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

ABSTRACT #LBA64

Nima Nabavizadeh; Charles McDonnell; Dax Kurbegov; Marc Matrana; Shirish Gadgeel; Raymond H. Kim; Gretchen Stipec; Kevin Oeffinger; Michael J. Demeure; Roland Matthews; Rebecca Kaltman; Tamar Toronjadze; Cora N. Sternberg; Jennifer Tran; Natalia Colocci; Leonardo Forero; Margarita Lopatin; Margaret McCusker; Karthik Giridhar

Proffered Presentation presented at: European Society for Medical Oncology (ESMO) Congress; October 17-21, 2025; Berlin, Germany.

DECLARATION OF INTERESTS

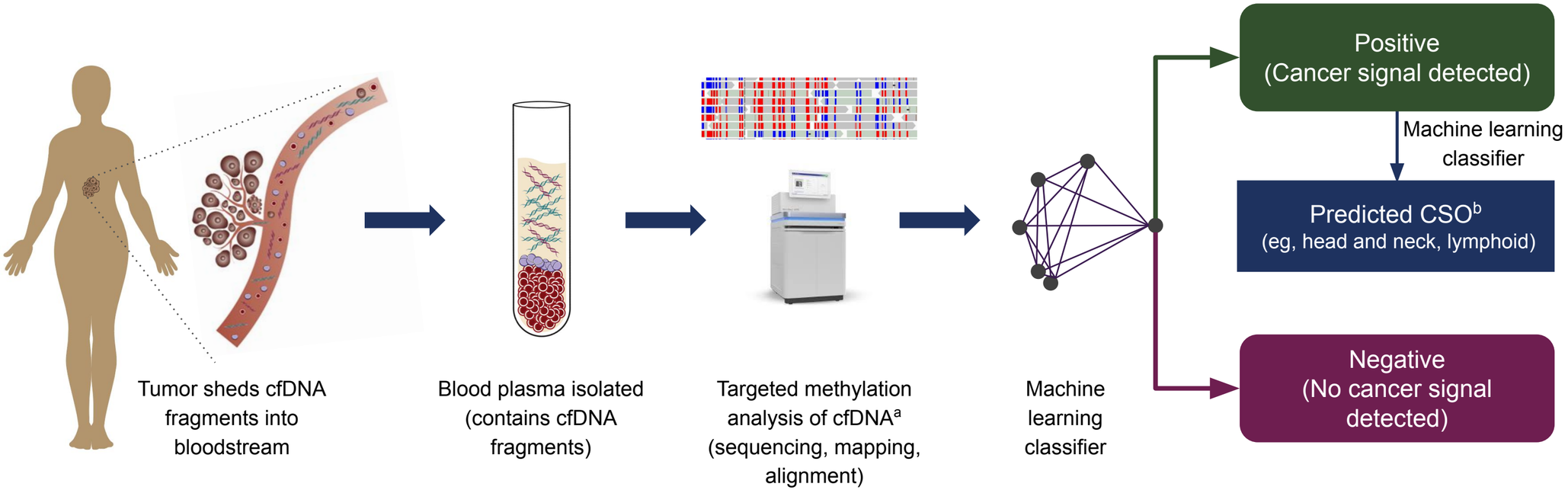
Nima Nabavizadeh, MD
Cancer Early Detection Advanced Research Center
Knight Cancer Institute, Oregon Health & Science University
Portland, OR

Presenting author declarations:

- **GRAIL:** Advisory Board
- **MJH Life Sciences:** Writing Engagement
- **Quattro Consulting:** Market Research Consulting
- **Roche:** Invited Speaker

GRAIL's MCED Blood-Based Targeted Methylation Test

The MCED test (Galleri®, GRAIL, Inc.) detects cancer signals from cell-free DNA (cfDNA) in blood and predicts cancer signal origin (CSO) to guide diagnostic evaluation

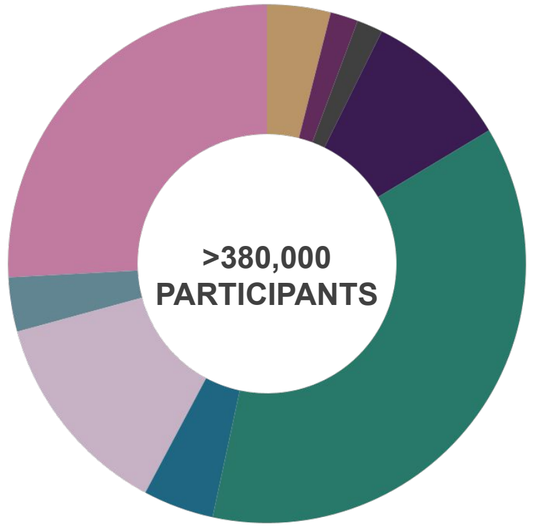


MCED, multi-cancer early detection.
[a]Bisulfite treatment; targeted probes pull out fragments matching regions of interest. [b]For a detected signal, this MCED test version predicts 1-2 CSOs that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid). Adapted from Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759.

GRAIL Clinical Development Program

Test Development, Validation, and Implementation in Population-Scale Studies

1	**CCGA** (n=15,254)	**Develop and validate a cell-free DNA-based MCED test** *Enrollment: complete, published*	*Annals of Oncology* and *Cancer Cell* 2020-2023[1-3]
2	**PATHFINDER** (n=6,662)	**Evaluate clinical implementation and perceptions of MCED test** *Enrollment: complete, published*	*The Lancet* 2023[4]
3	**PATHFINDER 2** (n=35,878)	**Evaluate MCED test performance in eligible screening population** *Enrollment: complete*	
4	**SYMPLIFY** (n=6,238)	**Assess MCED test in individuals with signs/symptoms of cancer** *Enrollment: complete, published*	*Lancet Oncology* 2023[5]
5	**NHS-GALLERI** (n≈142,321)	**Assess clinical utility of MCED for population screening in the UK** *Enrollment: complete*	
6	**REFLECTION** (n≈14,000)	**Understand the real-world experience of Galleri® in clinical settings** *Enrollment: complete*	
7	**REACH** (n≈50,000)	**Understand health equity impact of Galleri in a Medicare population** *Enrollment: ongoing*	
8	**SUMMIT** (n=13,035)	**Clinical validation in individuals at high risk of lung cancer** *Enrollment: complete*	
9	**STRIVE** (n=99,481)	**Observational study in women undergoing mammography screening** *Enrollment: complete*	



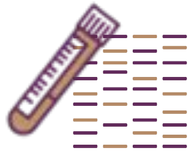
CCGA, Circulating Cell-free Genome Atlas; MCED, multi-cancer early detection; NHS, National Health System.

1. Jamshidi A, et al. *Cancer Cell*. 2022;40(12):1537-1549. 2. Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759. 3. Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177. 4. Schrag D, et al. *Lancet*. 2023;402(10409):1251-1260. 5. Nicholson BD, et al. *Lancet Oncol*. 2023;24(7):733-743.

PATHFINDER 2[a]: The Largest Interventional MCED Study Conducted in the US to Date

Prospective, interventional study of an MCED test including 35,878 participants from 32 North American healthcare systems with 3 years of follow-up[b]

35,878 participants age ≥50 years



Blood drawn/ processed and MCED test report generated

Negative (No cancer signal detected) → **Participant informed of MCED test result**

Positive (Cancer signal detected) → **Participant informed of MCED result; diagnostic follow-up procedures[c]** (recommended in protocol based on CSO)

- **Cancer identified** → **Diagnostic resolution[b,d]**
- **No cancer identified** → **Protocol-specified diagnostic PET-CT[e]; Diagnostic resolution[b,d]**

Key Exclusion Criteria:

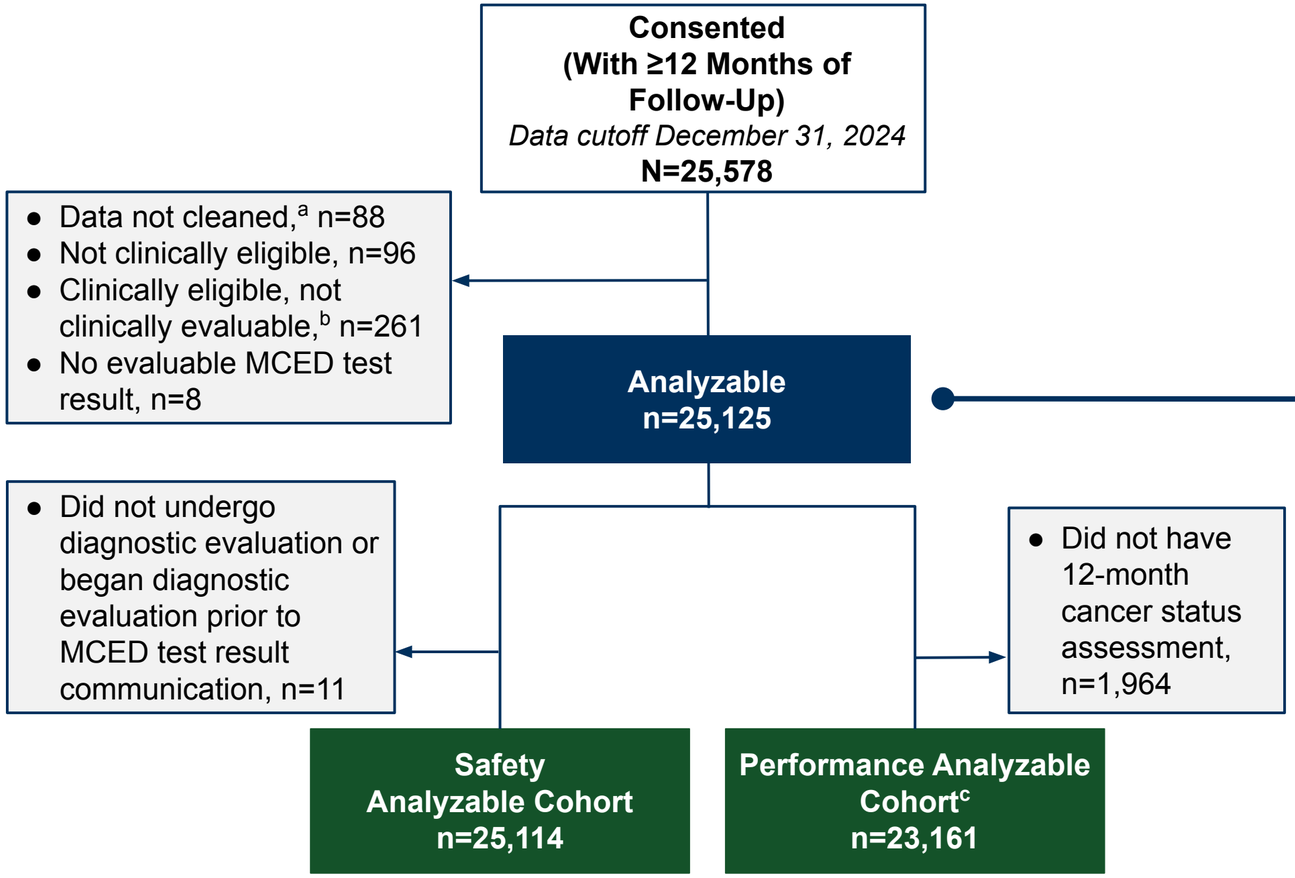
- Undergoing or referred for diagnostic revaluation due to clinical suspicion for cancer
- Personal history of invasive solid tumor or hematologic malignancy and/or prior cancer treatment within 3 years prior to enrollment

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.
[a]NCT05155605. [b]All participants are actively followed by enrolling institutions for 3 years to assess cancer status and utilization of cancer screening tests on an annual basis. [c]Diagnostic evaluations based on CSO are recommended in the protocol. [d]Clinical information including, but not limited to, cancer type, histology, and staging information will be collected. [e]Research blood draw also collected to understand the clinical utility 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.

Enrolled a Diverse Participant Population That Reflects Intended Use Population



Baseline Demographics and Characteristics[d]	
Median Age (IQR), years	65 (59-71)
Age Groups	
50-59 years	27.0%
60-69 years	44.4%
≥70 years	28.6%
Sex, Male	43.2%
Race/Ethnicity	
Non-Hispanic White	76.0%
Non-Hispanic Black or African American	8.0%
Non-Hispanic Asian	5.6%
Hispanic or Latino	6.9%
Education, Bachelor's Degree or Higher	58.5%
Smoking History	
Former Smoker	27.6%
Current Smoker	3.7%
Prior Cancer History	10.0%

IQR, interquartile range; MCED, multi-cancer early detection.
[a]Includes participants whose clinical data were not fully cleaned and/or were not fully verified per the study data lock plan. [b]Includes 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). [c]Includes individuals with 12 months of follow-up and cancer status assessment. [d]For 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.

Observed PPV Was ~62% Across All Cancers

		Cancer Status Over 12 Months of Follow-up (Performance Analyzable Cohort)			Performance Metric (95% CI)
		Cancer Diagnosis (n=329)	No Cancer Diagnosis (n=22,832)	Total (N=23,161)	
MCED Test Result	Positive	133	83	216	PPV 61.6% (54.9-67.8%)
	Negative	196	22,749	22,945	NPV 99.1% (99.0-99.3%)
Performance Metric (95% CI)		Episode Sensitivity[a] 40.4% (35.3-45.8%)	Specificity 99.6% (99.5-99.7%)		

Cancer Signal Detection Rate = 0.93%

CI, confidence interval; MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

[a]The proportion of cancers diagnosed within 12 months of MCED testing that were correctly identified by the test at the time it was performed.

1. Schrag D, et al. *Lancet.* 2023;402(10409):1251-1260. 2. Klein EA, et al. *Ann Oncol.* 2021;32(9):1167-1177. 3. Matrana M, et al. Poster presented at American Association for Cancer Research (AACR) Annual Meeting; April 25-30, 2025; Chicago, Illinois. 4. Atwood C, et al. Presented at Early Detection of Cancer Conference (EDCC); October 22-24, 2024; San Francisco, California. 5. Lehman CD, et al. *Radiology.* 2017;283:49–58. 6. Bailey SER, et al. *Br J Cancer* 2021;124:1231–1236. 7. Pinsky PF, et al. *Ann. Intern. Med.* 2015;162:485–491. 8. Sekiguchi M, et al. *Sci Rep.* 2020;10, 18202. 9. Pickhardt PJ, et al. *AJR Am J Roentgenol.* 2021;217:817–830.

Observed PPV Was ~62% Across All Cancers

		Cancer Status Over 12 Months of Follow-up (Performance Analyzable Cohort)			Performance Metric (95% CI)
		Cancer Diagnosis (n=329)	No Cancer Diagnosis (n=22,832)	Total (N=23,161)	
MCED Test Result	Positive	133	83	216	**PPV 61.6%** (54.9-67.8%)
	Negative	196	22,749	22,945	**NPV 99.1%** (99.0-99.3%)
Performance Metric (95% CI)		**Episode Sensitivity[a] 40.4%** (35.3-45.8%)	**Specificity 99.6%** (99.5-99.7%)		

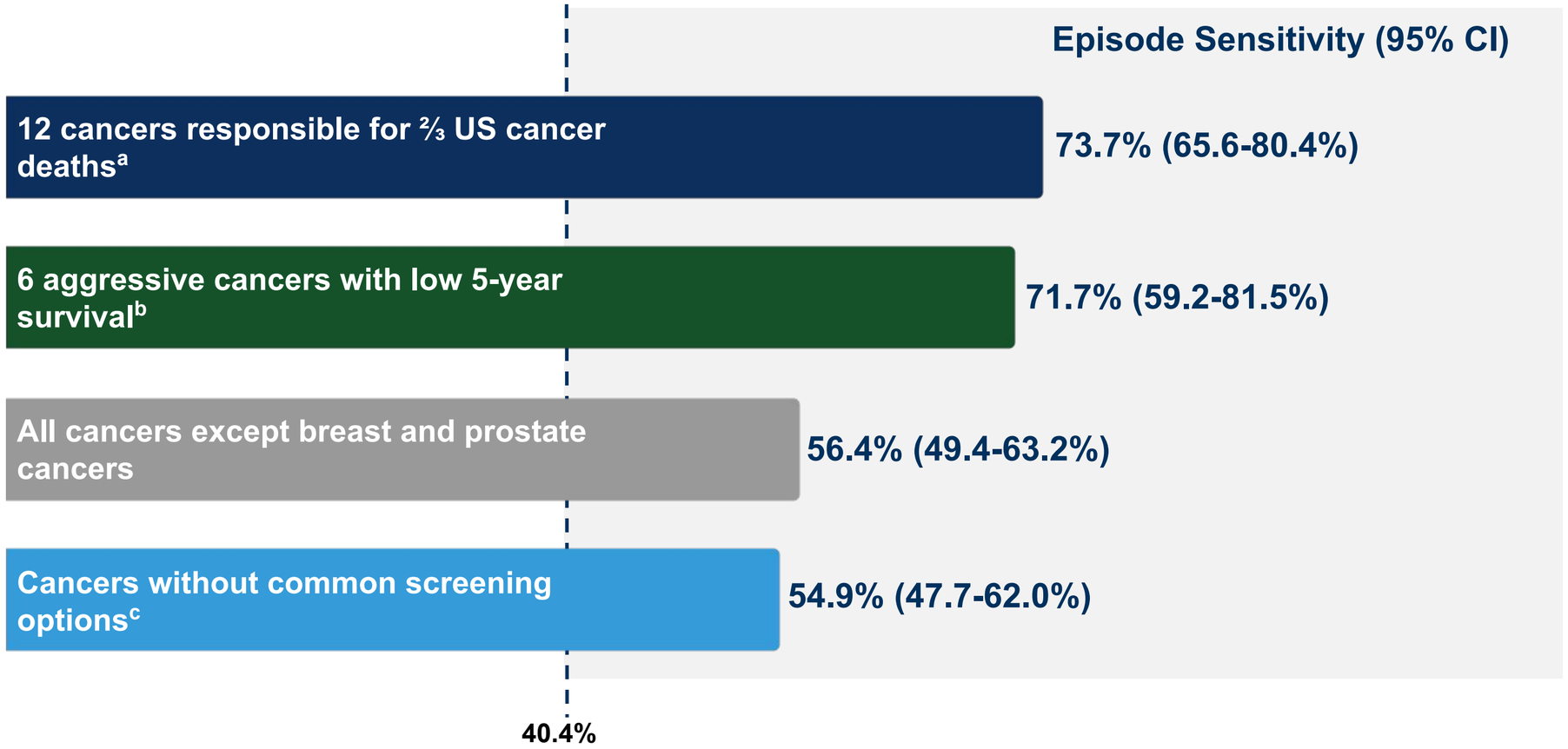
- MCED test PPV ranged from **42.9%-49.4%** in prior clinical studies and real-world experience[1-4]
- The MCED test PPV is an **order of magnitude higher** than established single-cancer screening tests[5-9]

CI, confidence interval; MCED, multi-cancer early detection; NPV, negative predictive value; PPV, positive predictive value.

[a]The proportion of cancers diagnosed within 12 months of MCED testing that were correctly identified by the test at the time it was performed.

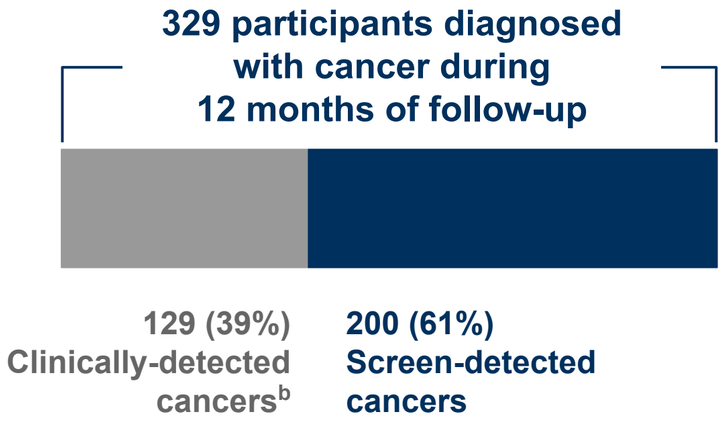
1. Schrag D, et al. *Lancet.* 2023;402(10409):1251-1260. 2. Klein EA, et al. *Ann Oncol.* 2021;32(9):1167-1177. 3. Matrana M, et al. Poster presented at American Association for Cancer Research (AACR) Annual Meeting; April 25-30, 2025; Chicago, Illinois. 4. Atwood C, et al. Presented at Early Detection of Cancer Conference (EDCC); October 22-24, 2024; San Francisco, California. 5. Lehman CD, et al. *Radiology.* 2017;283:49–58. 6. Bailey SER, et al. *Br J Cancer* 2021;124:1231–1236. 7. Pinsky PF, et al. *Ann. Intern. Med.* 2015;162:485–491. 8. Sekiguchi M, et al. *Sci Rep.* 2020;10, 18202. 9. Pickhardt PJ, et al. *AJR Am J Roentgenol.* 2021;217:817–830.

Demonstrated Robust 12-Month Episode Sensitivity in Clinically Relevant Subgroups



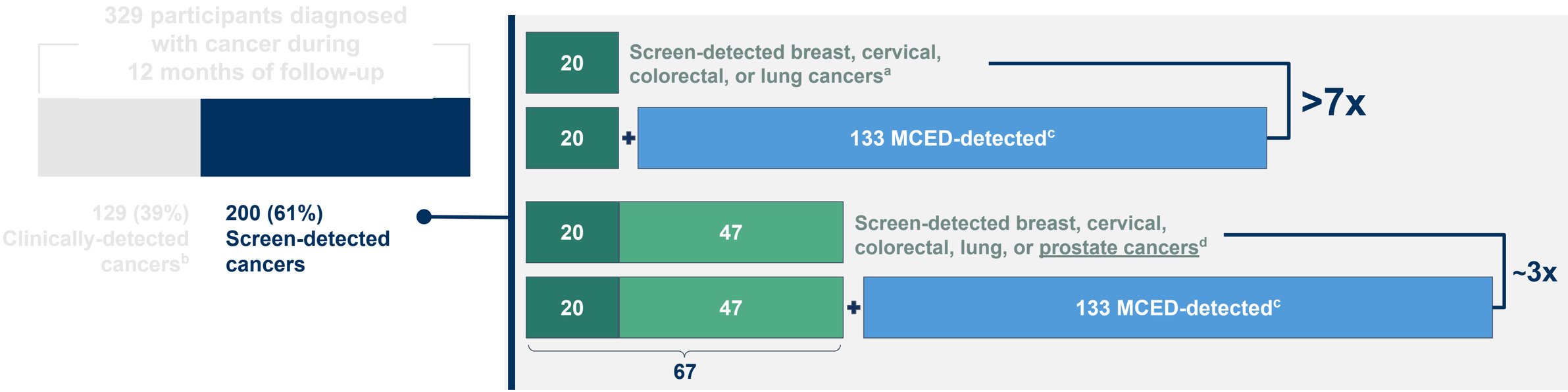
CI, confidence interval.
[a]Anus, Bladder/urothelial tract, Colon/rectum, Esophagus, Head and neck, Liver/intrahepatic bile duct, Lung, Lymphoid lineage, Ovary/fallopian tube, Pancreas/extrahepatic bile duct/gallbladder, Plasma cell lineage, Stomach.
[b]Esophagus, Liver/intrahepatic bile duct, Lung, Ovary/fallopian tube, Pancreas/extrahepatic bile duct/gallbladder, Stomach. [c]Anus, Bladder/urothelial tract, Bone/soft tissue sarcoma, Esophagus, Head and neck, Kidney, Liver/intrahepatic bile duct, Lung, Lymphoid lineage, Myeloid lineage, Ovary/fallopian tube, Pancreas/extrahepatic bile duct/gallbladder, Plasma cell lineage, Skin, Stomach, Thyroid, Uterus, Other.

MCED Testing Increased the Number of Screen-Detected Cancers Over 7x When Added to Recommended Screening[a]



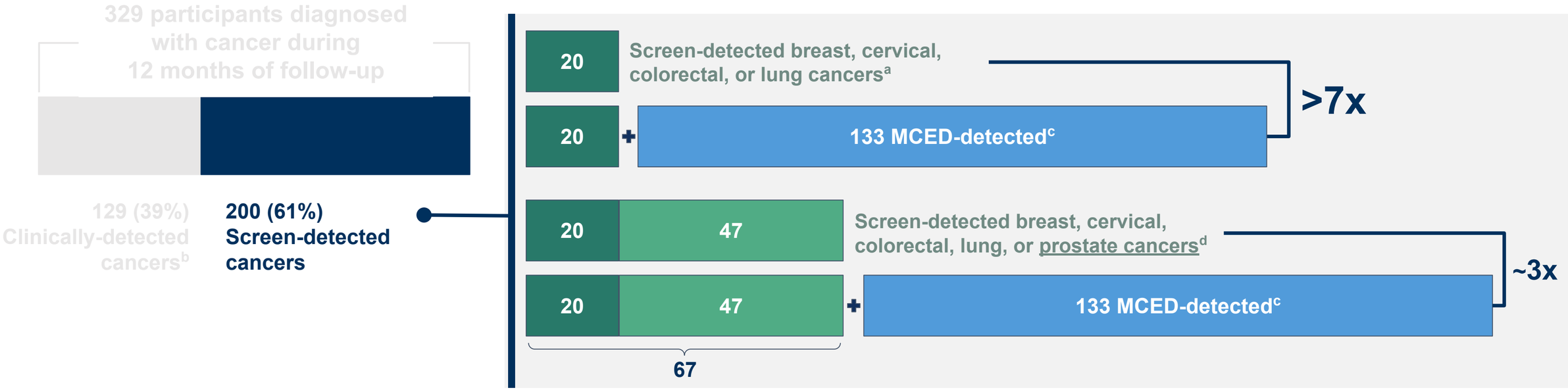
MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.
[a]USPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers. [b]Clinically-detected cancers included those detected incidentally (n=62), by signs and symptoms (n=40), by surveillance (n=21), and other (n=6; 3 were follow-up after an abnormal test result, 2 were incidental findings, and 1 was unknown). [c]MCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. [d]USPSTF grade A/B/C recommendations include screening for breast, cervical, colorectal, lung, and prostate cancers.

MCED Testing Increased the Number of Screen-Detected Cancers Over 7x When Added to Recommended Screening[a]



MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.
[a]USPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers. [b]Clinically-detected cancers included those detected incidentally (n=62), by signs and symptoms (n=40), by surveillance (n=21), and other (n=6; 3 were follow-up after an abnormal test result, 2 were incidental findings, and 1 was unknown). [c]MCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. [d]USPSTF grade A/B/C recommendations include screening for breast, cervical, colorectal, lung, and prostate cancers.

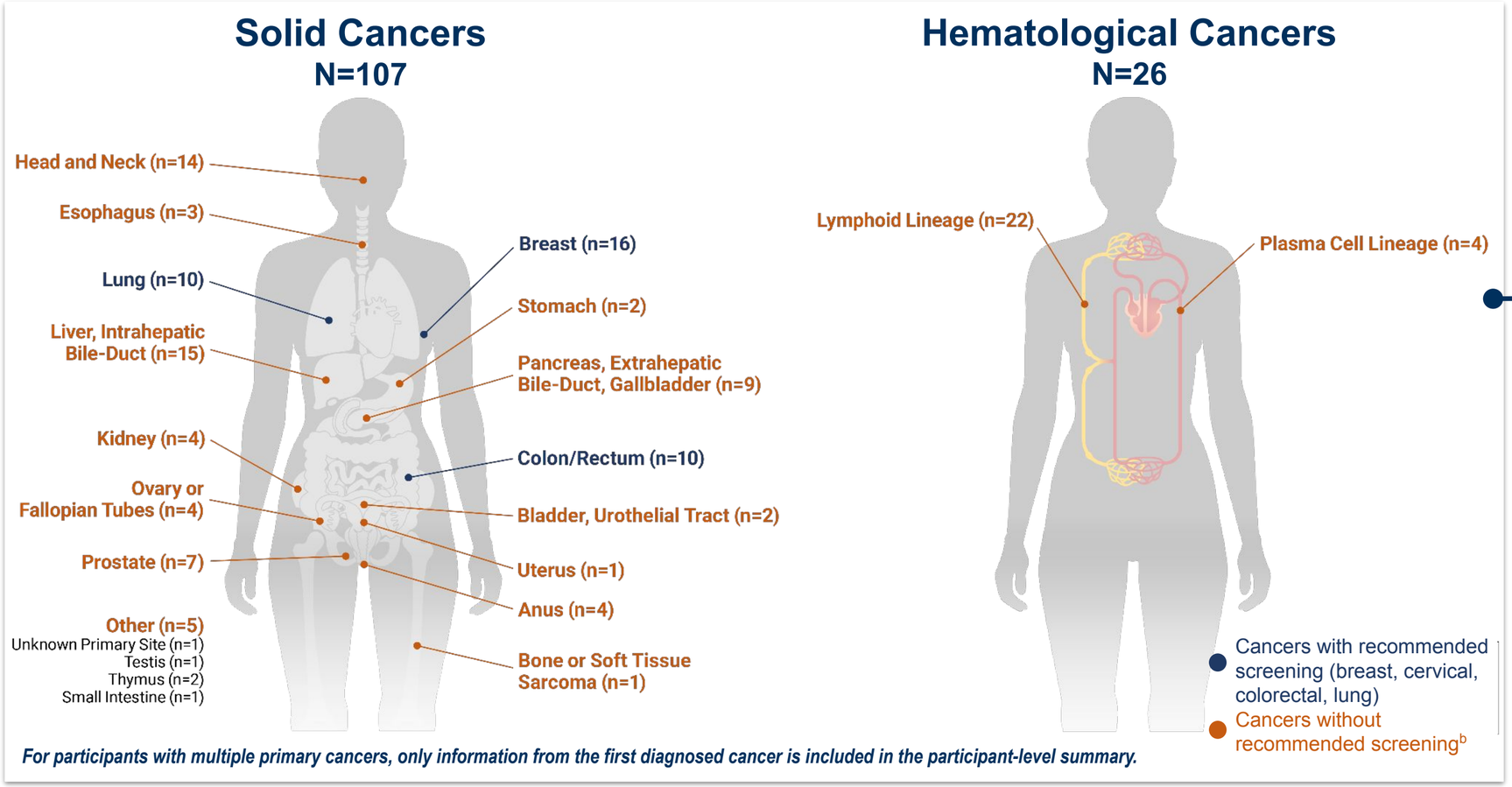
MCED Testing Increased the Number of Screen-Detected Cancers Over 7x When Added to Recommended Screening[a]



MCED cancer detection rate was 0.57%, translating to a number needed to screen of 174 to detect 1 cancer.

MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.
[a]USPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers. [b]Clinically-detected cancers included those detected incidentally (n=62), by signs and symptoms (n=40), by surveillance (n=21), and other (n=6; 3 were follow-up after an abnormal test result, 2 were incidental findings, and 1 was unknown). [c]MCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. [d]USPSTF grade A/B/C recommendations include screening for breast, cervical, colorectal, lung, and prostate cancers.

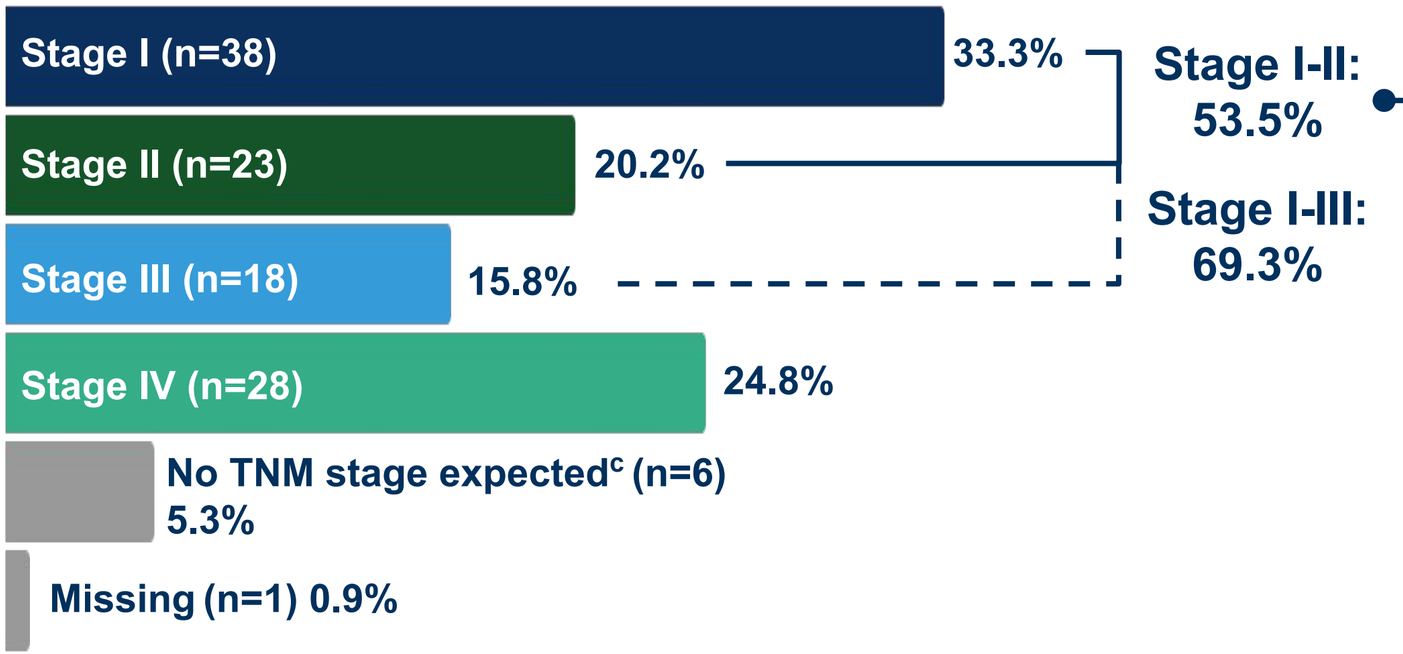
Majority of MCED-Detected Cancers[a] Do Not Have Recommended Screening[b]



- 133 participants with cancers diagnosed across a broad range of cancer types
  - 114 new primary cancers, 18 recurrent cancers, 1 unknown primary site
- **73%** of all MCED-detected cancers[a] **do not have recommended screening**[b]

MCED, multi-cancer early detection; USPSTF, United States Preventive Services Task Force.
[a]MCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. [b]USPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers.

Most MCED-Detected New Cancers[a,b] Were Detected at Early Stages

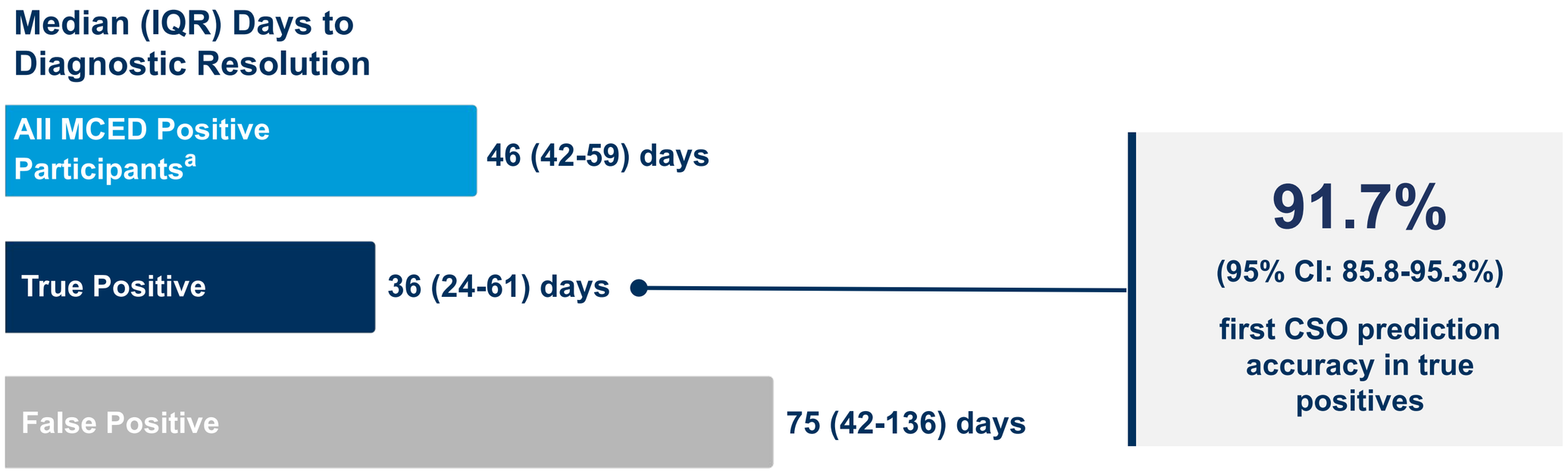


74% of stage I-II cancers do not have recommended screening[d]

- **Head & Neck (n=14)**
- **Liver (n=10)**
- Colon/Rectum (n=8)
- **Lymphoid lineage (n=7)**
- Breast (n=5)
- **Pancreas (n=4)**
- **Anus (n=3)**
- **Kidney (n=3)**
- Lung (n=3)
- **Plasma cell lineage (n=2)**
- **Bladder, Urothelial tract (n=1)**
- **Other - Testis (n=1)**

MCED, multi-cancer early detection; TNM, tumor node metastasis; USPSTF, United States Preventive Services Task Force.
[a]MCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. [b]For participants with multiple primary cancers, only information from the first diagnosed cancer is included in the participant-level summary. [c]No TNM stage is expected for cancers such as brain and spinal cord, leukemia, myeloma and plasma cell disorders, polycythemia vera, and cancer of unknown primary. [d]USPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers.

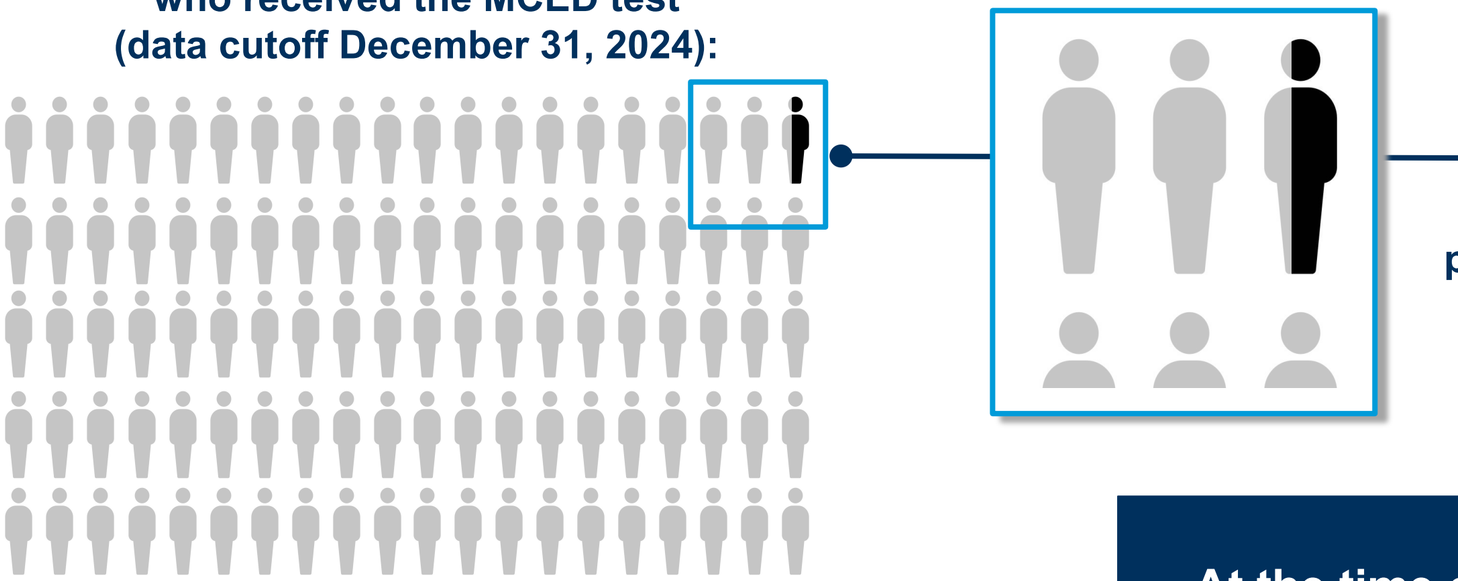
Accurate CSO Predictions Guided Rapid Diagnosis Following a Positive MCED Test Result



CI, confidence interval; CSO, cancer signal origin; IQR, interquartile range; MCED, multi-cancer early detection.
[a]Based on Kaplan-Meier analysis.

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

Of 25,114 safety analyzable participants who received the MCED test (data cutoff December 31, 2024):

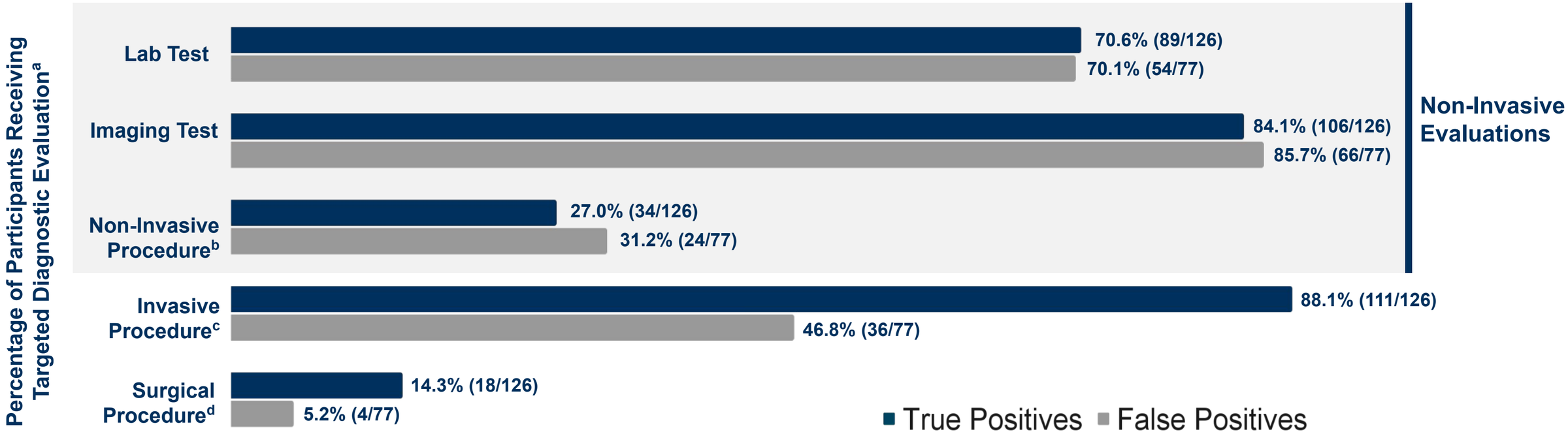


0.6%
had an invasive procedure to evaluate a positive MCED result

At the time of the initial analysis, no serious, study-related adverse events reported during the diagnostic workup

MCED, multi-cancer early detection.

Invasive Procedures Were ~2x More Common for True Positives Compared to False Positives



MCED, multi-cancer early detection; PET-CT, positron emission tomography-computed tomography.
[a]Includes diagnostic evaluations performed after positive MCED test result and before the protocol-directed PET-CT (if any) or prior to diagnostic resolution. [b]Includes electrocardiogram, pulmonary function tests, and physical exams. [c]Includes surgical and non-surgical procedures (eg, biopsy, endoscopy, Pap smear, etc). [d]Surgeries in participants with false-positive MCED test results were clinically justifiable and found premalignant neoplasms (n=2), benign neoplasm (n=1), and chronic infectious process (n=1).

Initial PATHFINDER 2 Results Demonstrated Robust Performance and Safety Across a Broad Population

In the largest interventional MCED study conducted in the US to date, the MCED test:

- Increased the number of cancers detected by >7x when added to recommended screening[a]
- Demonstrated robust performance, with a ~62% PPV — substantially higher than that observed in prior clinical studies[1-2]
- Enabled prompt, efficient diagnostic resolution with a favorable safety profile

MCED, multi-cancer early detection; PPV, positive predictive value; USPSTF, United States Preventive Services Task Force.
[a]USPSTF grade A/B recommendations include screening for breast, cervical, colorectal, and lung cancers.
1. Schrag D, et al. *Lancet*. 2023;402(10409):1251-1260. 2. Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.