Performance of a Multi-Cancer Early Detection (MCED) Test in Adults Aged ≥65 Years: Results From the PATHFINDER 2 Study

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INTRODUCTION

- Because the cumulative risk of cancer increases with age,[1] cancer is an important clinical concern for adults aged ≥65 years, who comprise the majority of the Medicare population in the US
  - Cancer screening with an MCED test may be beneficial for this increasingly large age demographic
- Galleri® (GRAIL, Inc.) is an MCED test that detects a shared cancer signal in cell-free DNA and predicts the cancer signal origin (CSO) to guide diagnostic evaluation
- This MCED test has previously demonstrated robust performance in both case-control and interventional (return of results) studies[2–4]
- The PATHFINDER 2 study was designed to expand clinical evidence for the MCED test in a large and diverse intended-use population[5,6]

OBJECTIVE

- To describe MCED test performance in PATHFINDER 2 participants aged ≥65 years at enrollment

KEY RESULTS: IN PARTICIPANTS AGED ≥65 YEARS, THE MCED TEST DEMONSTRATED HIGH SPECIFICITY, PPV, AND CSO PREDICTION ACCURACY AND DETECTED CANCER TYPES WITH AND WITHOUT GUIDELINE-RECOMMENDED SCREENING

Demographics and Baseline Characteristics

- Of 35,878 participants enrolled in the PATHFINDER 2 study, 35,350 participants were analyzable, of whom 17,284 (48.9%) were aged ≥65 years (**Table 1**)
  - In this subset, 53.4% were female, and 11.9% had a prior cancer history
  - A total of 15,953 (92.3%) participants aged ≥65 years completed a 12-month cancer status assessment and were included in the performance analyzable set

Table 1. Baseline Characteristics of PATHFINDER 2 Participants Aged ≥65 Years and the Overall Analyzable Population.[a]

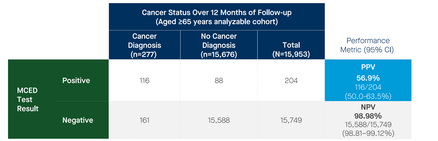
	Aged ≥65 years (N = 17,284)	All Analyzable Participants[b] (N = 35,350)
Age (years)		
Median (Q1, Q3)	70.0 (67.0, 74.0)	64.0 (58.0, 70.0)
Age group, n (%)		
50–64 years	0	18,066 (51.1)
65–79 years	16,300 (94.3)	16,300 (46.1)
≥80 years	984 (5.7)	984 (2.8)
Sex, n (%)		
Female	9235 (53.4)	19,877 (56.2)
Ethnicity (self-reported), n (%)		
Hispanic or Latino	849 (4.9)	2632 (7.4)
Not Hispanic or Latino	16,217 (93.8)	32,274 (91.3)
Missing	218 (1.3)	444 (1.3)
Race (self-reported),[c] n (%)		
American Indian or Alaska Native only	98 (0.6)	246 (0.7)
Asian only	650 (3.8)	2091 (5.9)
Black or African American only	1322 (7.6)	3105 (8.8)
Native Hawaiian or other Pacific Islander only	32 (0.2)	80 (0.2)
White only	14,679 (84.9)	28,321 (80.1)
>1 race reported	186 (1.1)	474 (1.3)
Missing	317 (1.8)	1033 (2.9)
Highest education level, n (%)		
Bachelor's degree or higher	9942 (57.5)	20,803 (58.8)
Prior cancer history,[d] n (%)	2064 (11.9)	3264 (9.2)
Smoking status		
Currently smokes	537 (3.1)	1308 (3.7)
Formerly smoked	5691 (32.9)	9550 (27.0)
Never smoked	11,056 (64.0)	24,492 (69.3)

MCED, multi-cancer early detection; NHANES, National Health and Nutrition Examination Survey.
[a]PATHFINDER 2 enrolled a diverse participant population whose demographics were generally reflective of the US population aged ≥50 years, although participants more often reported characteristics associated with better health than the NHANES population.[7]
[b]Participants without analyzable results included those who were not clinically evaluable or did not have an evaluable MCED test result.
[c]Race categories are reported alone or as part of multiple race categories (not mutually exclusive).
[d]Non-melanotic basal cell carcinoma and squamous cell carcinoma of the skin are not included.

MCED Test Performance

- Among participants aged ≥65 years in the performance analyzable set, the MCED test positive rate in the first 12 months was 1.28% (204/15,953; 95% CI: 1.12–1.47%), and the cancer detection rate was 0.73% (116/15,953; 95% CI: 0.61–0.87%)
  - The number needed to screen to detect 1 cancer was 138 (15,953/116; 95% CI: 115–165)
- The positive predictive value (PPV) of the MCED test across all cancer types was 56.9% (116/204; 95% CI: 50.0–63.5%); negative predictive value and specificity were both ≥98% (**Figure 1**)
  - The false-positive rate was 0.56% (88/15,676; 95% CI: 0.46–0.69%)

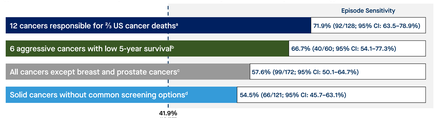
Figure 1. The MCED Test Demonstrated Robust Performance for Participants Aged ≥65 Years.



[a]The proportion of participants with a positive MCED test result out of all participants with a cancer diagnosis within the 12-month follow-up period.
MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

- 12-month episode sensitivity was 41.9% (116/277; 95% CI: 36.2–47.8%) across all cancers and was 54.5% to 71.9% in clinically relevant cancer subgroups (**Figure 2**)

Figure 2. 12-Month Episode Sensitivity in Participants Aged ≥65 Years.



[a]Anus, bladder/urothelial tract, colon/rectum, esophagus, head and neck, liver/intrahepatic bile duct, lung, lymphoid lineage, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, plasma cell lineage, stomach.
[b]Esophagus, liver/intrahepatic bile duct, lung, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, stomach.
[c]Post hoc analysis.
[d]Anus, bladder/urothelial tract, bone/soft tissue sarcoma, esophagus, head and neck, kidney, liver/intrahepatic bile duct, lung, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, skin, stomach, thyroid, uterus, other.
[e]The proportion of participants with a positive MCED test result out of all participants with a cancer diagnosis within the 12-month follow-up period.

MCED-Detected Cancers

- Of 116 participants with MCED-detected cancers, 101 had new primary cancers, and 16 had recurrences, including 1 participant with both a new primary cancer and a recurrent cancer
  - Among the 101 participants with new primary cancers, 51 (50.5%) were diagnosed with stage I–II cancers and 70 (69.3%) with stage I–III cancers (**Table 2**)
  - Among the 70 participants with stage I–III cancers, 59 (84.3%) received curative-intent treatment (**Table 2**)

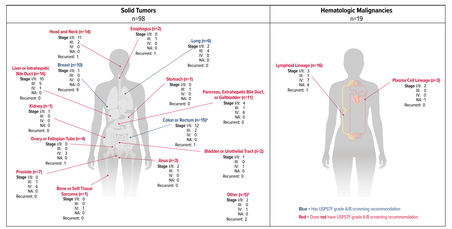
Table 2. The Majority of Stage I–III MCED-Detected Cancers Were Treated With Curative Intent.

	Positive MCED Test Result and New Primary Cancer Diagnosis Within 12 Months (n=101), n (%)[a]	Participants Treated With Curative Intent, n (%)
Stage I	30 (29.7)	27 (90.0)
Stage II	21 (20.8)	20 (95.2)
Stage III	19 (18.8)	12 (63.2)
Stage IV	26 (25.7)	9 (34.6)[b]
Stage I–II	51 (50.5)	47 (92.2)
Stage I–III	70 (69.3)	59 (84.3)

[a]n=5 MCED-detected cancers not expected to have TNM stage.
[b]Includes 3 lymphoid lineage cancers, 3 ovarian cancers, 2 prostate cancers, and 1 pancreas/extrahepatic bile duct/gallbladder cancer.

- Accuracy of the first or second CSO prediction was 89.7% (104/116; 95% CI: 82.8–94.0%)
- Of MCED-detected cancers, 79/116 (68.1%) were types without United States Preventive Services Task Force (USPSTF) A/B screening recommendations (**Figure 3**)
  - The most common new primary cancer types were liver/intrahepatic bile-duct (16), lymphoid lineage (15), colorectal (14), head and neck (14), and pancreas/extrahepatic bile-duct/gallbladder (11)
  - The most common recurrent cancer type was breast (9)

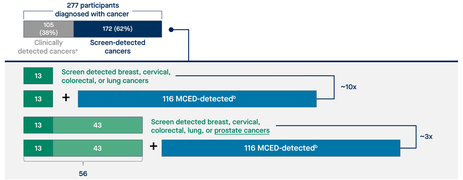
Figure 3. MCED Test Detected Cancers Across a Wide Range of Types and Anatomical Locations, Including Many Without Guideline-Recommended Screening.



*One participant was diagnosed with both a new and a recurrent colorectal cancer; each are included in the stage/recurrent summary.
†Other cancer types include testis (2), thymus (2), uveal melanoma (1).
MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.

- MCED testing increased the number of screen-detected cancers by approximately 10-fold when added to recommended USPSTF A/B screening (129 vs 13; 9.9-fold) and by approximately 3-fold when added to recommended USPSTF A/B/C screening (172 vs 56; 3.1-fold; **Figure 4**)
- Of the participants with MCED-detected breast, colorectal, and lung cancers, 8/10, 9/14, and 0/6 were eligible for USPSTF-recommended screening at the time of diagnosis, respectively

Figure 4. MCED Testing Increased the Number of Screen-Detected Cancers in Participants Aged ≥65 Years When Added to USPSTF-Recommended Screening.



For participants with multiple primary cancers, only the first diagnosed cancer is included.
[a]Clinical detection includes cancers detected based on participant-reported signs and symptoms (42), incidental findings on imaging, physical exam, laboratory test, surgical procedures (43), through surveillance for prior imaging findings (16), or post-treatment recurrence (7).
[b]MCED screen-detected cancer includes all cancer diagnosed following a positive MCED test result.
MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.

Cancers Not Detected by the MCED Test

- A total of 161 participants had a false-negative MCED test result; 148 were diagnosed with new primary cancers and 13 with recurrent cancers
  - Among the 161 participants with false-negative test results, 62.1% (100/161) were diagnosed with cancer types with existing guideline-recommended screening: prostate (59), breast (29), lung (11), and colorectal cancer (1)
  - Among the 148 participants with false-negative MCED test results and new primary cancers, 63 (42.6%) were diagnosed at stage I and 95 (64.2%) at stage I–II

Diagnostic Resolution

- Among participants with a positive MCED test result and a cancer diagnosis (n=109), the median (Q1–Q3) time to diagnostic resolution was 38.0 (24.0–59.0) days
- Among participants who achieved diagnostic resolution and were not diagnosed with cancer (n=86), the median (Q1–Q3) time to diagnostic resolution was 59.0 (37.2–106.0) days
- 11 participants did not achieve diagnostic resolution during the 12-month follow-up window
  - For 10 participants, several factors limited or deferred further diagnostic evaluation, including participant preference, loss to follow-up, medical/procedural considerations, logistical barriers, and ongoing surveillance
  - One participant had an unresolved diagnosis of a hematologic neoplasm for which benign versus malignant status could not be determined

CONCLUSIONS

- In adults aged ≥65 years, an MCED test demonstrated clinically meaningful cancer detection with high specificity, PPV, and CSO prediction accuracy, supporting its value in guiding diagnostic workups
- When added to existing cancer screening recommendations, MCED testing increased the number of screen-detected cancers
- Among MCED-detected new primary cancers, 69% were diagnosed at stages I–III, and 84% of those stage I–III cancers received curative-intent treatment
- These findings highlight the potential benefit of MCED testing as an addition to existing screening approaches to enable earlier detection of cancers, including cancers without guideline-recommended screening, in the Medicare-eligible population of individuals aged ≥65 years

METHODS

- PATHFINDER 2 (NCT05155605) is a multicenter, prospective, interventional study that enrolled participants aged ≥50 years[5]
  - Key exclusion criteria included undergoing or being referred for diagnostic evaluation due to clinical suspicion of cancer, any personal history of cancer ≤3 years prior to enrollment, and/or prior cancer treatment <3 years prior to enrollment
- A blood sample was drawn from each participant for MCED testing; for those with a positive MCED test result (ie, cancer signal detected), 1 or 2 CSOs were predicted
- All participants were actively followed for 3 years to assess cancer status and utilization of cancer screening tests on an annual basis
  - This analysis includes the first 12 months of follow-up after the MCED test blood draw
- All endpoints reported in this analysis were designed to be descriptive; no prespecified success criteria or formal hypothesis testing were applied

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Disclosures

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