

Safety and Performance Results From PATHFINDER 2, a Registrational Study of a Multi-Cancer Early Detection (MCED) Test in an Intended-Use Population

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Key Takeaways

In PATHFINDER 2, the largest **interventional** MCED study in an intended-use population in North America to date:

The MCED test identified many cancer types without recommended screening at early stages when there are options for treatment with curative intent

The MCED test had robust performance in a representative intended-use population, facilitating efficient diagnostic evaluations

MCED screening had a favorable safety profile, with a low false-positive rate, a low rate of invasive procedures, and no serious study-related AEs during the time of diagnostic evaluation^a

AE, adverse event; MCED, multi-cancer early detection.

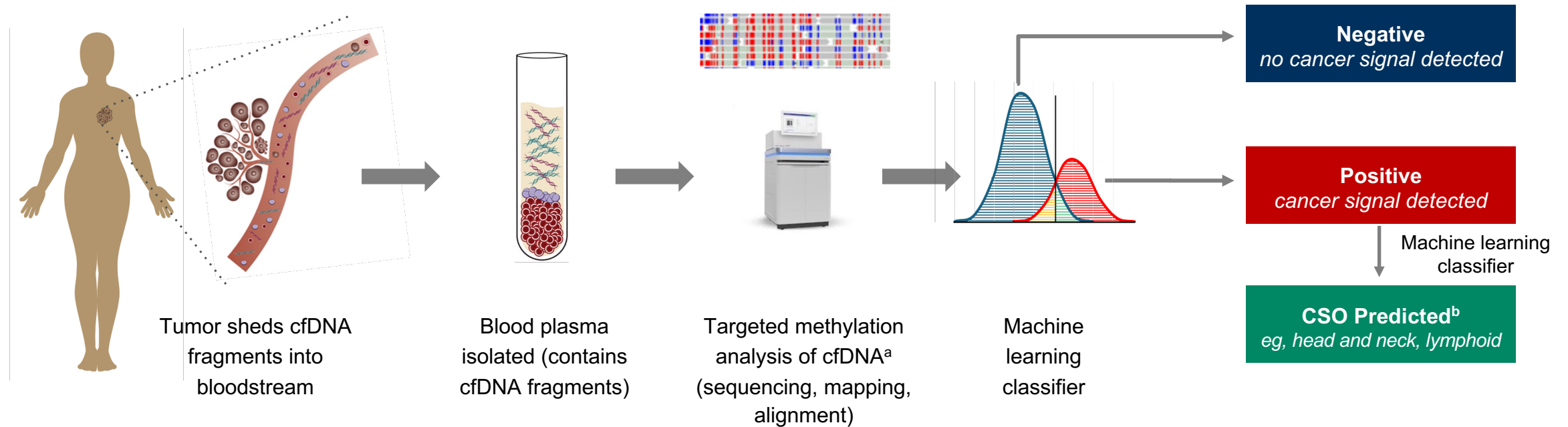
^a1 serious AE related to the diagnostic workup was identified after the data lock. Follow-up is ongoing; this and any other findings after data lock will be reported in full in the next interim analysis.

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A Clinically Validated Targeted Methylation MCED Test

The MCED test detects a cancer signal from cell-free DNA (cfDNA) in blood and predicts cancer signal origin (CSO) to guide diagnostic evaluation



Clinically validated in case-control and population-scale intended-use studies¹⁻³
Clinical evidence program includes >380,000 participants across 9 studies in North America and the United Kingdom

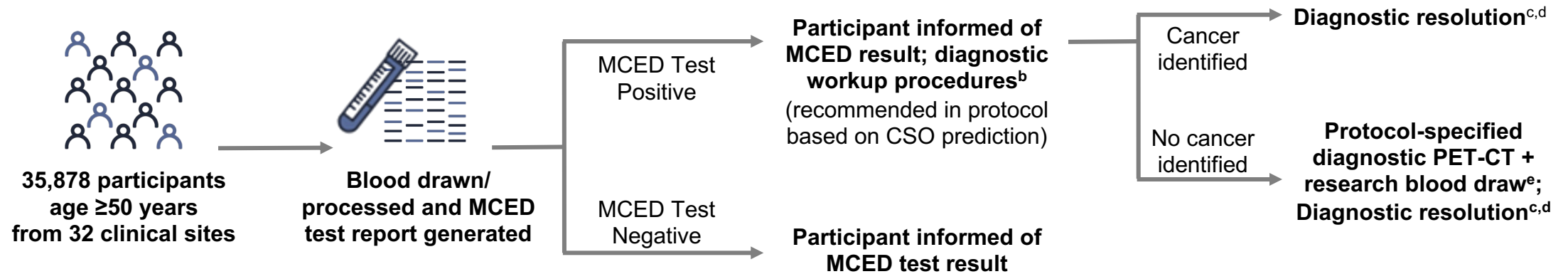
MCED, multi-cancer early detection.

^aBisulfite treatment; targeted probes pull out fragments matching regions of interest. ^bFor a detected signal, this MCED test version predicts 1 to 2 CSOs that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid). Adapted from Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759. 1. Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759. 2. Klein EA, et al. *Ann Oncol.* 2021;32(9):1167-1177. 3. Schrag D, et al. *Lancet.* 2023;402(10409):1251-1260.

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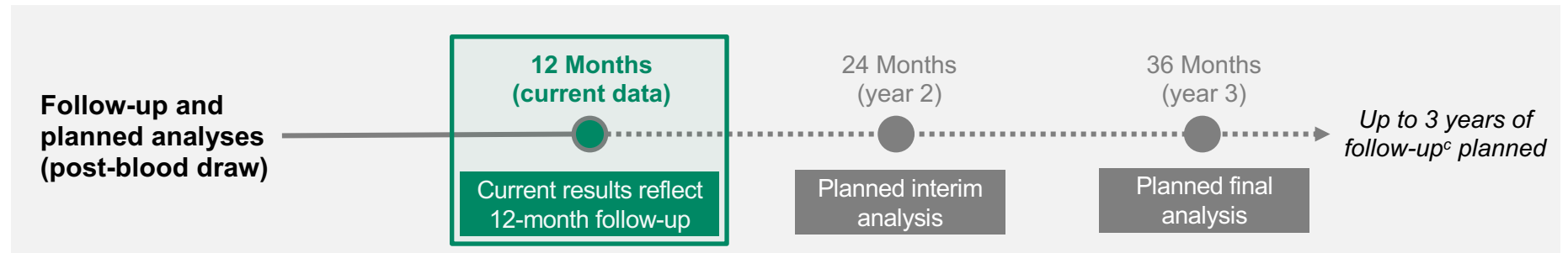
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PATHFINDER 2^a: The Largest Prospective, Interventional MCED Study Conducted in North America to Date



Key Exclusion Criteria:

- Clinical suspicion of cancer
- Cancer diagnosis and/or prior cancer treatment ≤3 years prior to enrollment



Primary Objectives: Evaluate safety and performance of the MCED test in a large, diverse intended-use population

CSO, cancer signal origin; MCED, multi-cancer early detection; PET-CT, positron emission tomography-computed tomography.

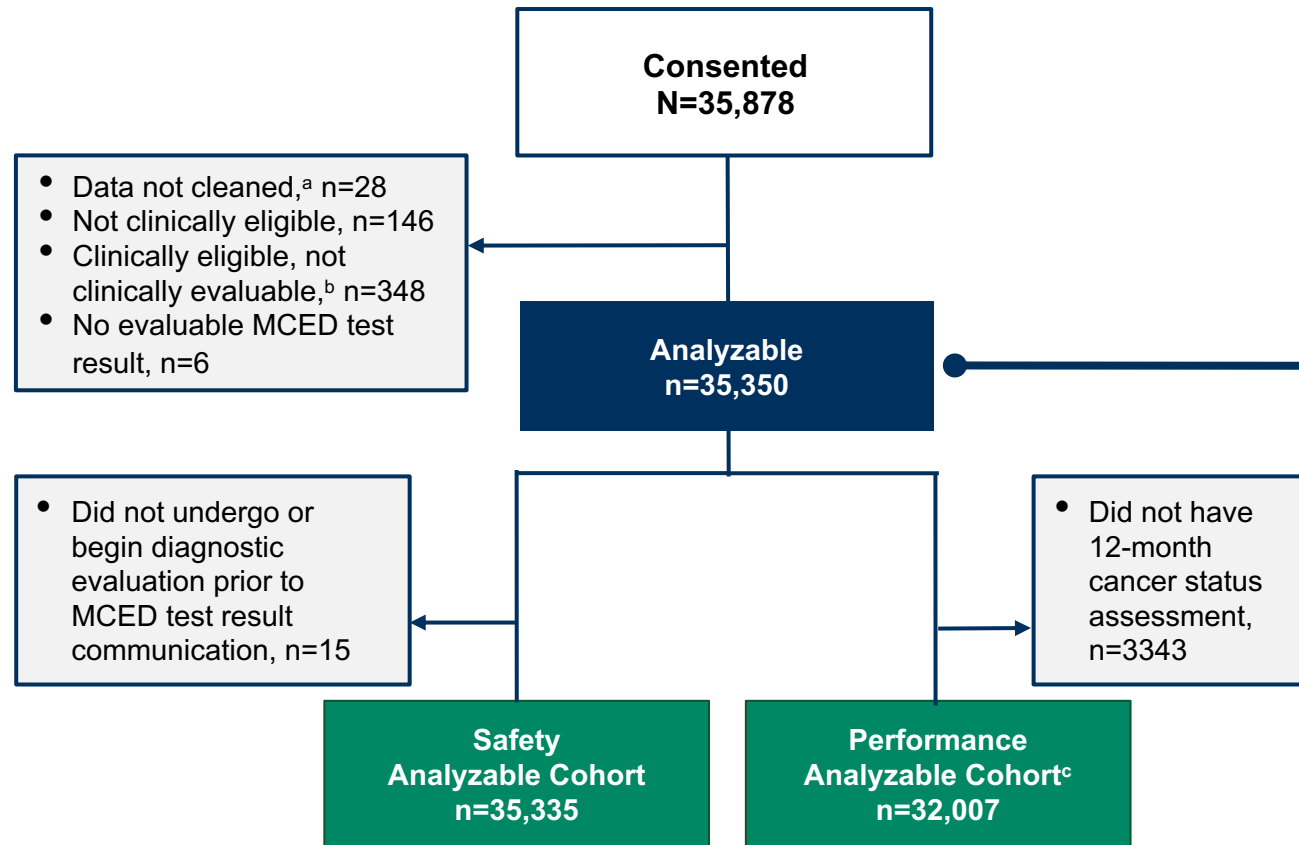
^aNCT05155605. ^bDiagnostic evaluations based on CSO were recommended in the protocol. ^cAll participants are actively followed by enrolling institutions for 3 years to assess cancer status and utilization of cancer screening tests on an annual basis. ^dClinical information including, but not limited to, cancer type, histology, and staging information were collected. ^eResearch blood draw also collected to understand the clinical benefit of an MCED retest; results of research blood draw were not returned.

Giridhar KV, et al. Poster presented at: American Association for Cancer Research (AACR) Annual Meeting; April 5-10, 2024; San Diego, California.

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Diverse Participant Population Reflects the MCED Intended-Use Population



Baseline Demographics and Characteristics ^d	
Median age (Q1-Q3), years	64 (58-70)
Age groups	
50-59 years	28.4%
60-69 years	44.0%
≥70 years	27.6%
Sex, Female	56.2%
Race/ethnicity	
Non-Hispanic White	80.1%
Non-Hispanic Black or African American	8.8%
Non-Hispanic Asian	5.9%
Hispanic or Latino	7.4%
Education, Bachelor's degree or higher	58.8%
Smoking history	
Former smoker	27.0%
Current smoker	3.7%
Prior cancer history	9.2%

MCED, multi-cancer early detection.

^aIncludes participants whose clinical data were not fully cleaned and/or were not fully verified per the study data lock plan. ^bIncludes consented participants who met study inclusion/exclusion criteria but were not clinically evaluable (eg, lacked the presence of an evaluable blood draw, withdrew consent before blood draw). ^cIncludes individuals with 12 months of follow-up and cancer status assessment. ^dFor detailed PATHFINDER 2 baseline demographics analysis, see Gadgeel S, et al. Poster presented at AACR Conference on the Science of Cancer Health Disparities; September 18-21, 2025; Baltimore, Maryland.

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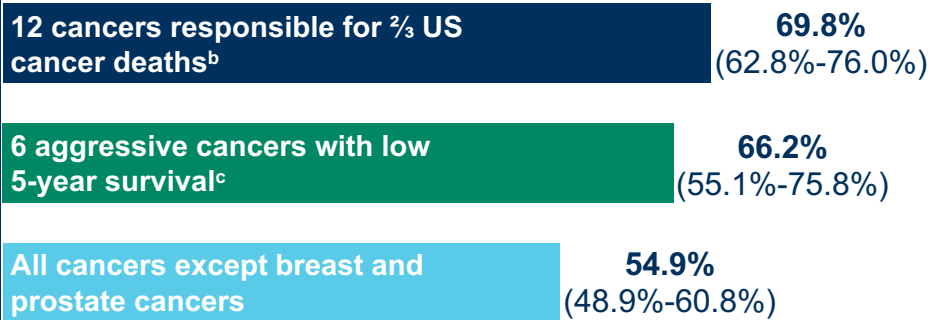
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Performance: Overall 60% PPV Observed

		Cancer Status Over 12 Months of Follow-up (Performance Analyzable Cohort)			Performance Metric (95% CI)
		Cancer Diagnosis (n=440)	No Cancer Diagnosis (n=31,567)	Total (n=32,007)	
MCED Test Result	Positive	173	114	287	PPV 60.3% (54.5%-65.8%)
	Negative	267	31,453	31,720	NPV 99.2% (99.1%-99.3%)

Episode Sensitivity (95% CI)



Positive likelihood ratio 108.9
10-fold higher than mammography¹

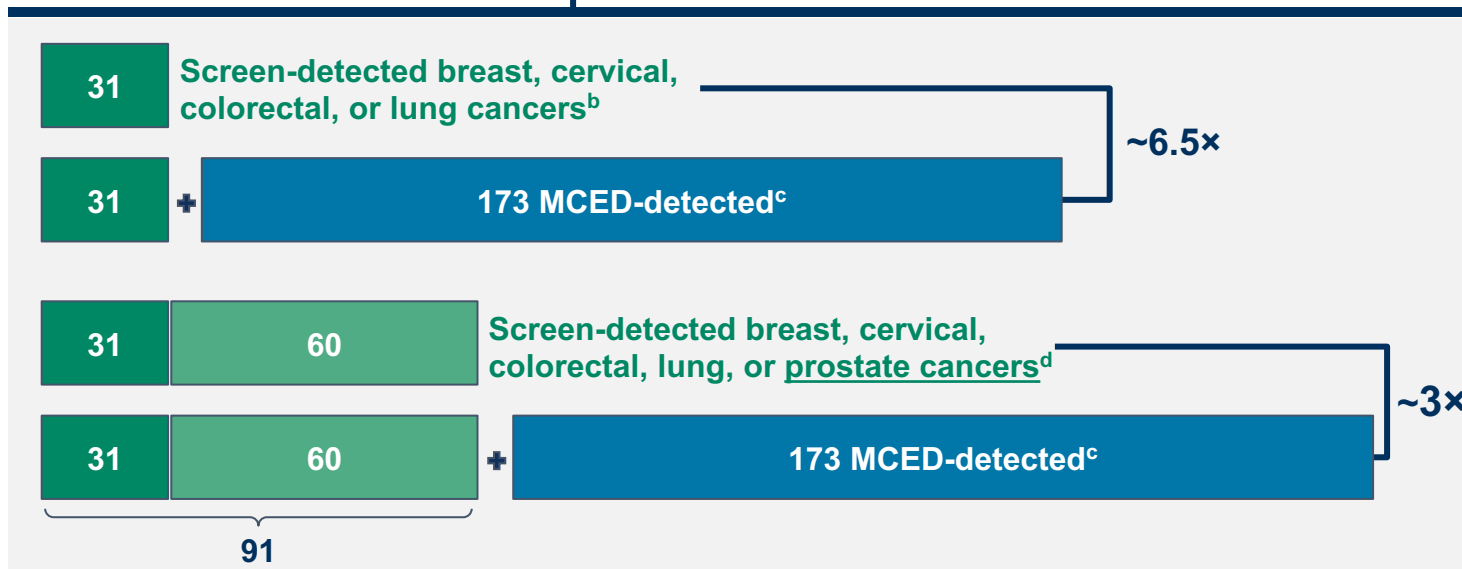
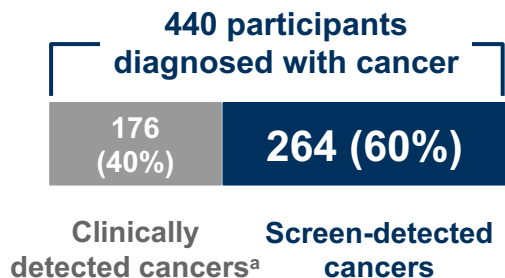
Performance Metric (95% CI)

Episode Sensitivity^a 39.3%
(34.9%-44.0%)

Specificity 99.6%
(99.6%-99.7%)

MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.
^aThe proportion of cancers diagnosed within 12 months of MCED testing that were correctly identified by the test at the time it was performed. ^bAnus, 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. ^cEsophagus, Liver/intrahepatic bile duct, Lung, Ovary/fallopian tube, Pancreas/extrahepatic bile duct/gallbladder, Stomach.
 1. Lee CI, et al. *Radiology*. 2023;307(4):e222499.

MCED Testing Increased the Number of Screen-Detected Cancers 6.5× When Added to USPSTF-Recommended Screening^a



Of MCED-detected^c new primary cancers:

- 53.0% were stage I-II
- 70.9% were stage I-III

Of MCED-detected^c cancers:

- 67.6% were types *without* USPSTF grade A/B/C screening recommendations^d
- 17 broad cancer types and 81 histologically distinct types represented

Of 267 participants with cancers not detected by the MCED test^e:

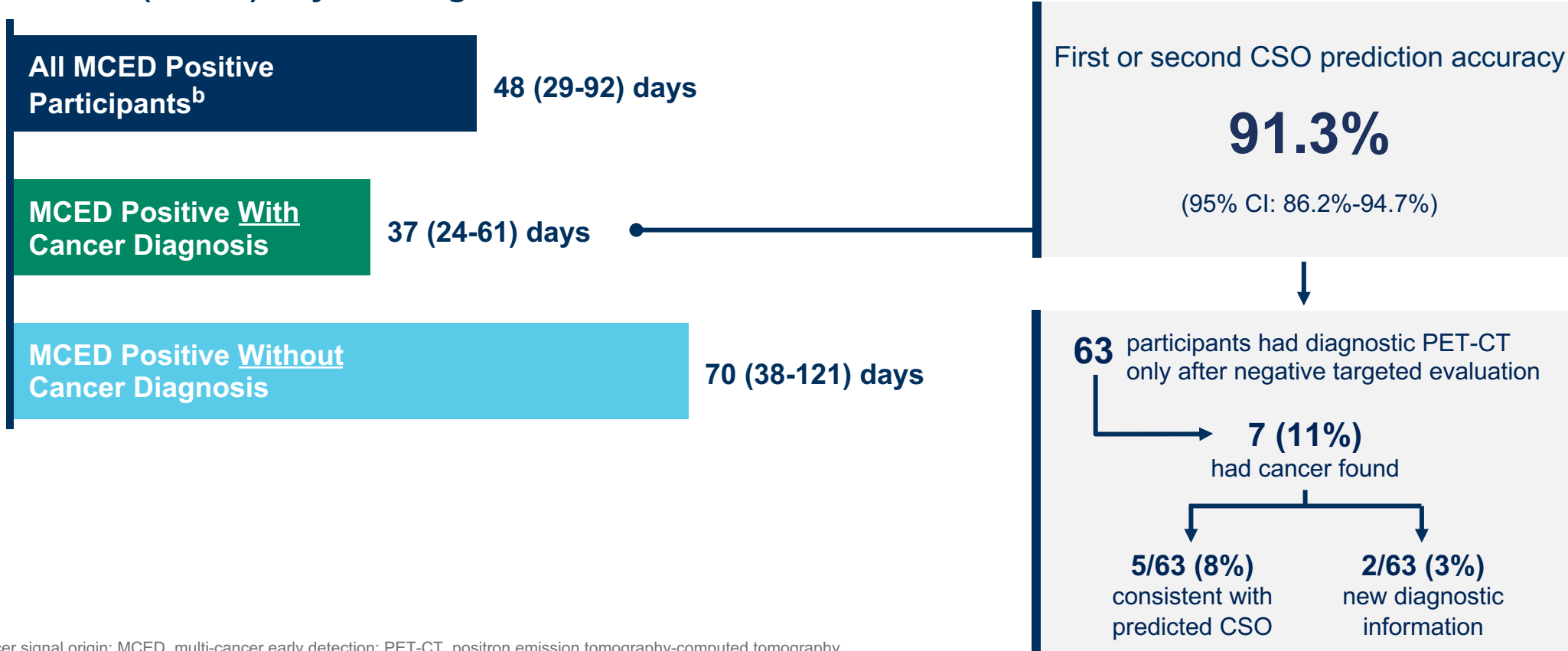
- 61.0% (163/267) had types *with* grade A/B/C screening recommendations^d
- 54.8% (57/104) *without* grade A/B/C screening were **stage I**

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

^aClinically detected cancers included those detected incidentally (n=74), by signs and symptoms (n=66), by surveillance (n=27), and other (n=9; 4 were follow-up after an abnormal test result, 2 were incidental findings, and 3 were unknown). ^bUSPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers. ^cMCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. ^dUSPSTF grade A/B/C recommendations include screening for breast, cervical, colorectal, lung, and prostate cancers. ^eThese 267 participants had cancers clinically detected (n=176) and detected by USPSTF screening (n=91).

Accurate CSO Predictions Facilitated Efficient Targeted Evaluations Following a Positive MCED Test Result^a

Median (Q1-Q3) Days to Diagnostic Resolution



CSO, cancer signal origin; MCED, multi-cancer early detection; PET-CT, positron emission tomography-computed tomography.
^aTargeted evaluations were mainly CSO-guided (254/290; 87.6%). ^bBased on Kaplan-Meier analysis.

The MCED Test Was Safe When Implemented in the Intended-Use Population

Low false-positive rate

0.36%
false-positive rate

Low risk of unnecessary diagnostic workup due to false-positive MCED tests

Low rate of invasive procedures

0.6% (213/35,335)
of MCED-tested participants had an invasive procedure after a positive MCED test result

90.5% of invasive procedures were nonsurgical

85.2% of evaluations were noninvasive

Few adverse events (AEs)

5 study-related AEs^a
(0 serious^b)
occurred during the time of diagnostic evaluation and only in those with a cancer diagnosis

MCED, multi-cancer early detection.

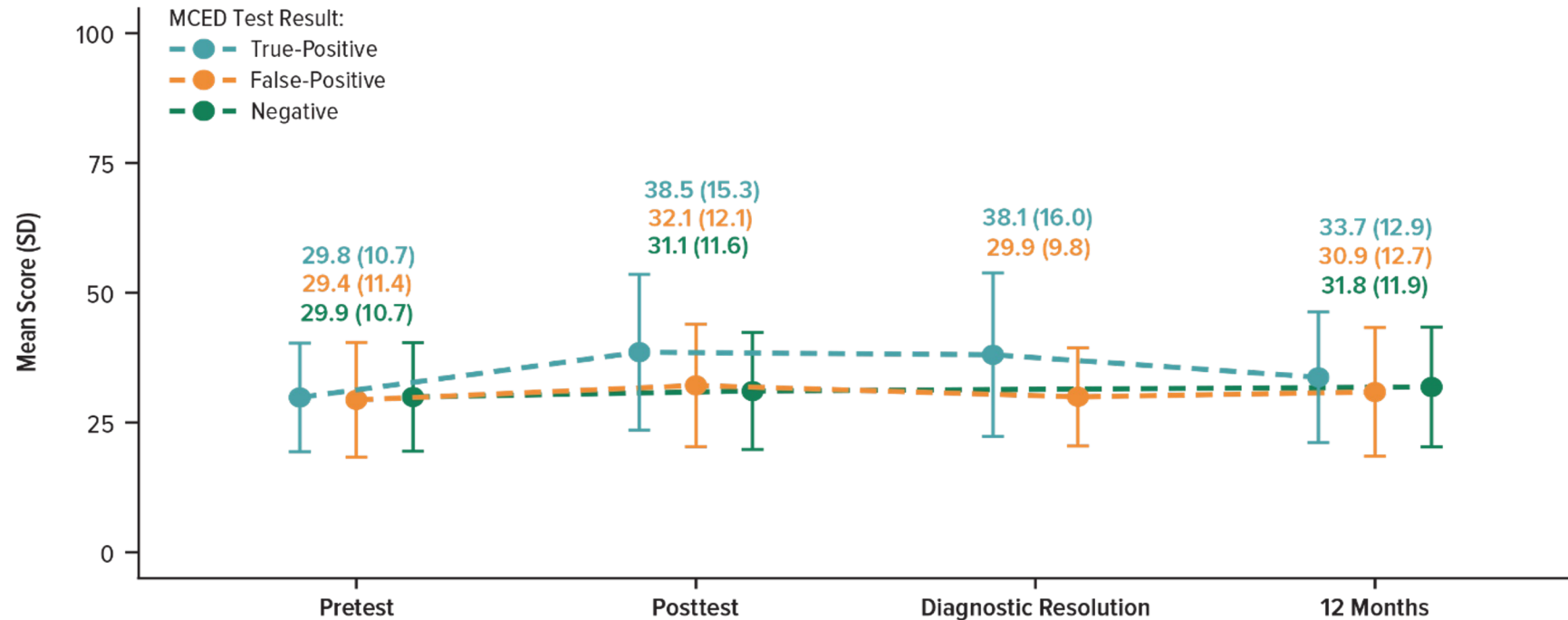
^aEmergency department visit; planned hospitalization for pain control; anxiety after receipt of a cancer signal detected MCED test result; postoperative pain; and postoperative constipation and acid reflux. ^b1 serious AE related to the diagnostic workup was identified after the data lock. Follow-up is ongoing; this and any other findings after data lock will be reported in full in the next interim analysis.

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Changes in Participant-Reported Anxiety Were Temporary and Returned to Pretest Levels by 12 Months



Number of Participant Responses				
MCED Test Result	Pretest	Posttest	Diagnostic Resolution	12 Months
True-Positive	167	110	74	101
False-Positive	130	81	60	71
Negative	33,617	25,519	NA	21,137

MCED, multi-cancer early detection.

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Key Takeaways

In PATHFINDER 2, the largest **interventional** MCED study in an intended-use population in North America to date:

The MCED test identified many cancer types without recommended screening at early stages when there are options for treatment with curative intent

3- to 6.5-fold increase in screen-detected cancers with MCED

The MCED test had robust performance in a representative intended-use population, facilitating efficient diagnostic evaluations

69.8% episode sensitivity for 12 cancers responsible for $\frac{2}{3}$ US cancer deaths^a

60% PPV

99.6% specificity

91.3% CSO prediction accuracy

MCED screening had a favorable safety profile

0.36% false-positive rate
0.6% invasive procedure rate after a positive MCED test
5 study-related AEs during the time of diagnostic evaluation, **none serious**^b

AE, adverse event; CSO, cancer signal origin; MCED, multi-cancer early detection; PPV, positive predictive value.

^aAnus, 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. ^b1 serious AE related to the diagnostic workup was identified after the data lock. Follow-up is ongoing; this and any other findings after data lock will be reported in full in the next interim analysis.

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Acknowledgments

- We acknowledge the contributions to this effort of the participants of the study and their families, the clinical site staff, and investigators

Lay Summary

WHAT WE DID & WHAT WE FOUND



Who we studied: 35,878 adults aged ≥ 50 years across North America with no suspicion of cancer



What the MCED test does: A single blood draw can screen for many cancers and directs physicians to the likely site of origin



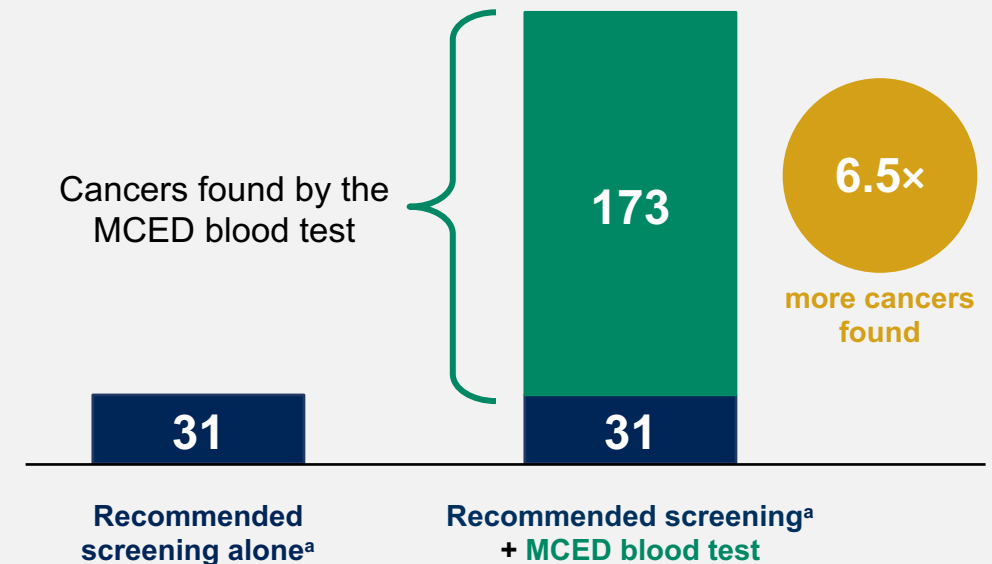
What we found: During the first of 3 years of follow-up, the MCED test worked well. About 6 in 10 people with a positive MCED test result had cancer. More than half of cancers found by the test were at early stages, when cancer is easier to treat and cure. The test also detected many types of cancer that aren't screened for today



The test is safe to use: Fewer than 4 in 1000 people in the study had a false alarm, and no serious side effects were linked to the MCED test

WHY IT MATTERS

Cancers found through screening



Using this MCED test could help find more cancers, including those we can't screen for today, at early and more treatable stages

MCED, multi-cancer early detection. ^aRecommended screening includes screening for breast, cervix, colorectum, and lung cancers.

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