens were reanalyzed with this refined test version in a prespecified analysis to evaluate test performance only; results were not returned to physicians/participants with this test version
- The refined MCED assay was intended to:
  - Reduce false positives with hematologic predictions
  - Improve prediction of the tumor origin
  - Refinements included:
    - Specificity threshold for hematologic signals was increased to reduce detection of pre-malignant heme proliferative conditions, and in turn, increase detectability of solid tumor signal
    - Removal of 'indeterminate' as a CSO and a maximum of two CSO predictions

Figure S1. Pathfinder Study Design



MCED, multi-cancer early detection.
[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.

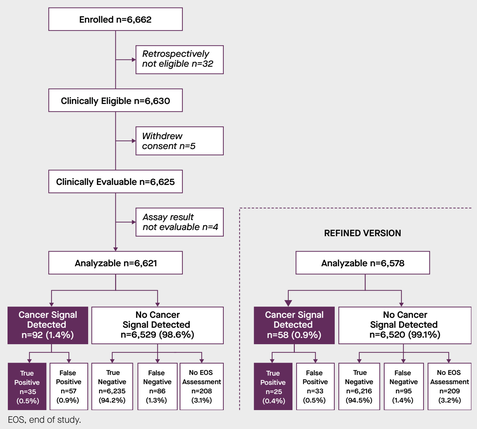
SUPPORTING DATA

- A total of 6662 participants were enrolled, 6625 were clinically evaluable, and 6621 had analyzable results (**Figure S2**)
- Participants were predominately white (92%) and highly educated (65% with college degrees), and fewer were current smokers (4.0%) compared to the general population. A quarter (24.5%) had a prior cancer history (**Table S1**)
- Adverse events were reported for 4 patients, 2 with events related to phlebotomy (anxiety and bruising at the venipuncture site) and 2 with anxiety reported before test results were returned
- There were no serious, study-related adverse events reported as a result of MCED testing or due to diagnostic workup prompted by receipt of a "signal detected" MCED test result

Table S1. Participant Demographics

	With Additional Risk[a] n = 3,681	Without Additional Risk n = 2,940	Total N = 6,621
Age (years)		≥50[b]	
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 Cancer Screening Prior to MCED Testing			
Colorectal Cancer Screening[c]	91%	92%	92%
Breast Cancer Screening[d]	78%	83%	80%

Figure S2. Participant Disposition



EOS, end of study.