REFLECTION: Real-World Evidence Study of Multi-Cancer Early Detection (MCED) Among Veterans in the Veterans Affairs Healthcare System (VA)

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INTRODUCTION

- 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)[1-3]
- 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[4]
- 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 status in veterans with 1 year of follow-up after their MCED test result, in a preliminary analysis of the Veterans Affairs (VA) cohort of the ongoing REFLECTION study

KEY RESULTS: 1-YEAR PPV IN THIS COHORT OF VETERANS WAS CONSISTENT WITH OTHER CLINICAL STUDIES OF THE MCED TEST WITH UP TO 1 YEAR OF FOLLOW-UP

Participants

- As of June 30, 2024, a total of 3587 veterans were enrolled in the REFLECTION study through 7 VA Healthcare System sites (**Figure S1**); of these, 3355 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**

Table 1. Characteristics of the VA Cohort

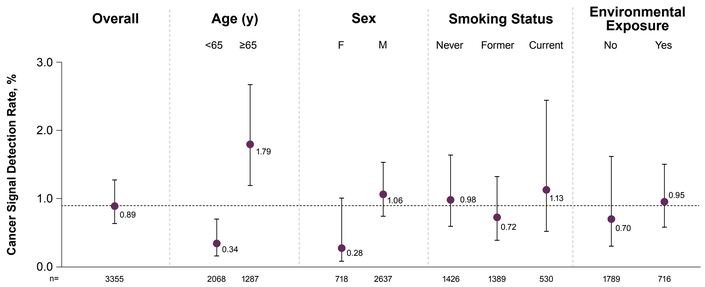
	VA Cohort (N=3355)
Age, median (IQR), y	61.0 (50.0-70.0)
Participants Aged ≥65 y, n (%)	1287 (38.4)
Male, n (%)	2637 (78.6)
BMI, mean (SD), kg/m², n=3334	29.7 (5.6)
Race, n (%)	
American Indian or Alaska Native	15 (0.4)
Asian, Native Hawaiian, or Pacific Islander	44 (1.3)
Black or African American	690 (20.6)
White	2465 (73.5)
Mixed Race	53 (1.6)
Missing	88 (2.6)
Ethnicity, n (%)	
Hispanic or Latino	489 (14.6)
Not Hispanic or Latino	2618 (78.0)
Missing	248 (7.4)
Smoking Status, n (%)	
Current	530 (15.8)
Former	1389 (41.4)
Never	1426 (42.5)
Missing	10 (0.3)
Prior History of Cancer, n (%)	361 (10.8)
First-Degree Relative With History of Cancer, n (%)	1925 (57.4)

BMI, body mass index; IQR, interquartile range; SD, standard deviation; VA, Veterans Affairs Healthcare System; y, years.

Cancer Signal Detection Rate

- The overall cancer signal detection rate was 0.89% (95% CI: 0.63-1.27%; 30/3355 participants) (**Figure 1**)
  - Cancer signal detection rates were lower in female participants than in male participants, consistent with the younger female age mix (≥65 years: 23% vs 43%) and the generally higher cancer incidence in men than women, especially at older ages[5]
- The cancer signal detection rate varied greatly across the 7 VA sites, ranging from 0% to 5.0%, although the largest variation was seen in sites with small numbers of participants. Among sites with >200 participants, the range was 0.4% to 2.1%

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

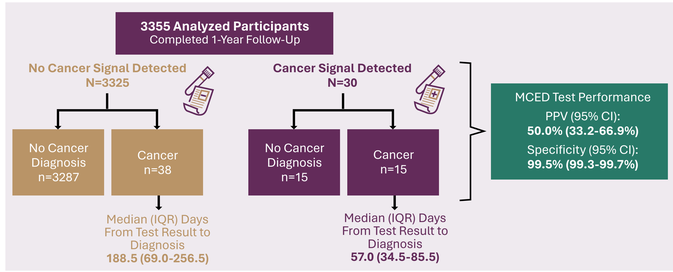


The horizontal line denotes the overall cancer signal detection rate in the REFLECTION VA Cohort. Error bars denote the 95% confidence interval.
F, female; M, male; VA, Veterans Affairs Healthcare System.

MCED Test Performance

- The distribution of the most common CSO predictions for the 30 participants with a cancer signal detected (positive) MCED test result were lung (n=6), stomach/esophagus (n=4), breast (n=4), prostate (n=3), lymphoid lineage (n=3), head and neck (n=3), and colon/rectum (n=3)
- Of the 30 participants with a positive MCED test result, 15 were diagnosed with cancer (**Figure 2**)
- The 1-year positive predictive value (PPV) of 50.0% (95% CI: 33.2-66.9%) observed in this cohort is comparable to PPVs from prior clinical studies of this MCED test with up to 1 year of follow-up (44.4% [28.6-79.9%],[2] 43.1% [31.2-55.9%],[3] and 61.6% [54.9-67.8%][6])
- Specificity observed in this cohort was 99.5% (95% CI: 99.3-99.7%) and consistent with prior clinical studies of this MCED test (99.5% [99.0-99.8%],[2] 99.5% [99.3-99.6%],[3] and 99.6% [99.5-99.7%][6])
- Of the 3325 participants with a no cancer signal detected (negative) MCED test result, 38 were diagnosed with cancer (false negatives)
  - Most of these cancers were prostate (42.1%; 16/38) or lung (21.1%; 8/38), for which recommended screenings exist for eligible populations
- The median time from MCED test result to cancer diagnosis was 57.0 days (interquartile range: 34.5-85.5 days) for true positives and 188.5 days (interquartile range: 69.0-256.5 days) for false negatives

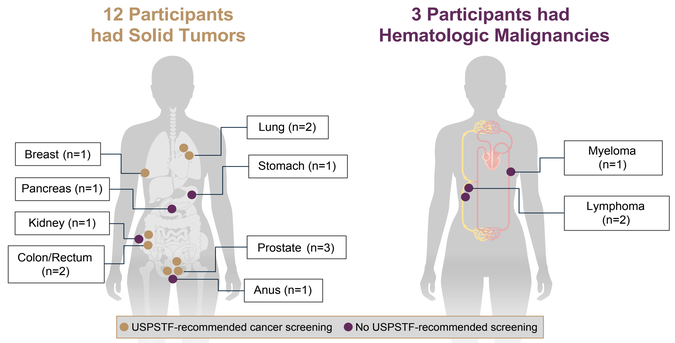
Figure 2. Clinical Status at 1 Year of Follow-Up After the MCED Test Result



CI, confidence interval; IQR, interquartile range; MCED, multi-cancer early detection; PPV, positive predictive value.

- Of the 15 diagnosed cancers following a positive MCED test result (**Figure 3**), the most common were prostate (n=3), lung (n=2), colon/rectum (n=2), and lymphoma (n=2)
  - CSO prediction accuracy based on the first or second CSO was 93.3% (14/15)
  - 14 (93.3%) participants had new, non-recurrent cancer (1 had unknown recurrence status)
  - Of cases with reported stage, 57.1% (8/14) were detected at stages I–III and the remaining at stage IV

Figure 3. A Variety of Cancers Were Diagnosed Within 1 Year of a Positive MCED Test Result



USPSTF, US Preventive Services Task Force.

CONCLUSIONS

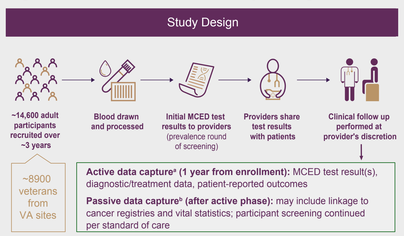
- REFLECTION has successfully recruited a diverse population of veterans
- The MCED test had a high CSO prediction accuracy, specificity, and PPV for cancer signal detection that was consistent with other clinical studies of this test[2,3,6]
- Longer-term data will provide cancer outcomes (status, type, and stage) and veteran-reported experience with MCED testing (eg, SF-12v2 Health Survey, Cancer Worry Scale, parameters related to attitudes about the MCED test)

METHODS

Study Design

- REFLECTION is a multicenter, prospective, noninterventional, cohort study of the real-world experience of the MCED test in clinical settings (October 2022 – ongoing)[7] (**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 June 30, 2024 from 7 VA sites
  - Participants had 1 year of follow-up after the MCED test result and no active cancer or history of prior cancer within 3 years of the MCED test

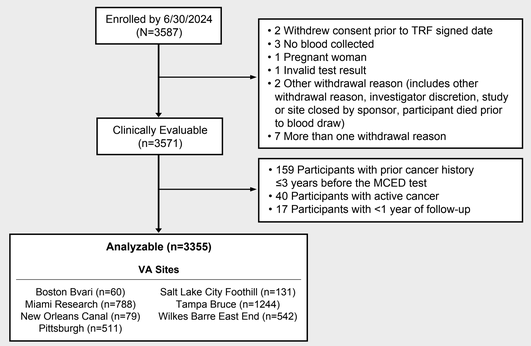
Figure S1. REFLECTION Study Design



[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 1 year 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; VA, Veterans Affairs Healthcare System.

- Cancer signal detection rates were estimated by 100% × (cancer signal detected) / (total number of participants tested by the MCED test)
- PPV for those with 1 year of follow-up after the MCED test result was estimated by 100% × (true positives) / (cancer signal detected [including those without any follow-up diagnostic work-up])
- Specificity was estimated by 100% × (true negatives) / (true negatives + false positives)
- CSO predictions were considered accurate when the first or second CSO matched the diagnosed cancer type

Figure S2. VA Cohort Disposition



MCED, multi-cancer early detection; TRF, test requisition form; VA, Veterans Affairs Healthcare System.

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Disclosures

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