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Early Real-World Experience With a Multi-Cancer Early Detection Test

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INTRODUCTION

- Approximately 70% of deaths in the US among those 50-79 years of age are caused by cancers without recommended screening[1]
- Recent technological advances in genome sequencing and machine learning have facilitated development of blood-based multi-cancer early detection (MCED) tests intended to complement single-cancer screening tests[2]
- An MCED test intended for detecting a shared cancer signal across multiple cancers, including those without recommended screening, in individuals with an elevated risk of cancer, such as those aged 50 or older, has been available as a validated lab developed test since April 2021[3-5]
  - When a cancer signal is detected, a "cancer signal detected" (CSD) result is reported with a cancer signal origin (CSO) prediction, a critical aspect of MCED tests that directs diagnostic evaluation
- Examining real-world experience with the MCED test across age, sex, and geographic location can demonstrate how the MCED test is adopted and performs in the real-world setting
  - This is the first time populations have been tested with an MCED test and the observations are influenced by the backlog of undiagnosed cancers in the population

OBJECTIVES

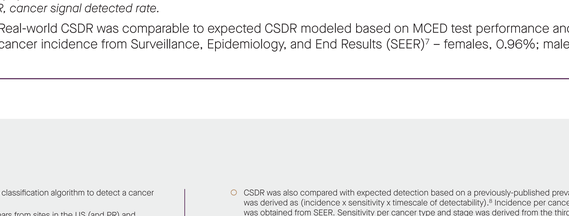
- To report real-world experience with the initial 53,744 MCED tests delivered
- To compare real-world results to those observed in the prospective, return-of-results PATHFINDER study[6]

REAL-WORLD MCED TEST PERFORMANCE IS AS EXPECTED AND CONSISTENT WITH PREVIOUS CLINICAL STUDIES

Population Characteristics

- Mean (standard deviation) age of the tested population was 58.9 (11.7) years for females (n=24,016) and 59.2 (12.0) years for males (n=29,728) (**Figure 1A**)
- Tests were ordered and processed from across all US states (including DC and PR) (**Figure 1B**)

Figure 1. Population Characteristics. (A) Age Distribution by Sex, and (B) Geographical Distribution of Test Orders



Analytical Performance

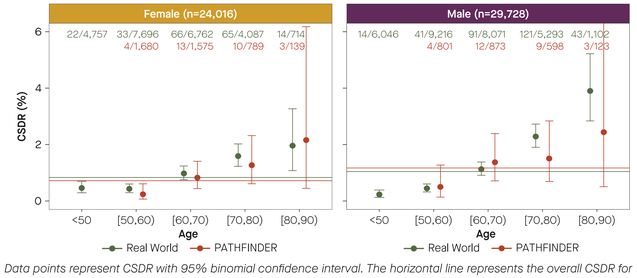
- Results were returned for >98% of MCED tests that were ordered, with a mean turnaround time of 6.7 business days

Clinical Performance

Cancer Signal Detected Rate (CSDR)

- The real-world CSDR was 0.95% (95% CI, 0.87–1.0; 510/53,744)
- Real-world CSDR was lower in females (0.8% [0.7–1.0; 200/24,016]) vs males (1.0% [0.9–1.2; 310/29,728]) (**Figure 2**)
- Real-world CSDR increased with age, which as expected was a significant predictor of CSDR ($p < 1e-13$) (**Figure 2**)
- Real-world CSDR was consistent with PATHFINDER
  - In PATHFINDER, CSDR was lower in females 0.7% (0.5–1.0) vs males 1.2% (0.8–1.7), and increased with age ($p<0.001$) (**Figure 2**)

Figure 2. CSDR in the Real World and PATHFINDER by Age in Females and Males



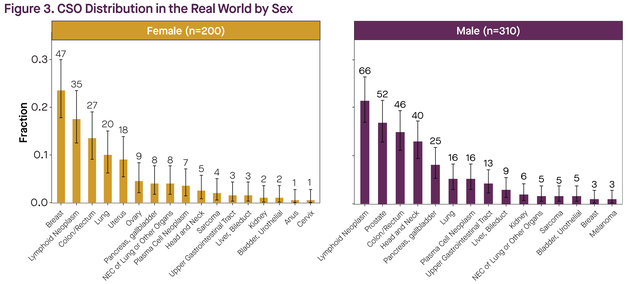
Data points represent CSDR with 95% binomial confidence interval. The horizontal line represents the overall CSDR for each population.
CSDR, cancer signal detected rate.

- Real-world CSDR was comparable to expected CSDR modeled based on MCED test performance and cancer incidence from Surveillance, Epidemiology, and End Results (SEER)[7] – females, 0.96%; males, 1.1%

CSO Predictions

- The distribution of all CSOs in the real world by sex is presented in **Figure 3**

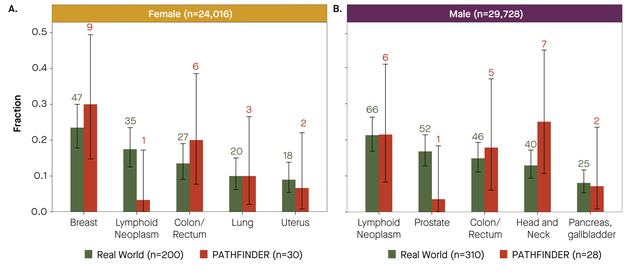
Figure 3. CSO Distribution in the Real World by Sex



Height of bars represents the fraction of given CSO prediction of all CSO predictions with 95% binomial confidence interval. Numbers above bars indicate number of given CSO prediction.
CSO, cancer signal origin; NEC, neuroendocrine cells.

- In females, the five most common CSO predictions were breast (24% [47/200]), lymphoid neoplasm (18% [35/200]), colon/rectum (14% [27/200]), lung (10% [20/200]), and uterus (9% [18/200]) (**Figure 4A**)
- In males, the five most common CSO predictions were lymphoid neoplasm (21% [66/310]), prostate (17% [52/310]), colon/rectum (15.0% [46/310]), head/neck (13% [40/310]), and pancreas/gallbladder (8.0% [25/310]) (**Figure 4B**)
- Comparison with PATHFINDER
  - Most common CSO predictions were consistent to those observed in PATHFINDER (**Figure 4A and 4B**) with PATHFINDER having a potentially lower proportion of lymphoid neoplasm predictions in females and prostate in males. A detailed comparison is limited by the relatively smaller number of participants and consequently smaller number of detected cases and predicted CSOs in PATHFINDER (females, n=30; males, n=28), as well as differences between a real-world and controlled study population based on age and risk profile

Figure 4. Distribution of Five Most Common CSOs in the Real World and PATHFINDER in Females and Males



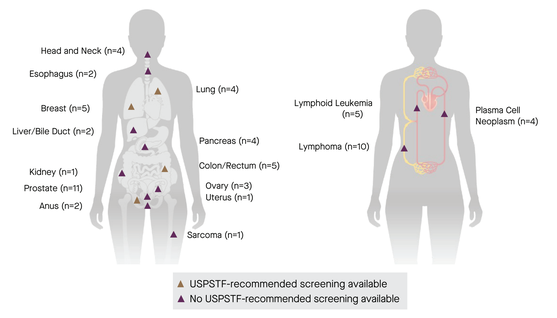
Height of bars represents the fraction of given CSO prediction of all CSO predictions with 95% binomial confidence interval. Numbers above bars indicate number of given CSO prediction.
CSO, cancer signal origin.

- In the real-world population, in both males and females, approximately two-thirds of CSO predictions were associated with cancers without recommended population screening
- CSO distribution is dependent on the distribution of cancer types in the sampled population. The observed early real-world use of the MCED test has been skewed toward a high health care utilizer population, which tends to be healthier than the general population. Thus, the CSO distribution is not expected to match what is observed in the population reflected in SEER
  - For example, lower rates of lung CSO prediction could be attributed to lower incidence of lung cancer in a largely healthy, well-screened, non-smoking population that are likely to be the early adopters of the MCED test
  - Additionally, higher than expected rate of lymphoid CSO prediction could be attributed to the prevalence round of screening – lymphoid cancers having longer than average dwell times leading to several years of incidence being detected the first time a population is screened

Clinical Outcomes

- Early clinical outcomes data from a controlled quality assurance (QA) program showed that a CSD result with a CSO prediction was associated with a diagnosis of invasive cancer across multiple cancer types, including early-stage cancers and cancers without recommended screening (**Figure 5**)
- Follow-up though the QA program has been attempted for all individuals with a CSD result and at least 3 months since the test result
  - 72 individuals have a confirmed invasive cancer diagnosis (age range, 25–87 years; male, 61%)
  - 80 individuals have no invasive cancer diagnosis at the time of reporting, additional follow-up is ongoing
  - 358 individuals remain under review
  - We are pursuing follow-up to determine cancer status for all individuals with CSD, as positive predictive value cannot be computed until cancer status has been established for this cohort
- Importantly, of the cases with reported stage (n=38/72), 32% (12/38) were detected at stages I/II, and 61% (23/38) were detected at stages I/II/III
- Cancers diagnosed among the 72 individuals included prostate (n=11), lymphoma (n=10), breast (n=5), colon/rectum (n=5), lymphoid leukemia (n=5), head and neck (n=4), lung (n=4), pancreas (n=4), plasma cell neoplasm (n=4), ovary (n=3), anus (n=2), esophagus (n=2), liver/bile-duct (n=2), kidney (n=1), sarcoma (n=1), uterus (n=1), and cancer type unavailable (n=8); most of these cancer types lack recommended screening tests (**Figure 5**)
- Notably, CSO prediction accuracy of cases with confirmed cancer diagnoses was high (91%; 59/65). It was consistent with PATHFINDER (84%) and the large-scale clinical validation Circulating Cell-Free Genome Atlas (CCGA) study (89%)

Figure 5. Cancer Diagnoses in Individuals who took the MCED Test



MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.

METHODS

- The cell-free DNA-based MCED test uses a targeted methylation assay and a machine learning classification algorithm to detect a cancer signal and predict CSO
- This report includes tests returned from 04/20/2021 to 12/31/2022 on individuals aged ≥22 years from sites in the US (and PR) and excludes tests from clinical studies, repeat tests, and sites limiting external data sharing
- Lab analytical performance in terms of percent test results returned and turnaround time were evaluated
- Performance in terms of CSDR and CSO prediction patterns was evaluated
  - In order to assess CSDR with age, logistic regression was performed with CSD as a binary response variable and age, sex, and age*sex interaction terms as linear predictor variables
  - Performance was compared to performance in PATHFINDER, a prospective cohort study (NCT04241796) that enrolled 6,662 participants to assess the feasibility of implementing the MCED test in outpatient settings for adults without symptoms of cancer aged ≥50 years[6]
  - CSDR was also compared with expected detection based on a previously-published prevalence model, where expected detection was derived as (incidence x sensitivity x timescale of detectability).[8] Incidence per cancer type and stage by year of age and sex was obtained from SEER. Sensitivity per cancer type and stage was derived from the third and final CCGA validation substudy of MCED test performance.[5] The timescale of detectability was assumed to be 1 year for all cancer types and stages
- Systematic collection of outcomes for cases with a CSD result was completed for a subset and continues via a small-scale, controlled QA program to monitor MCED testing in a real-world population. As part of the QA program, we follow up on CSD results by contacting ordering physicians (90 days or more after result) and capturing cancer outcomes. Currently, "cancer signal not detected" (CSND) results are recorded when spontaneously reported by the ordering physician. In the current report, we report on the subset of CSD results with a confirmed cancer diagnosis
  - All collected outcomes data was certified as statistically de-identified by an external privacy expert

CONCLUSIONS

- Real-world experience with the MCED test is as expected and consistent with previous large-scale clinical studies with an average CSDR of 0.95%, which increases with age
- The MCED test is able to detect a cancer signal from early-stage cancers and cancers without recommended screening and is able to predict CSO with high accuracy
- This data supports use of the MCED test at a population screening level

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