REFLECTION: Initial Findings From a Real-World Evidence Study of Multi-Cancer Early Detection (MCED) and Toxic Exposures Among Veterans in the Veterans Affairs Healthcare System (VA)

Early Detection of Cancer Conference (EDCC)
October 22-24, 2024
San Francisco, California

Charles Atwood, MD[1]; Si-yuen Moy, MD[2]; Mark S. Kindy, PhD[3]; Lynn M. Keenan, MD[4]; Jason L. Vassy, MD[5]; Nancy Vander Velde, MD[6]; Michelle Griffith, MA[7]; Cheng Chen, PhD[7]*; Jeffrey Venstrom, MD[7]*; Diana SM Buist, PhD[7]*; Greg Holt, MD, PhD[8]
[1]VA Pittsburgh Healthcare System; [2]VA Wilkes-Barre Healthcare System; [3]VA Tampa Healthcare System; [4]VA Salt Lake City Healthcare System; [5]VA Boston Healthcare System; [6]VA New Orleans Healthcare System; [7]GRAIL, Inc.; [8]VA Miami Healthcare System
*At time of study

INTRODUCTION

- Veterans may experience high rates of service-related toxic exposures and thus are at risk for developing adverse health outcomes, including several cancers[1-3]
- A multi-cancer early detection (MCED) test, Galleri® (GRAIL, Inc., Menlo Park, CA), uses targeted methylation sequencing of cell-free DNA in the bloodstream paired with machine learning algorithms to detect a cancer signal and predict a cancer signal origin (CSO)[4-6]
- When added to standard-of-care screening, MCED blood tests may address unmet medical needs, as >70% of cancer deaths are from cancers that do not have population-based screening strategies[7]
- The REFLECTION study (NCT05205967) aims to understand the real-world experience of using the MCED test in routine clinical settings

OBJECTIVE

- To evaluate cancer signal detection and cancer outcomes in veterans with 180 days of follow-up after the MCED test result, in a preliminary analysis of the ongoing REFLECTION study

KEY RESULTS: CANCER SIGNAL DETECTION RATE AND 6-MONTH PPV IN THIS COHORT OF VETERANS WERE CONSISTENT WITH OTHER CLINICAL STUDIES OF THE MCED TEST WITH UP TO 1 YEAR OF FOLLOW-UP

Participants

- As of April 26, 2024, a total of 2924 veterans were enrolled in the REFLECTION study through 7 Veterans Affairs Healthcare System (VA) sites (**Figure S1**); of these, 2854 are currently analyzable (**Figure S2**)
  - VA sites had different underlying demographics and leveraged different recruitment strategies involving primary care, specialty care, advertisements, targeted mailed letters, the VA Lung Precision Oncology Program, and a women's health clinic
- Overall characteristics of the cohort are shown in **Table 1**
  - Among the 2057 participants with data on environmental exposure, 70% reported exposure to one or more toxic environmental hazard

Table 1. Characteristics of the VA Cohort

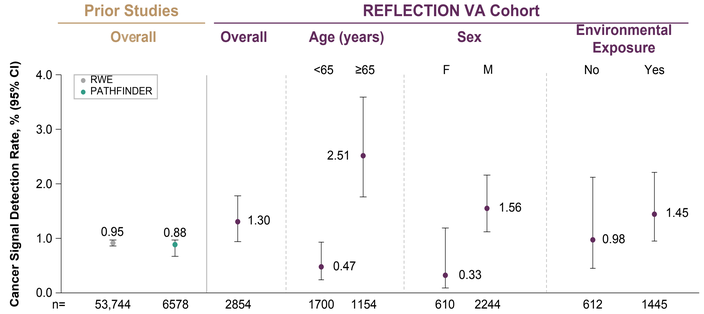
	VA Cohort (N=2854)
Age, median (Q1-Q3), years	62.0 (51.0-71.0)
Participants Aged ≥65 years, n (%)	1154 (40.4)
Male, n (%)	2244 (78.6)
BMI, mean (SD), kg/m², N=2843	29.7 (5.7)
Race, n (%)	
American Indian or Alaska Native	11 (0.4)
Asian, Native Hawaiian, or Pacific Islander	32 (1.1)
Black or African American	605 (21.2)
White	2087 (73.1)
Mixed Race	42 (1.5)
Missing	77 (2.7)
Ethnicity, n (%)	
Hispanic or Latino	410 (14.4)
Not Hispanic or Latino	2269 (79.5)
Missing	175 (6.1)
Smoking Status, n (%)	
Current	476 (16.7)
Former	1205 (42.2)
Never	1164 (40.8)
Missing	9 (0.3)
Prior History of Cancer, n (%)	400 (14.0)
Self-Reported First-Degree Relative With History of Cancer, n (%)	1666 (58.4)
Self-Reported Environmental or Occupational Toxic Exposures (participants marked all that apply), n (%)[a]	
Any Exposure, N=2057	1445 (70.3)
Open Burn Pits/Airborne Hazards, N=2011	746 (37.1)
Gulf War-Related Exposures, N=2011	221 (11.0)
Agent Orange, N=2011	319 (15.9)
Radiation, N=2011	235 (11.7)
Contaminated Water at Camp Lejeune, N=2011	147 (7.3)
Other, N=2016	473 (23.5)

[a]Percentages were calculated based on participants with available exposure data.
BMI, body mass index; VA, Veterans Affairs Healthcare System.

Cancer Signal Detection Rate

- The overall cancer signal detection rate was 1.30% (95% CI: 0.94 - 1.78%; 37/2854 participants) (**Figure 1**)
  - The point estimate is higher than what has been observed in other populations who received the MCED test (0.88%[6] [0.68 - 1.14%] and 0.95%[8] [0.87–1.09%])
  - The higher crude rates in those aged ≥65 years and males are largely driven by the older men in this cohort, which could be a confounding factor. However, in a multivariable-adjusted logistic regression model, the following factors remained associated with higher odds of having a cancer signal detected (CSD) test result:
    - Age ≥ 65 years
    - Male gender
    - Self-reported first-degree relative with a history of cancer
- The crude cancer signal detection rate varied greatly across the 7 VA sites, ranging from 0% to 8.70%, although the largest variation was seen in sites with small numbers of participants. Among sites with >100 participants, the range was 0.6% to 2.2%

Figure 1. Variation in Cancer Signal Detection Rate by Population and VA Cohort Subgroups

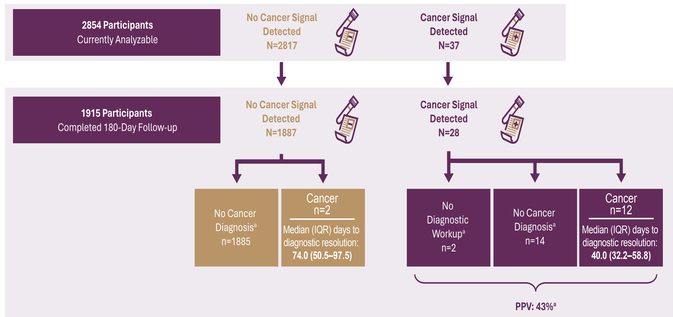


RWE[1]; PATHFINDER[6] (Supplementary appendix, data for the refined MCED test version).
CI, confidence interval; F, female; M, male; MCED, multi-cancer early detection; RWE, real-world evidence; VA, Veterans Affairs Healthcare System.

MCED Test Performance

- The distribution of the most common CSO predictions for the 37 participants with a CSD test result was lung (n=7), breast (n=5), stomach/esophagus, lymphoid lineage, colon/rectum (n=4 each), and prostate (n=3)
- Of the 37 participants with a CSD test result, 28 had 180 days of follow-up after the MCED test result, and of these, 12 participants were diagnosed with cancer (**Figure 2**)
- The 6-month positive predictive value (PPV; 42.9% [95% CI: 26.5 - 60.9%]) observed in this cohort is comparable to PPVs from prior clinical studies of this test with up to 1 year of follow-up (44.4% [28.6 - 79.9%][5] and 43.1% [31.2 - 55.9%][6])
- Two participants with no CSD (NCSD) were diagnosed with cancer (false negatives [FNs])
  - These cancers were new, non-recurrent stage III colorectal and stage non-informative liver cancers. The colorectal cancer was detected by a cancer screening exam, likely routine colonoscopy, while the liver cancer was detected by reported signs and symptoms.
- The median time from MCED test result to cancer diagnosis was 40 days (interquartile range: 32 - 59 days) for true positives (TPs) and 74 days (interquartile range: 51 - 98 days) for FNs

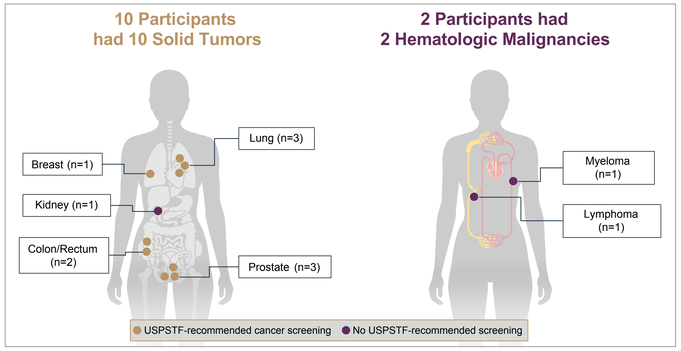
Figure 2. Clinical Status at 180 Days of Follow-Up After the MCED Test Result



[a]Based on participants with complete 180 days of follow-up after the MCED test result; additional cancers may be diagnosed during the remainder of the one-year follow-up period.
IQR, interquartile range; MCED, multi-cancer early detection; PPV, positive predictive value.

- Of the 12 diagnosed cancers following a CSD test result (**Figure 3**), the most common were lung and prostate (n=3 for both)
  - 11 (91.7%) participants had new, non-recurrent cancer (1 with unknown recurrence status)
  - Of cases with reported stage, 54.5% (6/11) were detected at stages I–III and the remaining at stage IV

Figure 3. A Variety of Cancers Were Diagnosed Within 180 Days of a CSD MCED Test Result



CSD, cancer signal detected; USPSTF, US Preventive Services Task Force.

CONCLUSIONS

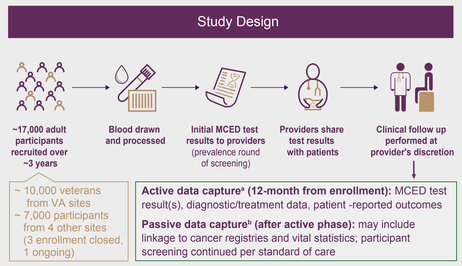
- REFLECTION has successfully recruited a diverse population of veterans with a broad range of toxic exposures
- The cancer signal detection rate was consistent with observations in other populations who received the MCED test[6,8]
- The MCED test had a high PPV for cancer signal detection that was consistent with other clinical studies of this test;[5,6] the PPV in this preliminary analysis may be underestimated as additional cancers may be diagnosed during the remainder of the one-year follow-up period
- Longer-term data will provide cancer outcomes and veteran-reported experience with MCED testing (eg, SF-12v2 Health Survey, Cancer Worry Scale, parameters related to attitudes about the MCED test), which will provide additional insights for veterans with service-related toxic exposures

METHODS

Study Design

- REFLECTION is a multicenter, prospective, non-interventional, cohort study of the real-world experience of the MCED test in clinical settings (October 2022 – ongoing)[9] (**Figure S1**)
- VA Cohort: Recruitment of veterans aged ≥22 years in the VA who opted to be screened with the MCED test; current analysis includes data through April 26, 2024 from 7 VA sites (participants with 180 days of follow-up after the MCED test result)

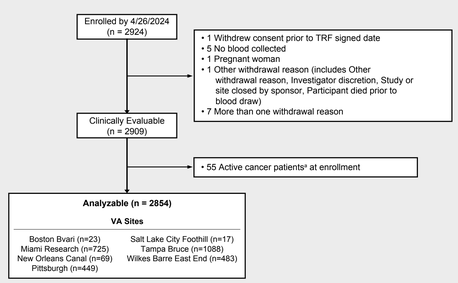
Figure S1. REFLECTION Study Design



[a]Patients are actively followed through medical record data collection and self-reported questionnaires administered pre-test, post-test (for a subset), 6-months (for a subset) and 12-months post consent. [b]Patients may be passively followed through linkages to cancer registries and other administrative health databases up to time of death, loss to follow-up, withdrawal of informed consent, or per institutional guidelines on duration of data collection, whichever occurs sooner.MCED, multi-cancer early detection.

- Cancer signal detection rates were estimated by 100% × (CSD) / (total number of participants tested by the MCED test)
- Using a multivariable-adjusted logistic regression model, the odds of signal detection were reported with the adjustment for age, sex, race/ethnicity, smoking status, alcohol use history, prior cancer history and screening history, BMI, family cancer history, and environmental or occupational exposures; missing data was handled as a separate category.
- PPV for those with 180 days of follow-up after the MCED test result was estimated by 100% × (TP) / (CSD [including those without any follow-up diagnostic work-up])

Figure S2. VA Cohort Disposition



[a]Defined as having a prior cancer history within 12 months of when the initial Galleri TRF was signed by a provider.
TRF, test requisition form; VA, Veterans Affairs Healthcare System.

References

1. Jester DJ et al. *Front Oncol*. 2024 Mar 13;14:1356001. **2.** Chemical or hazardous material exposure. US Department of Veterans Affairs. **3.** Military Burn Pits and Cancer Risk. American Cancer Society. **4.** Liu MC et al. *Ann Oncol*. 2020;31(6):745-759. **5.** Klein EA et al. *Ann Oncol*. 2021;32(9):1167-1177. **6.** Schrag D et al. *Lancet*. 2023;402(10409):1251-1260. **7.** Cancer Facts & Figures 2022. American Cancer Society. **8.** Westgate C et al. Poster presented at American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, IL. **9.** Gordon OK, et al. Poster presented at American Academy of Family Physicians (AAFP) FMX Scientific Informational eDisplays; September 28-October 2, 2021. Abstract: 11987.

Disclosures

Study funded by GRAIL, Inc. MG, CC, JV, and DB are current or former employees of GRAIL, Inc. and may have equity in the company. The other authors declare no conflicts of interest.

Acknowledgments

Funded by GRAIL, Inc. Writing, editorial, and graphic assistance provided by Prescott Medical Communications Group, a Citrus Health Group, Inc. company (Chicago, IL).