Next Generation Multi-Cancer screening: The future is here

Elizabeth Half, MD , MPH

Head, Cancer prevention and early detection

Rambam Medical Center, Technion Institute of Technology

Head, GI Malignancy group, IGA

22.1.26, IHTG

Current Early Detection Screening Programs: Half of current cancer incidence*

	Method of Screening	Eligible Population	Status	Number of Eligible Patients	Compliance (%) [4]	Sensitivity (%)	Specificity (%)	PPV (%)
Breast Cancer	M[illegible]	50-74+	Included in	1M[1]	70.9#	[illegible]	[illegible]	[illegible]**-25.6***
CRC								4.9 3.5-6
Lung Cancer[illegible]								3.8
Cervica cancer								[illegible] CIN3+ [illegible]5 cancer

Challenge:

- Low compliance, low PPV
- 70% of cancer deaths – malignancies that lack screening tests

^ Age 50-74 screened FIT past year, colono last 10 yrs, 2024
^^FIT positive and completed colono in 180 d ,2024
$ PAP at least once in past 3 yrs

2. העמותה הישראלית לסרטן ריאה (0.8% of all population)
3. משרד הבריאות, INHIS-4, 2018-2020סקר הבריאות הלאומי בישראל
4. מדדי איכות בקהילה,
5. USPSTF recommended screening. Precision Oncology 2024 (8):91

Current Early Detection Screening Programs: Half of current cancer incidence*

	Method of Screening	Eligible Population	Status	Number of Eligible Patients	Compliance (%) [4]	Sensitivity (%)	Specificity (%)	PPV (%)
Breast Cancer	M[illegible]	50-74+	Included in	1M[1]	70.9[#]	86.9	88.9	4.4**-25.6***
CRC								4.9 3.5-6
Lung Cancer[2]								3.8
Cervical cancer								) CIN3+ 5 cancer

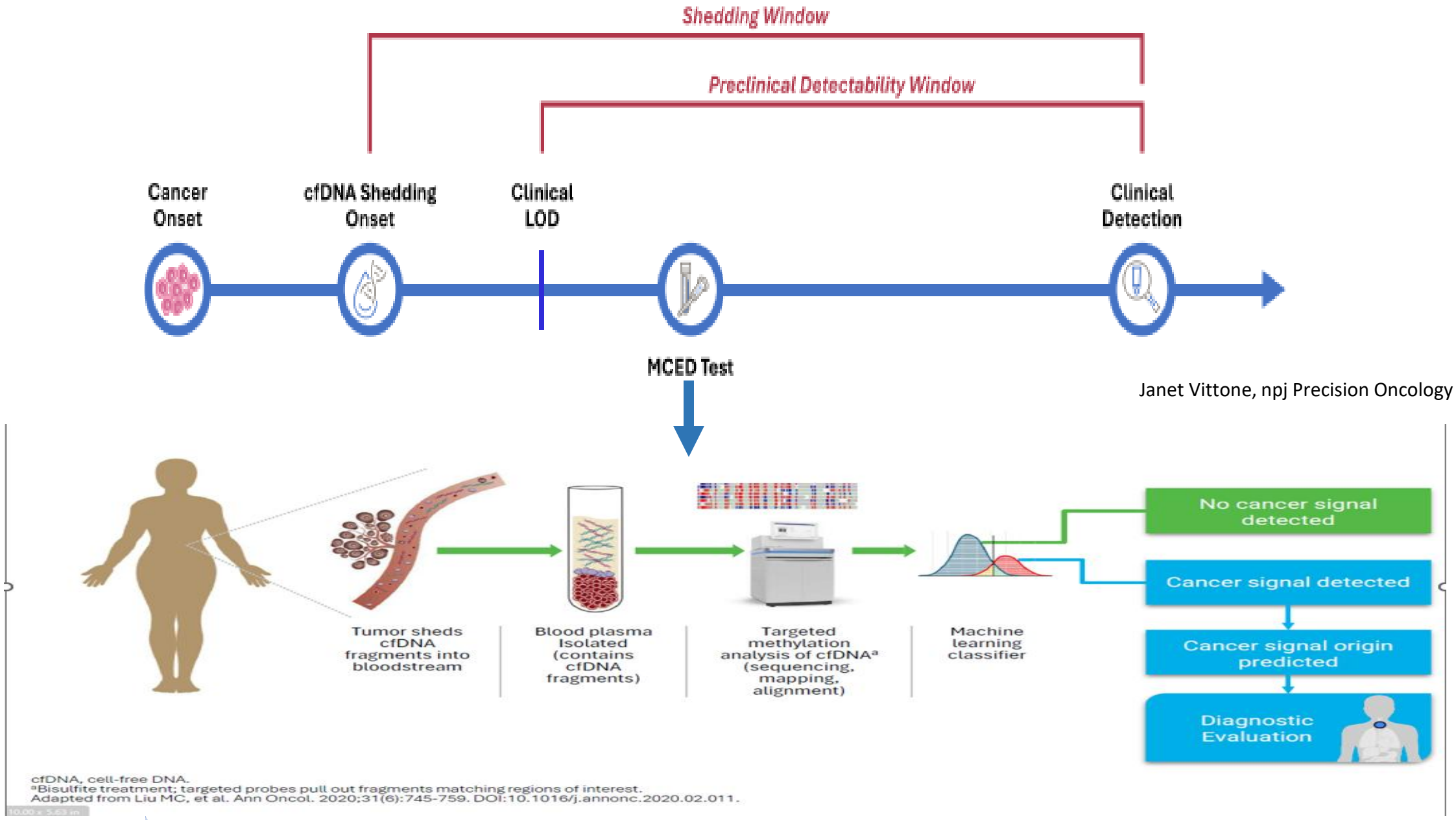
Challenge:

- Low compliance, low PPV
- 70% of cancer deaths – malignancies that lack screening tests

Will blood tests do the job?

^ Age 50-74 screened FIT past year, colono last 10 yrs, 2024
^^FIT positive and completed colono in 180 d ,2024
$ PAP at least once in past 3 yrs

2. העמותה הישראלית לסרטן ריאה (0.8% of all population)
3. משרד הבריאות, סקר הבריאות הלאומי בישראל INHIS-4, 2018-2020
4. מדדי איכות בקהילה,
5. USPSTF recommended screening. Precision Oncology 2024 (8):91



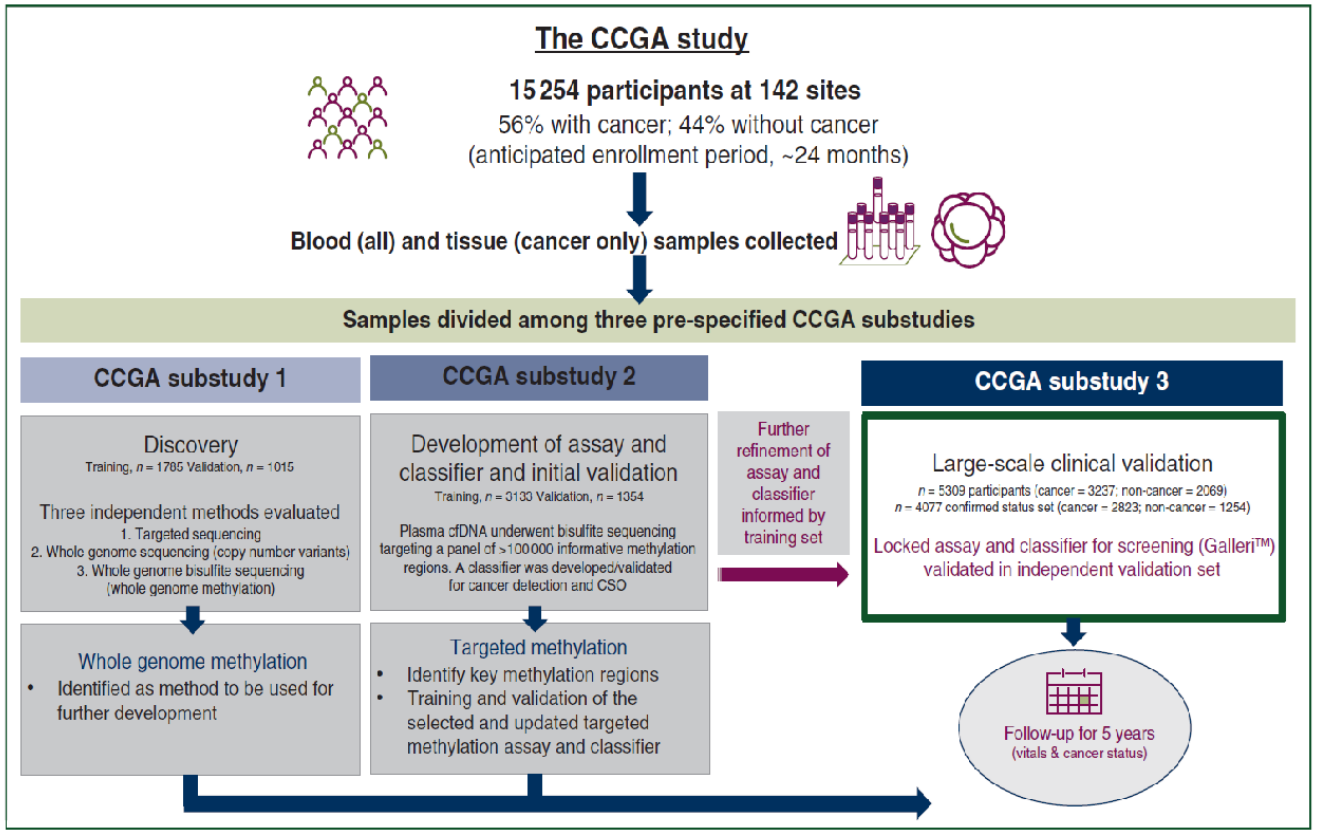
Janet Vittone, npj Precision Oncology (2024) 8:91

Fig. 1 | The MCED paradigm. cfDNA cell-free DNA, LOD limit of detection, MCED multi-cancer early detection.

ORIGINAL ARTICLE

Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set

E. A. Klein[1*], D. Richards[2], A. Cohn[3], M. Tummala[4], R. Lapham[5], D. Cosgrove[6], G. Chung[7], J. Clement[8], J. Gao[9], N. Hunkapiller[9], A. Jamshidi[9], K. N. Kurtzman[9], M. V. Seiden[10], C. Swanton[11,12] & M. C. Liu[13]

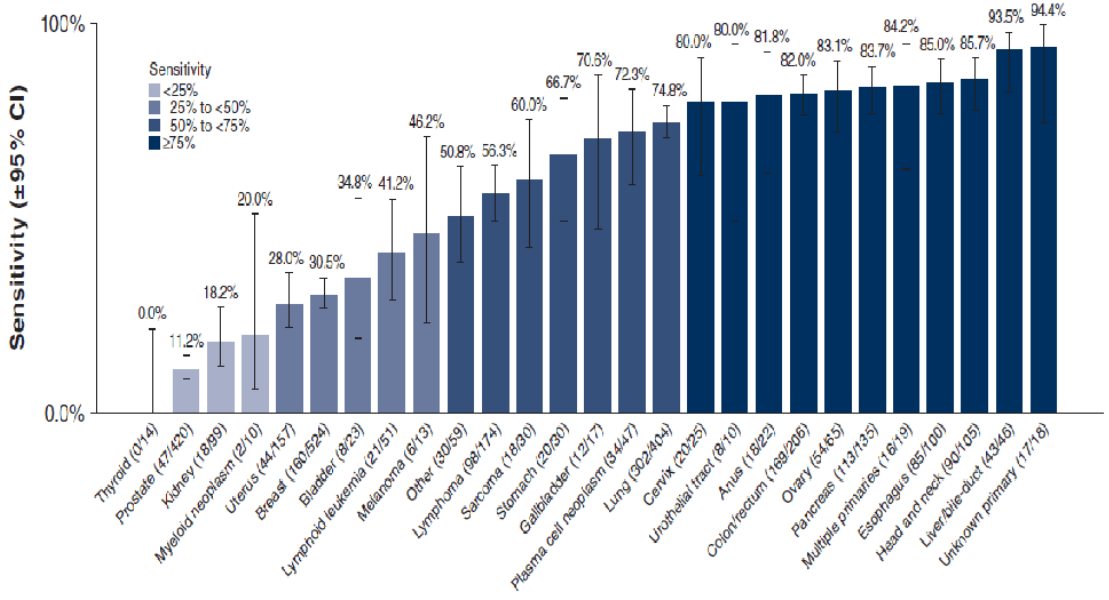


A

	Cancer	Non-cancer	Total
	2823	1254	4077
Test positive	1453	6	1459
Test negative	1370	1248	2618
	Sensitivity = 1453/2823 51.5% (49.6%-53.3%)	Specificity = 1248/1254 99.5% (99.0%-99.8%)	

Two-sided 95% Wilson confidence intervals were calculated.

B Sensitivity for various cancers

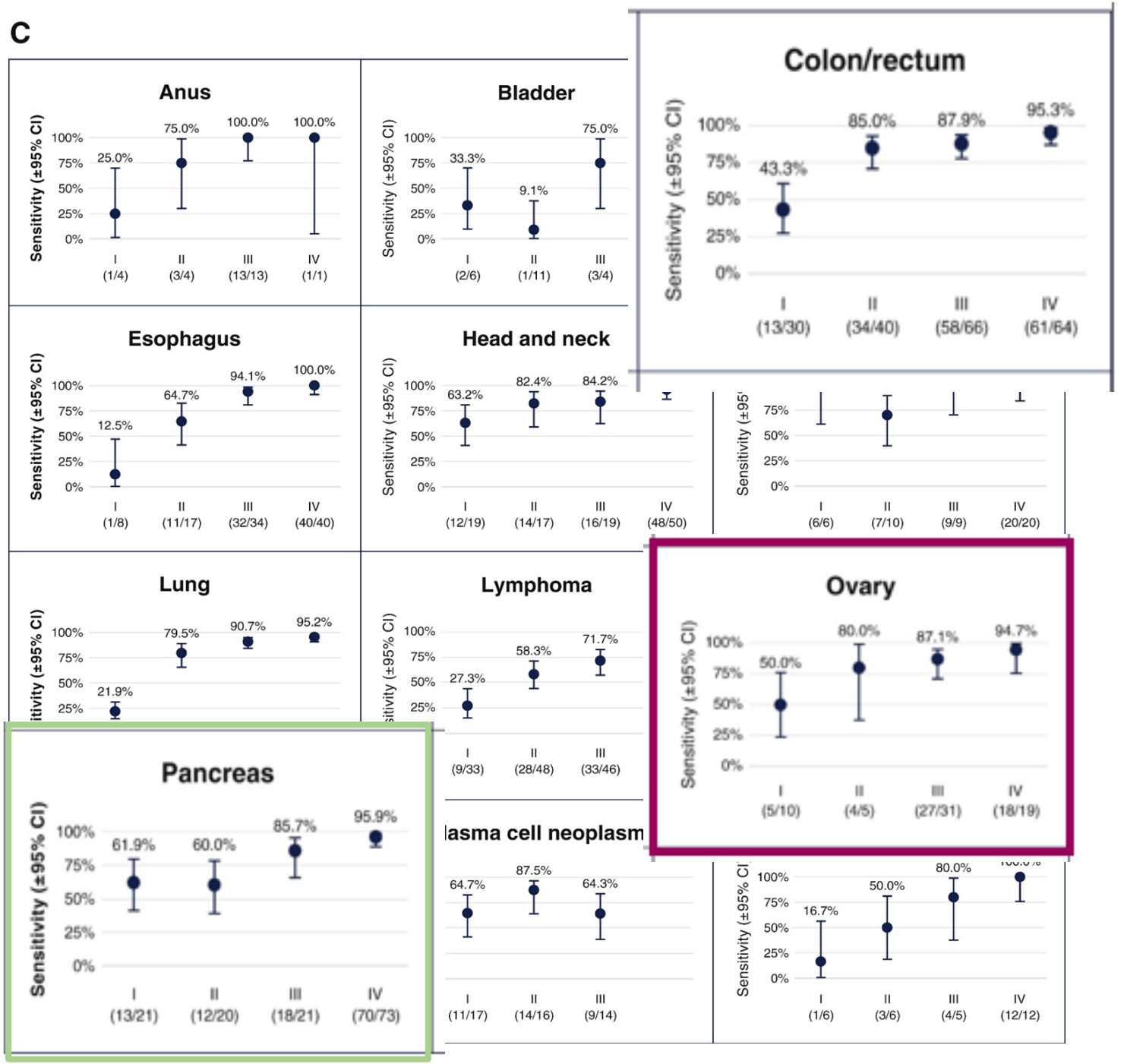


CCGA3: To validate the MCED test within an independent validation set with a further refined assay. Case control. Non-Cancer confirmed at 1 yr follow up.
Primary end point: test performance for cancer signal detection and site of origin.

Klein EA, Annals of Oncology 2021, 32;9:1167

Sensitivity by stage

Predicted correct site of origin in 89%



Klein EA, Annals of Oncology 2021, 32;9:1167

Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Deb Schrag, Tomasz M Beer, Charles H McDonnell III, Lincoln Nadauld, Christina A Dilaveri, Robert Reid, Catherine R Marinac, Karen C Chung, Margarita Lopatin, Eric T Fung, Eric A Klein

	Aged ≥50 years with additional cancer risk (n=3681)	Aged ≥50 years without additional cancer risk (n=2940)	Total (n=6621)	
Resolution				
All	56 (1·5%)	36 (1·2%)	92 (1.4%)	Cancer signal detected
True positive	24 (0·7%)	11 (0·4%)	35 (0·5%)	Diagnosed cancer, **48% stage 1,2**
False positive	32 (0·9%)	25 (0·9%)	57 (0·9%)	
Positive predictive value	24/56; 43% (30·8–55·9)	11/36; 31% (18·0–46·9)	35/92; 38% (28·8–48·3)	
Negative predictive value	3449/3502; 98·5% (98·0–98·8)	2786/2819; 98·8% (98·4–99·2)	6235/6321; 98·6% (98·3–98·9)	
Specificity	3449/3480; 99·1% (98·7–99·4)	2786/2810; 99·1% (98·7–99·4)	6235/6290; 99·1% (98·9–99·3)	
Yield rate	24/3681; 0·65% (0·41–0·92)	11/2940; 0·37% (0·17–0·61)	35/6621; 0·53% (0·36–0·71)	
Number needed to screen	3681/24; 153 (108–245)	2940/11; 267 (163–588)	6621/35; 189 (141–276)	

BMI, kg/m²			
<18·5	32 (0·9%)	18 (0·6%)	50 (0·8%)
18·5 to <25·0	1045 (28·4%)	956 (32·5%)	2001 (30·2%)
25·0 to <30·0	1297 (35·2%)	1039 (35·3%)	2336 (35·3%)
≥30·0	1264 (34·3%)	887 (30·2%)	2151 (32·5%)

Primary end point- time to diagnosis and extent of diagnostic testing required

Additional end points – test performance and CSO accuracy

Lancet. 2023 October 07; 402(10409): 1251–1260.

Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Deb Schrag, Tomasz M Beer, Charles H McDonnell III, Lincoln Nadauld, Christina A Dilaveri, Robert Reid, Catherine R Marinac, Karen C Chung, Margarita Lopatin, Eric T Fung, Eric A Klein

	Age ≥50 years with additional cancer risk (n=3681)	Age ≥50 years without additional cancer risk (n=2940)	Total (n=6621)
Resolution			
All	56 (1·5%)	36 (1·2%)	92 (1.4%) Cancer signal detected
True positive	24 (0·7%)	11 (0·4%)	35 (0·5%) Diagnosed cancer, **48% stage 1,2**
False positive	32 (0·9%)	25 (0·9%)	57 (0·9%)
Positive predictive value	24/56; 43% (30·8–55·9)	11/36; 31% (18·0–46·9)	35/92; 38% (28·8–48·3)
Negative predictive value	3449/3502; 98·5% (98·0–98·8)	2786/2819; 98·8% (98·4–99·2)	6235/6321; 98·6% (98·3–98·9)
Specificity	3449/3480; 99·1% (98·7–99·4)	2786/2810; 99·1% (98·7–99·4)	6235/6290; 99·1% (98·9–99·3)
Yield rate	24/3681; 0·65% (0·41–0·92)	11/2940; 0·37% (0·17–0·61)	35/6621; 0·53% (0·36–0·71)
Number needed to screen	3681/24; 153 (108–245)	2940/11; 267 (163–588)	6621/35; 189 (141–276)

	Aged ≥50 years with additional	Aged ≥50 years without additional	Total (n=6621)
Age, years[A]			
Age group, ye			
50–64			
65–79			
≥80			
Sex			
Female			
Male			
Smoking stat			
Current smo			
Former smo			
Non-smoke			
Eligible for lur			
Previous cance			
Cancer predisp			
BMI, kg/m			
<18·5	32 (0·9%)	18 (0·6%)	50 (0·8%)
18·5 to <25·0	1045 (28·4%)	956 (32·5%)	2001 (30·2%)
25·0 to <30·0	1297 (35·2%)	1039 (35·3%)	2336 (35·3%)
≥30·0	1264 (34·3%)	887 (30·2%)	2151 (32·5%)

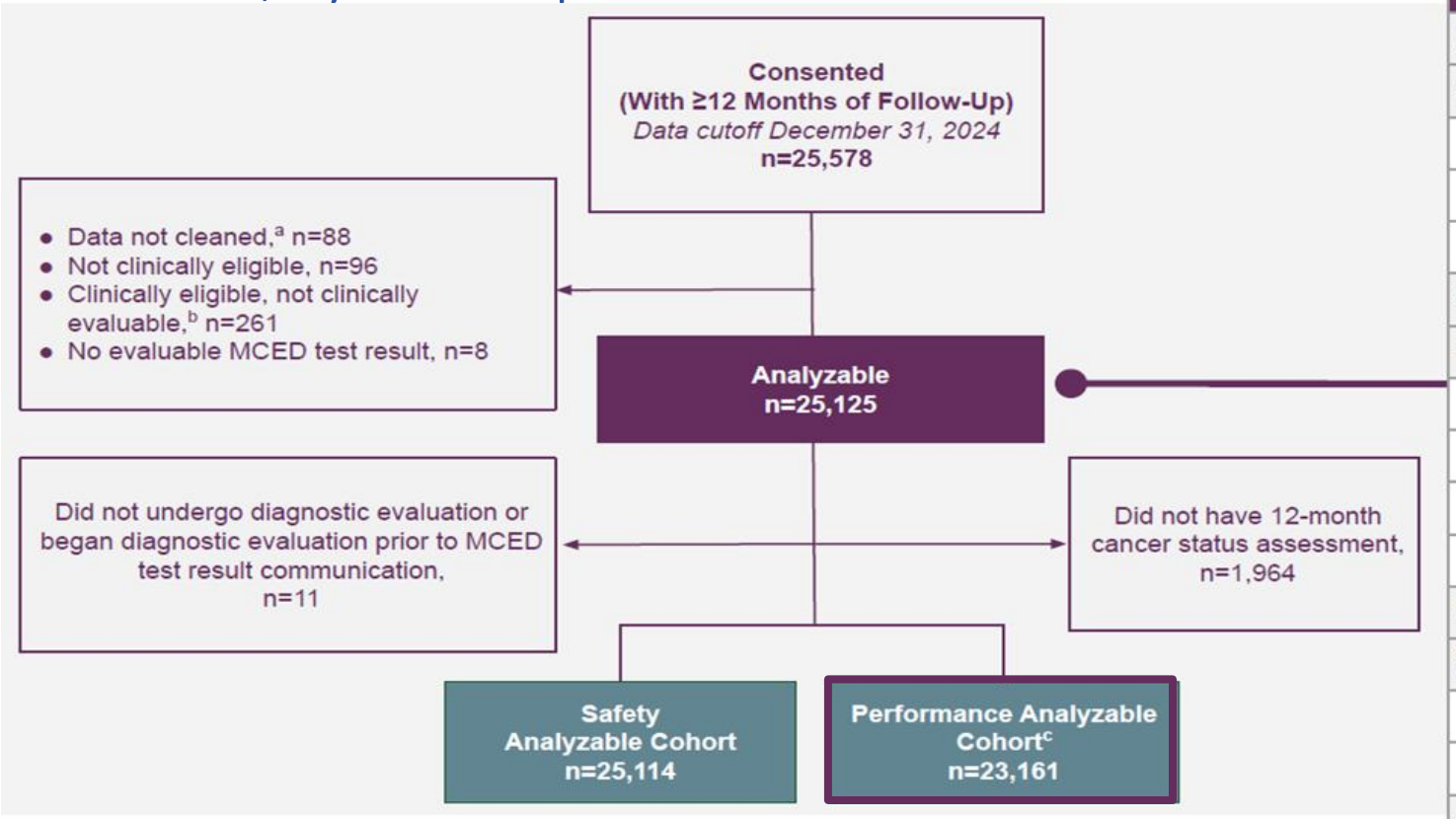
- 86 FNs @ 12 mo 73% were stage 1\2 [most lung, breast, prostate and brain (n=4)]
- Anxiety evaluated* increased in positive cases but returned to normal at the end of the study

Lancet. 2023 October 07; 402(10409): 1251–1260.
*Lancet Oncol. 2025 Feb;26(2):165-174

PATHFINDER 2:

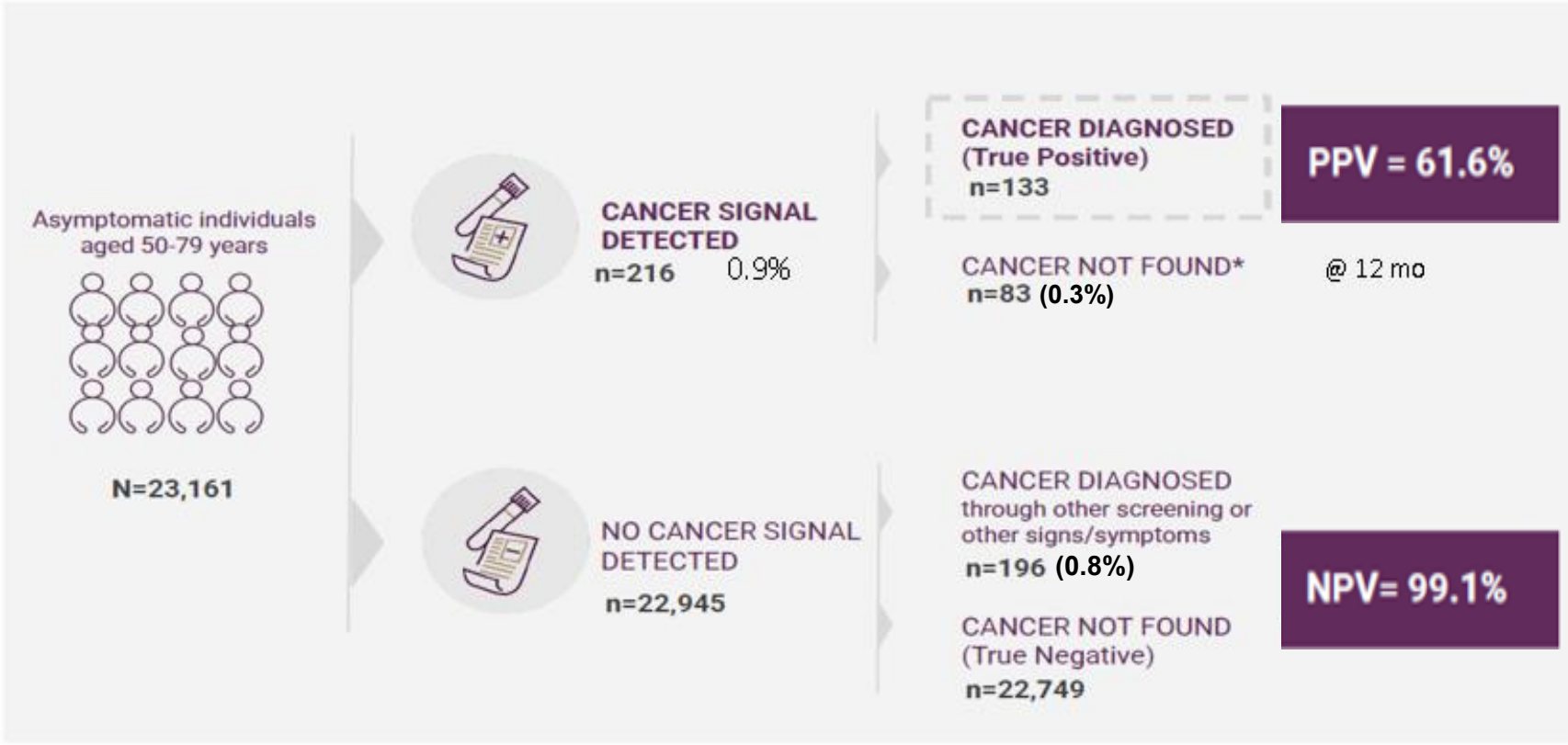
Prospective study, 35,878 participants
32 US health care systems, 3 yrs follow up.
Most average risk, over 50 yrs, no cancer tx past 3 yrs and no ongoing cancer work up

ESMO 2025, 1 yr follow-up



Initial 25,125 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%**

Results: PATHFINDER 2, ESMO 2025



PPV in intended to use population **61.6%**

(The probability that a person with a positive MCED test will have cancer)

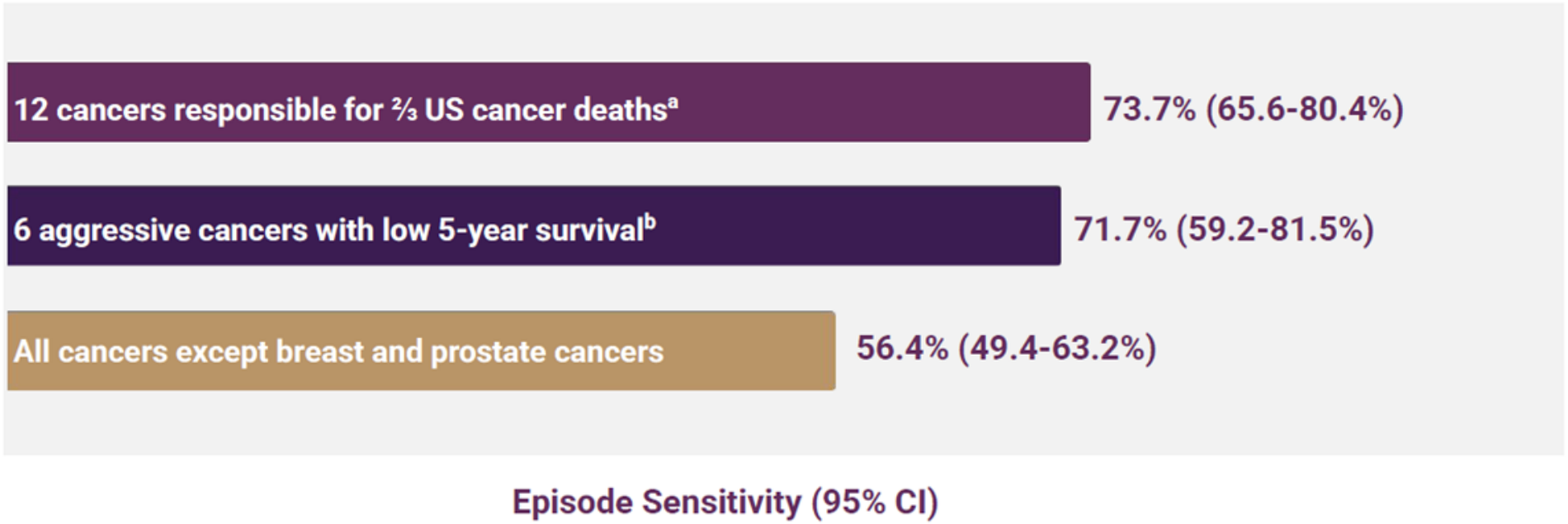
Results: PATHFINDER 2, ESMO 2025

	Cancer Status Over 12 Months of Follow-up (Performance Analyzable Cohort)			
	Cancer Diagnosis (N=329)	**No Cancer Diagnosis (N=22,832)**	**Total (N=23,161)**	**Performance Metric (95% CI)**
MCED Test Result Positive	133	83 (FP)	216	**PPV 61.6% (54.9-67.8%)**
MCED Test Result 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 **99.64%** (99.5-99.7%)		

Sensitivity for Clinically Relevant Subgroups

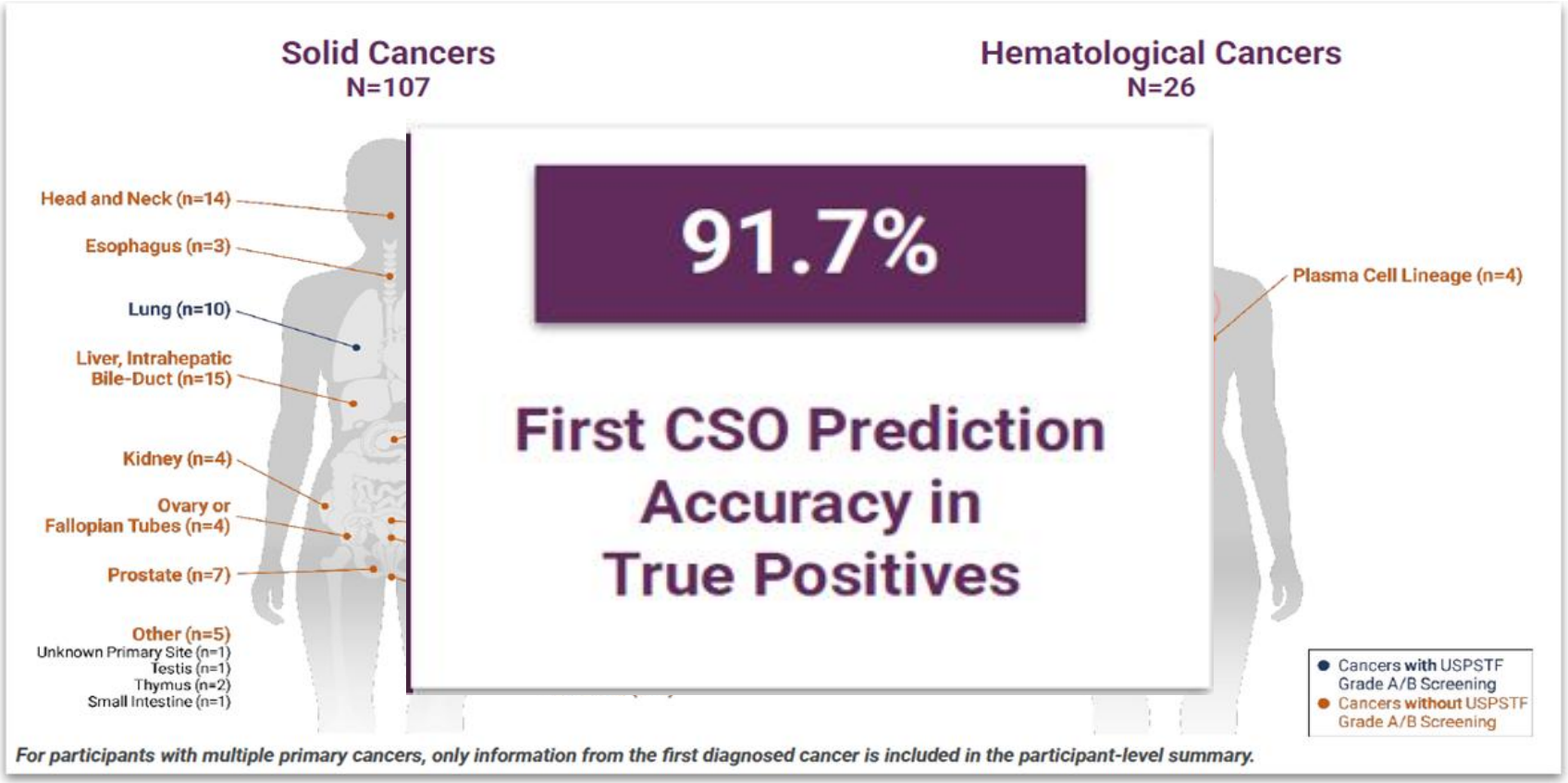
Overall Episode Sensitivity

40.4%



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

PATHFINDER 2: Cancers detected



133 participants with cancers diagnosed across 18 cancer types

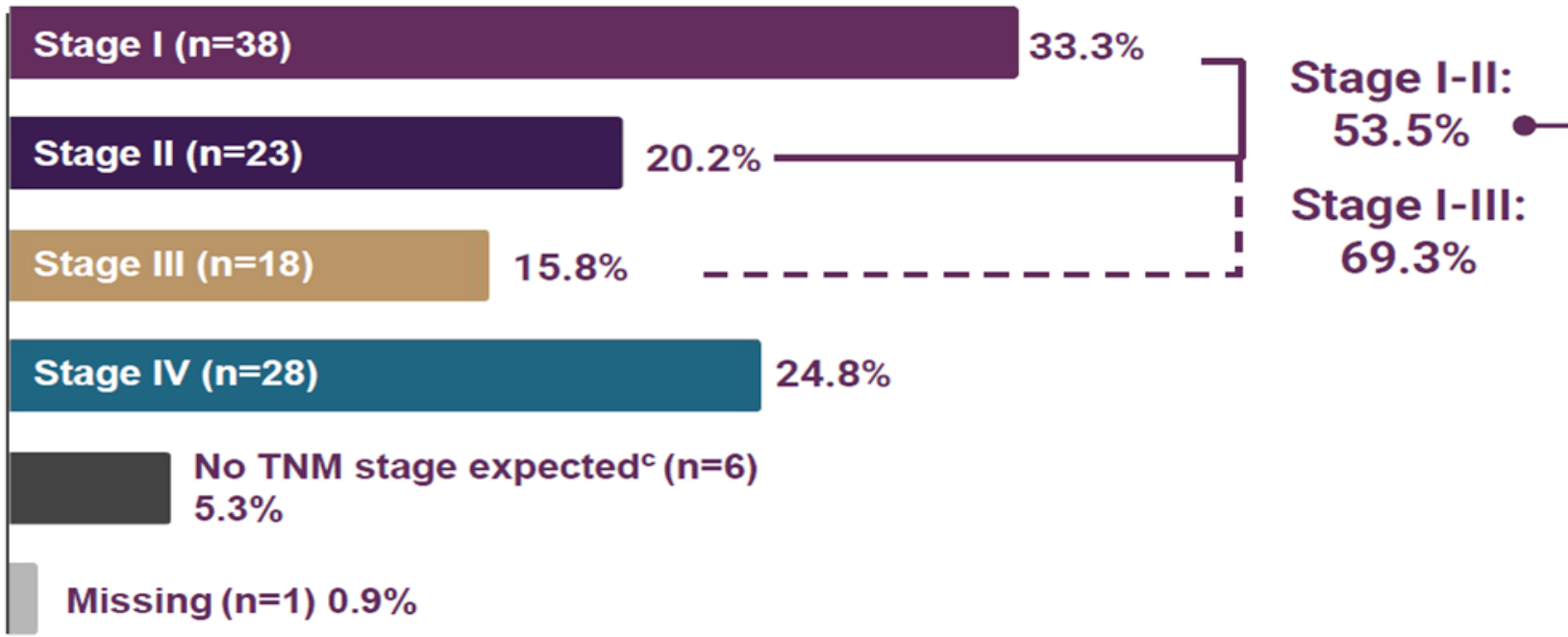
73%

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]Recommended screening options are for breast, cervix, colon/rectum, and lung cancers..

Stage of disease distribution

114 New Primary Cancers Were Diagnosed*



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

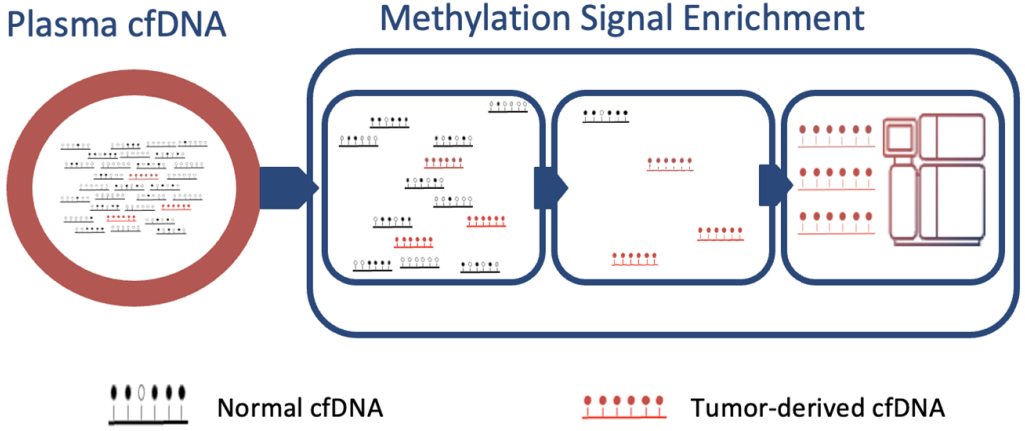
- **Head & Neck (n=14)**
- **Liver (n=10)**
- Colon/Rectum (n=8)
- **Lymphoid lineage (n=7)**
- Breast (n=5)
- **Pancreas (n=4)**
- **Anus (n=3)**
- **Kidney (n=3)**
- Lung (n=3)
- **Plasma cell lineage (n=2)**
- **Bladder, Urothelial tract (n=1)**
- **Other - Testis (n=1)**

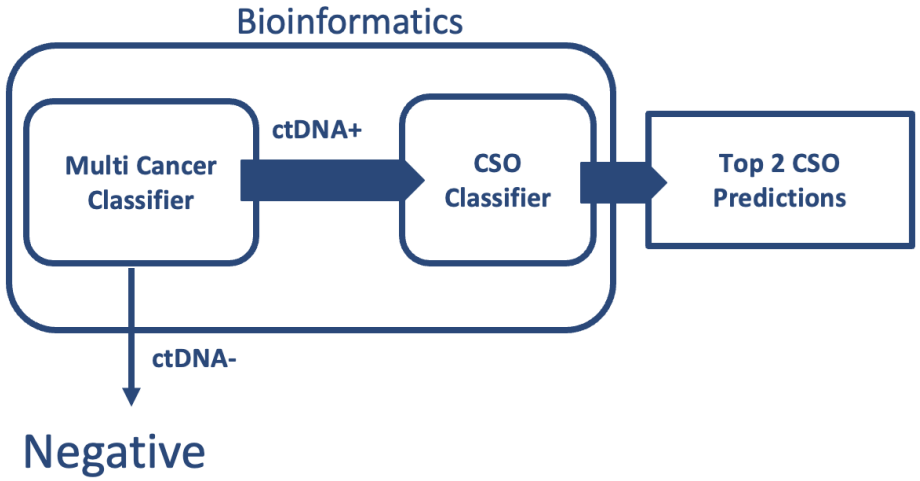
MCED, multi-cancer early detection; TNM, tumor node metastasis.
*114 new primary cancers, 18 recurrent cancers, 1 unknown primary site
[a]MCED-detected refers to cancers diagnosed within 12 months following a positive MCED test result. [b]For participants with multiple primary cancers, only information 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]Recommended screening options are for breast, cervical, colorectal and lung cancers. Nabavizadeh N, et al. Proffered Presentation presented at: European Society for Medical Oncology (ESMO) Congress; October 17-21, 2025; Berlin, Germany.

MCED Test (Guardant)

Uses NGS hybrid capture assay (Shield™) to measure DNA methylation in differentially methylated regions across solid cancers

Regression model trained to distinguish cancer from non-cancer at 98% specificity. Then, a cancer signal origin (CSO) model was trained to categorize 10 solid tumors.

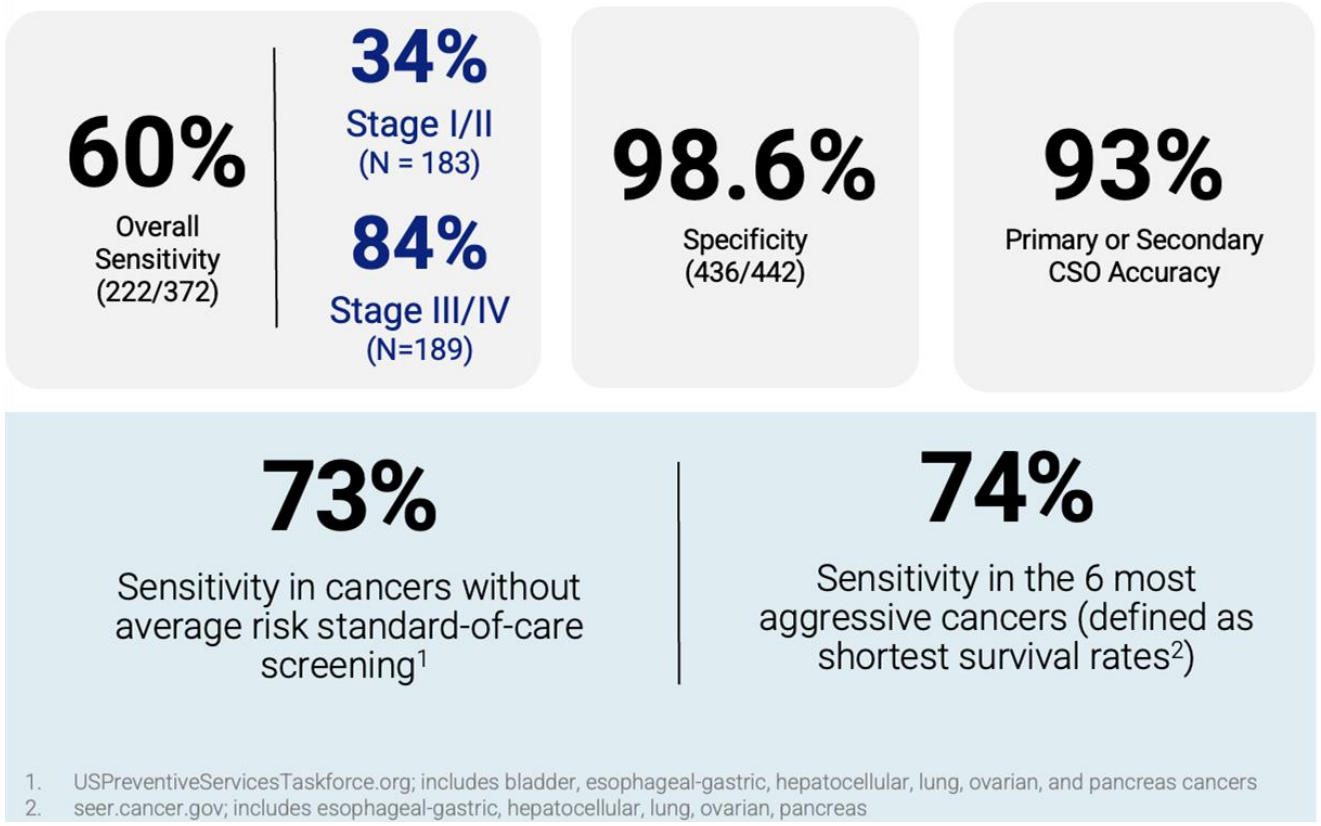




He, et al. ASCO 2025
Slide provided by Sinicrope FA

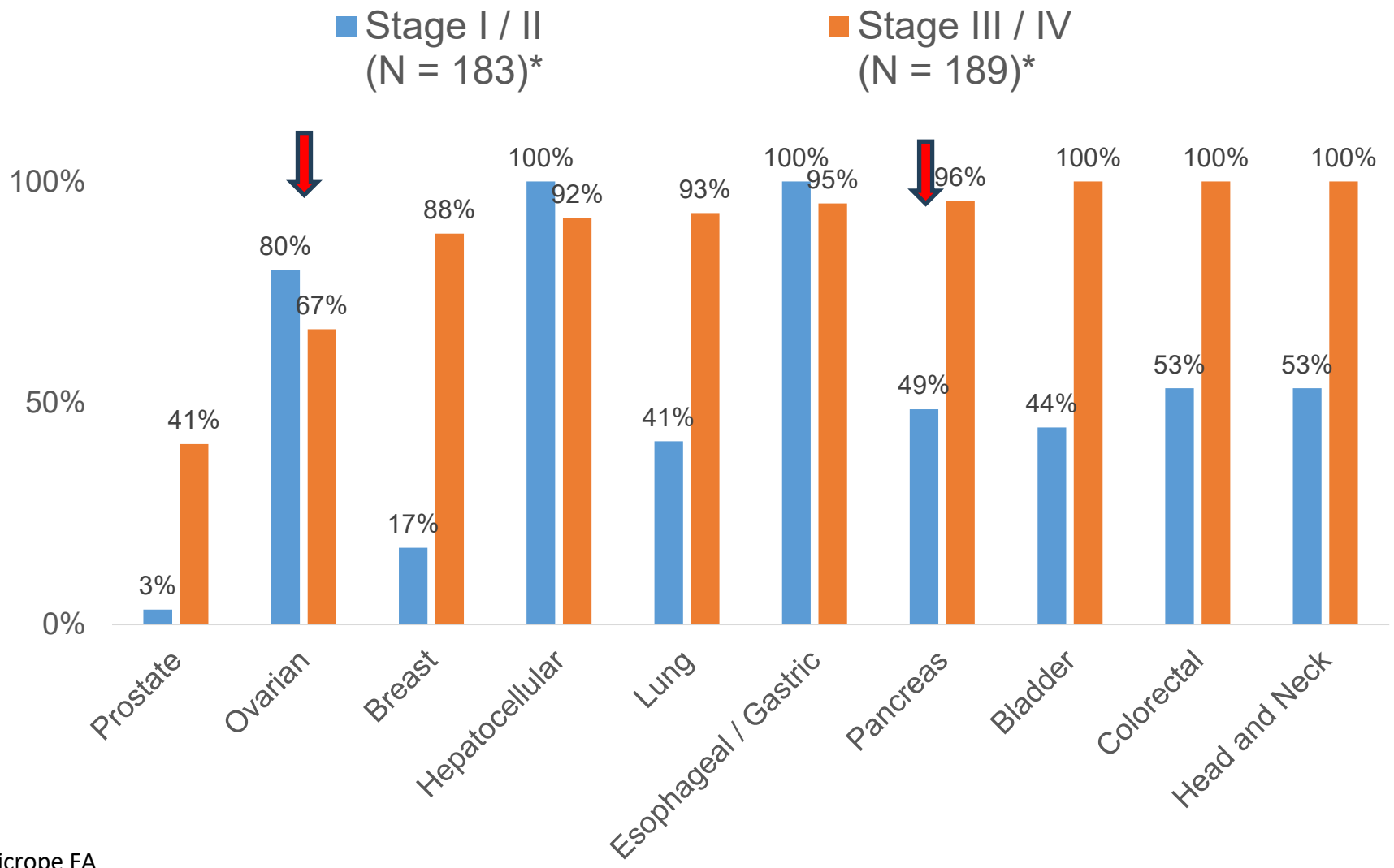
Study Cohort and Overall Performance

- Blinded case-control cohort of 962 adults ages 40-65+ with treatment naïve cancer, OR self-reported cancer free status with 1 year of follow-up.



He, et al. ASCO 2025
Slide provided by Sinicrope FA

Results:
Sensitivity influenced by by Cancer Stage



He, et al. ASCO 2025
Slide provided by Sinicrope FA

*Per stage numbers do not include Head and Neck

MCED: Here to stay !

- Target cancer in multiple organs without conventional screening test
- Better PPV than conventional recommended screening tools

  No data on mutation carriers
- Survival of detected cancers are equivalent to age and stage expected
- Predicted to have a better compliance rate - The Best Test is the One that Gets Done !!!

- However, limited data on FP outcomes (follow-up, retesting?), awaiting randomized control trial results, and no mortality data

Not instead of conventional screening!!!

- Thank you !!!

- A 35 yr old *BRCA2* mutation carrier, working mother one child
- No family history of ovarian cancer
- OBGYN follow up- normal
- Breast imaging is normal
- Still significant risk of cancer in multiple sites
- Will a liquid biopsy (MCED test) be the solution for screening

???

NOT YET!!!