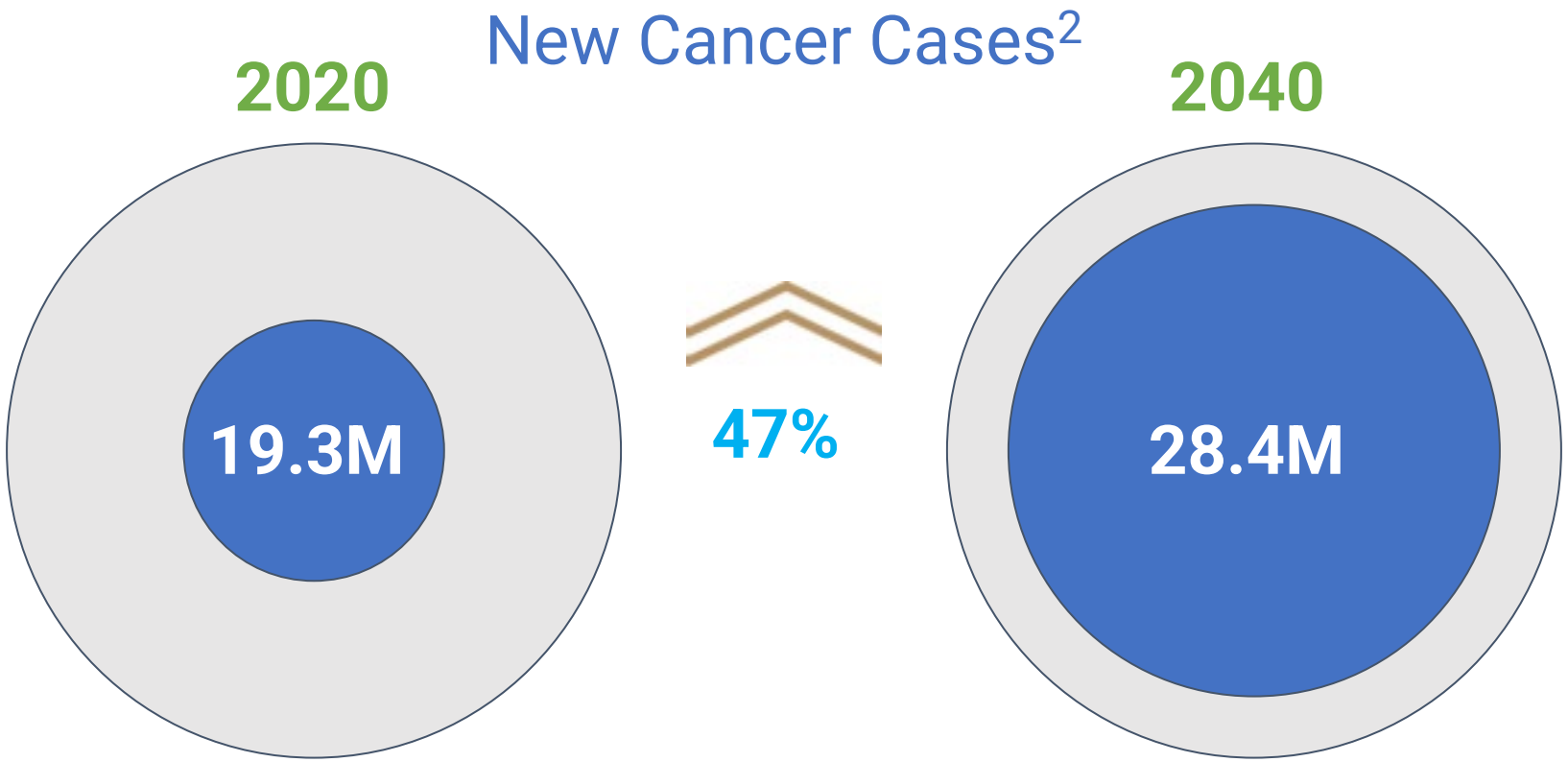
Multicancer Early Detection (MCED)

Eric A. Klein, MD
Distinguished Scientist, GRAIL, Inc

Emeritus Professor and Chair, Glickman Urological and Kidney Institute
Cleveland Clinic Lerner College of Medicine

Globally, Cancer Cases Are On the Rise

Annual ASIRs for all cancers combined increased between 2007 and 2017 in 123 countries[1]



ASIR, age-standardized incidence rate.

[1]Fitzmaurice C et al. *JAMA Oncol.* 2019;5:1749-1768. [2]Sung H et al. *CA Cancer J Clin.* 2021;71:209-249.

The Status Quo

Despite this:

USPSTF Recommendations for Cancer Screening

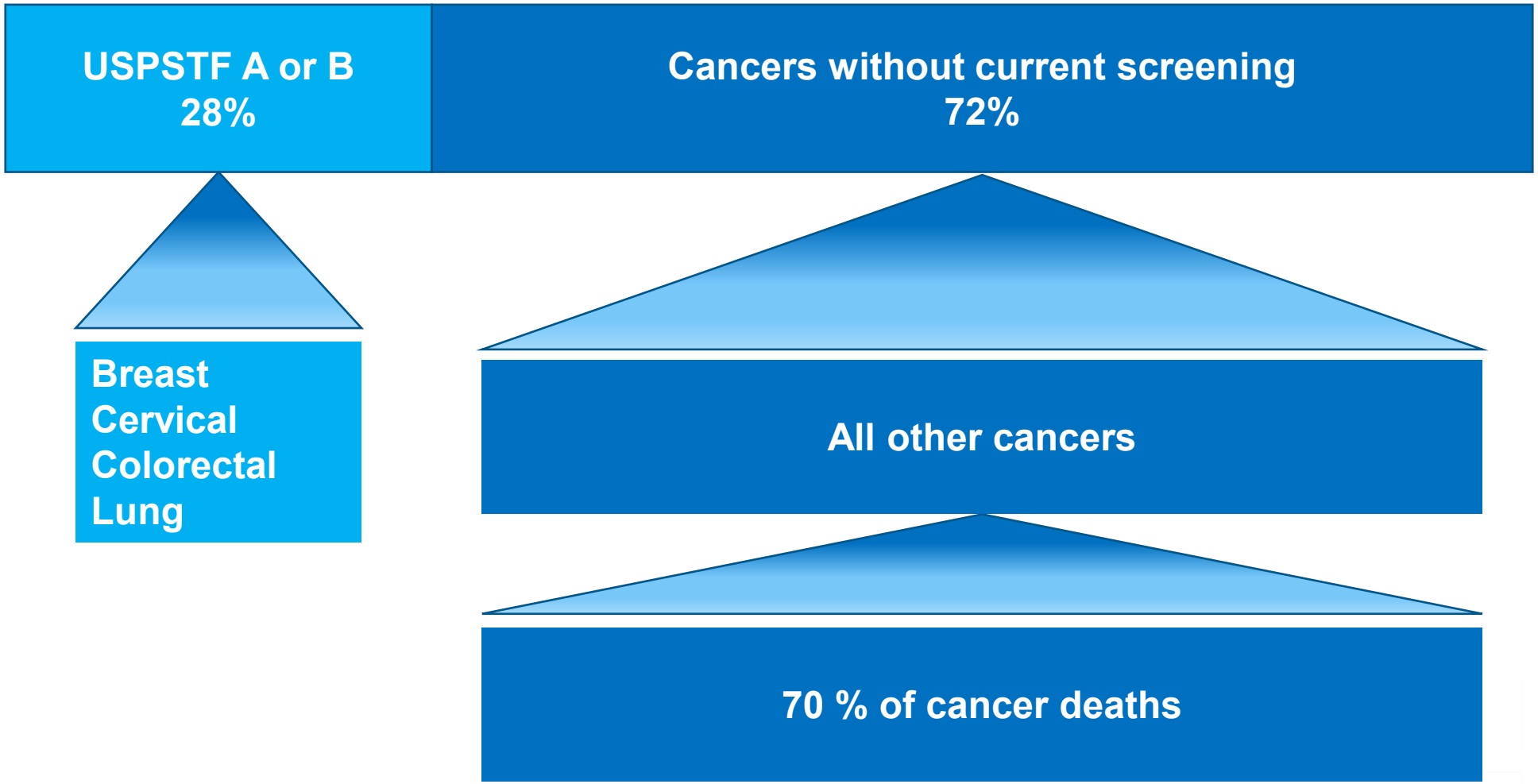
Cancer	Grade	Population	Modality/ Recommendation
Cervical	A	Women aged 21 to 65	Regular screening (3–5 years) using cervical cytology and/or HPV tests
Colorectal	A B	Adults aged 50 to 75 Adults aged 45-49	Regular annual screening, multiple effective methods available
Breast	B C	Women aged 50 to 74 Women aged 40 to 49	Biennial screening mammography
Lung	B	Adults aged 55–80, with history of smoking	Annual low-dose computed tomography (LDCT) screening
Prostate	C	Men aged 55 to 69	Periodic PSA screening on case-by-case basis

Mortality

> 600,000 people die of cancer every year In the US

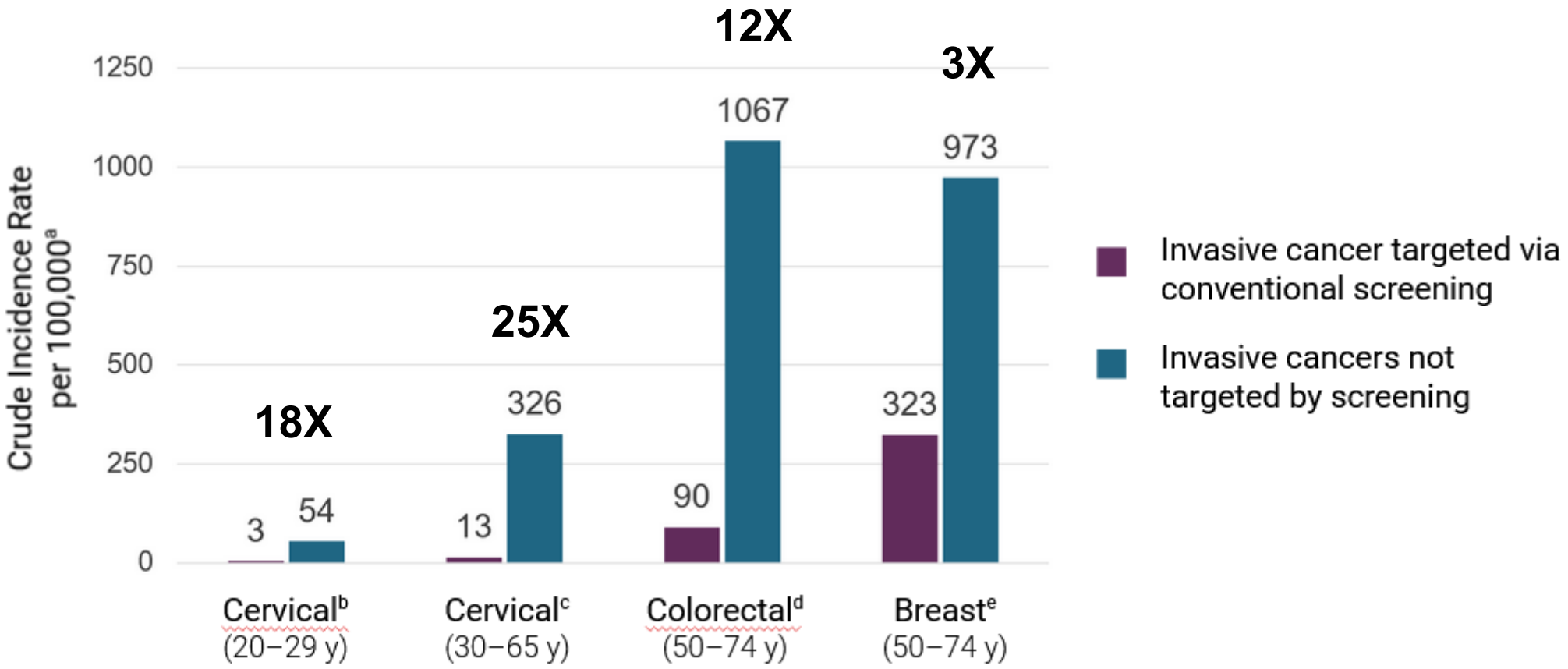
Why is this Necessary?

Annual invasive cancer incidence in persons aged 50-79



*SEER Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2017 Sub. Includes persons aged 50+ diagnosed 2006-2015

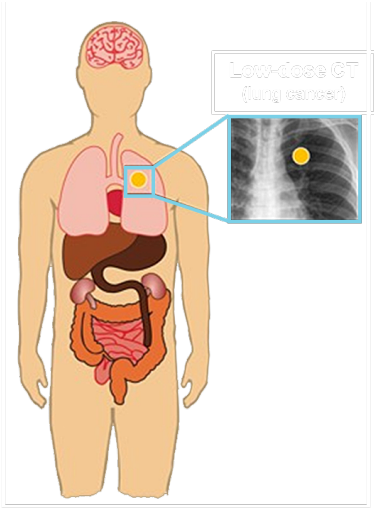
Screened Patients are More Likely to be Diagnosed with Non-Screened Cancers



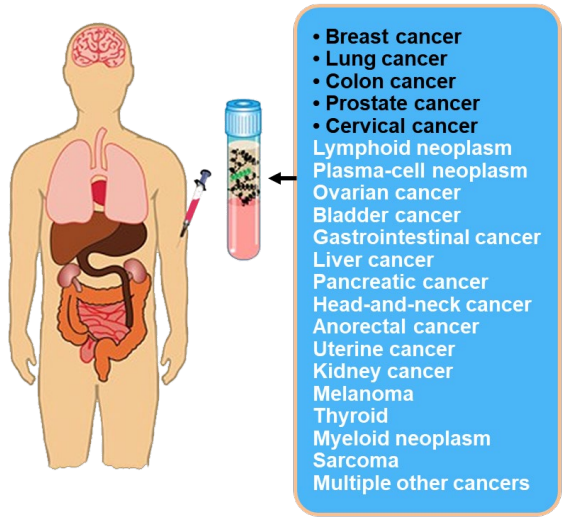
Source: https://seer.cancer.gov/
Clarke et al., Cancer Cell. 39:447, 2021

Paradigm Shift

Screening for individual cancers



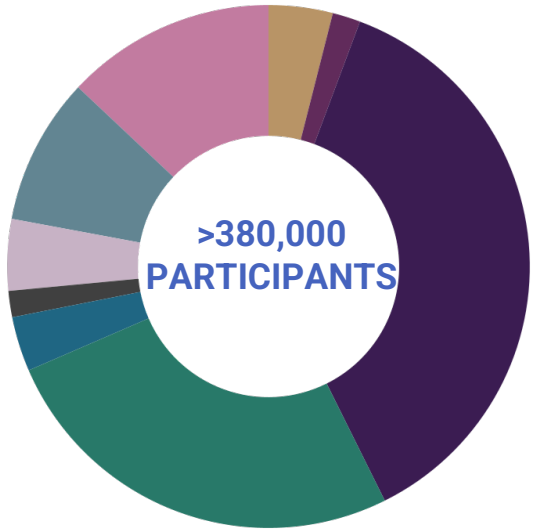
Screening individuals for cancer(s)



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*
2	**PATHFINDER** (n=6,662)	**Evaluate clinical implementation and perceptions of MCED test** *Enrollment: complete, published*	*The Lancet 2023*
3	**SYMPLIFY** (n=6,242)	**Assess MCED test in individuals with signs/symptoms of cancer** *Enrollment: complete, published*	*Lancet Oncology 2023*
4	**NHS-GALLERI** (n≈142,321)	**Assess clinical utility of MCED for population screening in the UK** *Enrollment: complete*	
5	**STRIVE** (n=99,481)	**Evaluate MCED test performance in women to detect invasive cancers**[a] *Enrollment: complete*	
6	**SUMMIT** (n=13,035)	**Clinical validation in individuals at high risk of lung cancer** *Enrollment: complete*	
7	**REFLECTION** (n≈17,000)	**Assess experience/clinical outcomes in real-world setting** *Enrollment: ongoing*	
8	**PATHFINDER 2** (n≈35,000)	**Evaluate MCED test performance in eligible screening population** *Enrollment: completed*	
9	**REACH** (n≈50,000)	**Understand health equity impact of Galleri in a Medicare population** *Enrollment: ongoing*	



Cancer types detected in Substudy 3 of CCGA
45 cancer types lack recommended screening

Breast	Cervical	Colorectal
Lung		Prostate

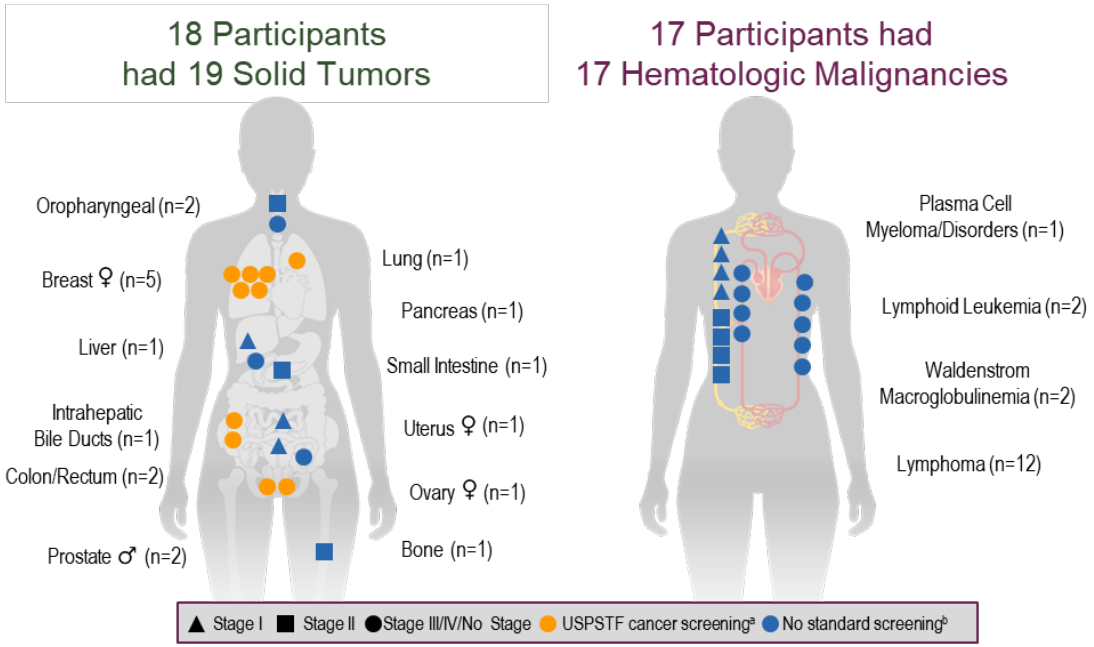
Adrenal Cortical Carcinoma
Ampulla of Vater
Anus
Appendix, Carcinoma
Bile Ducts, Distal
Bile Ducts, Intrahepatic
Bile Ducts, Perihilar
Bladder, Urinary
Bone
Esophagus and
Esophagogastric Junction
Gallbladder
Gastrointestinal Stromal Tumor
Gestational Trophoblastic Neoplasms
Kidney
Larynx
Leukemia
Liver
Lymphoma (Hodgkin and Non-Hodgkin)
Melanoma of the Skin
Merkel Cell Carcinoma
Mesothelioma, Malignant Pleural
Nasal Cavity and Paranasal Sinuses
Nasopharynx
Neuroendocrine Tumors of the Appendix
Neuroendocrine Tumors of the Colon and Rectum
Neuroendocrine Tumors of the Pancreas
Oral Cavity
Oropharynx (HPV-Mediated, p16+)
Oropharynx (p16-) and Hypopharynx
Ovary, Fallopian Tube and Primary Peritoneum
Pancreas, exocrine
Penis
Plasma Cell Myeloma and Plasma Cell Disorders
Small Intestine
Soft Tissue Sarcoma of the Abdomen and
Thoracic Visceral Organs
Soft Tissue Sarcoma of the Head and Neck
Soft Tissue Sarcoma of the Retroperitoneum
Soft Tissue Sarcoma of the Trunk and Extremities
Soft Tissue Sarcoma Unusual Histologies and Sites
Stomach
Testis
Ureter, Renal Pelvis
Uterus, Carcinoma and Carcinosarcoma
Uterus, Sarcoma
Vagina
Vulva

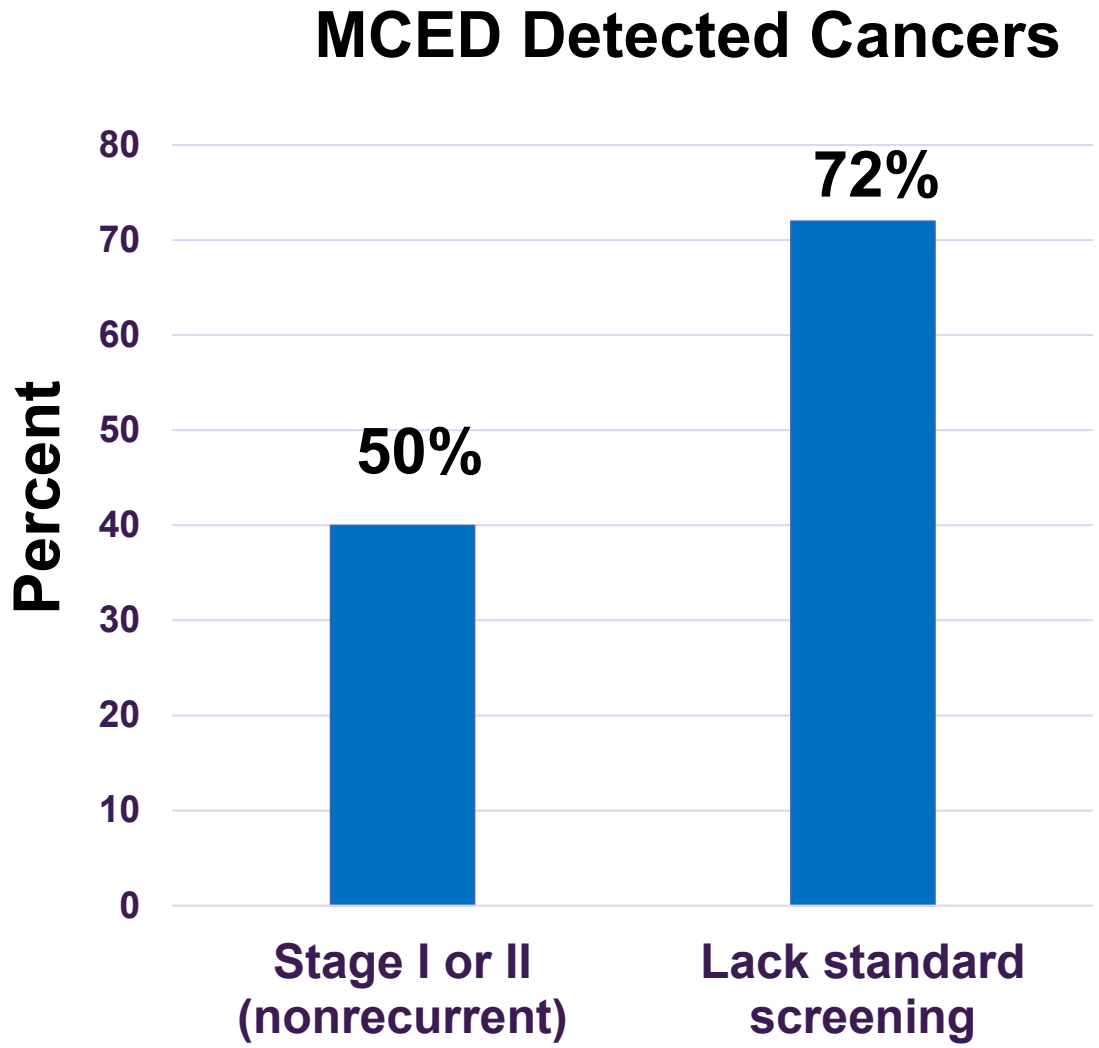
Galleri does not detect all cancers and all cancers cannot be detected in the blood. False positive and false negative results do occur.

Klein EA, et al. Ann Oncol. 32:1167

PATHFINDER

Cancer signal was detected in 1.4% (92/6621 participants)





Schrag et al. *The Lancet*. 2023;402(10409):1251

Cancer Signal Origin May Aid in the Time to Diagnostic Resolution

PATHFINDER[2] (n=90)

57 days

Median time to diagnostic resolution

73% of true positives reached resolution in <3 months

GITLIN et al[1] (n=)

156.2 days

Mean time to diagnosis for all cancer patients

Retrospective analysis of over 458,818 patients and their time to a cancer diagnosis

PATHFINDER true positive participants had a faster time to diagnosis than previous retrospective analysis of cancer patients

Schrag et al. Lancet 2023 (in press)
Gitlin et al. J Manag Care Spec Pharm. 29:659, 2023

Consistent Results Across Studies

Clinical Validation Study (CCGA3)

0.5%	44%	89%
False positive rate	Positive predictive value	Localization accuracy

Confirmatory Intended Use Population Study (PATHFINDER)*

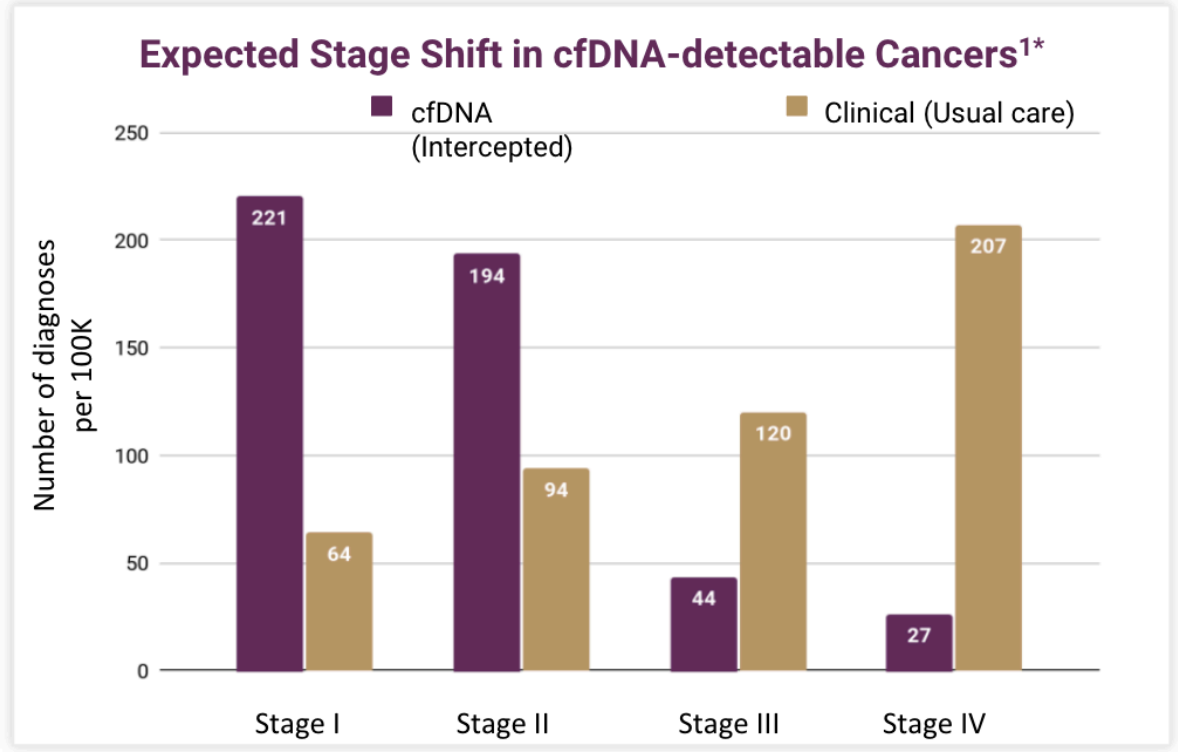
0.5%	43%	88%
False positive rate	Positive predictive value	Localization accuracy**

Refined test used commercially; **1st or 2nd location prediction

Klein EA, et al. Ann Oncol. 32:1167, 2021
Schrag et al. Lancet 402:1251, 2023

Modeled Stage Shift

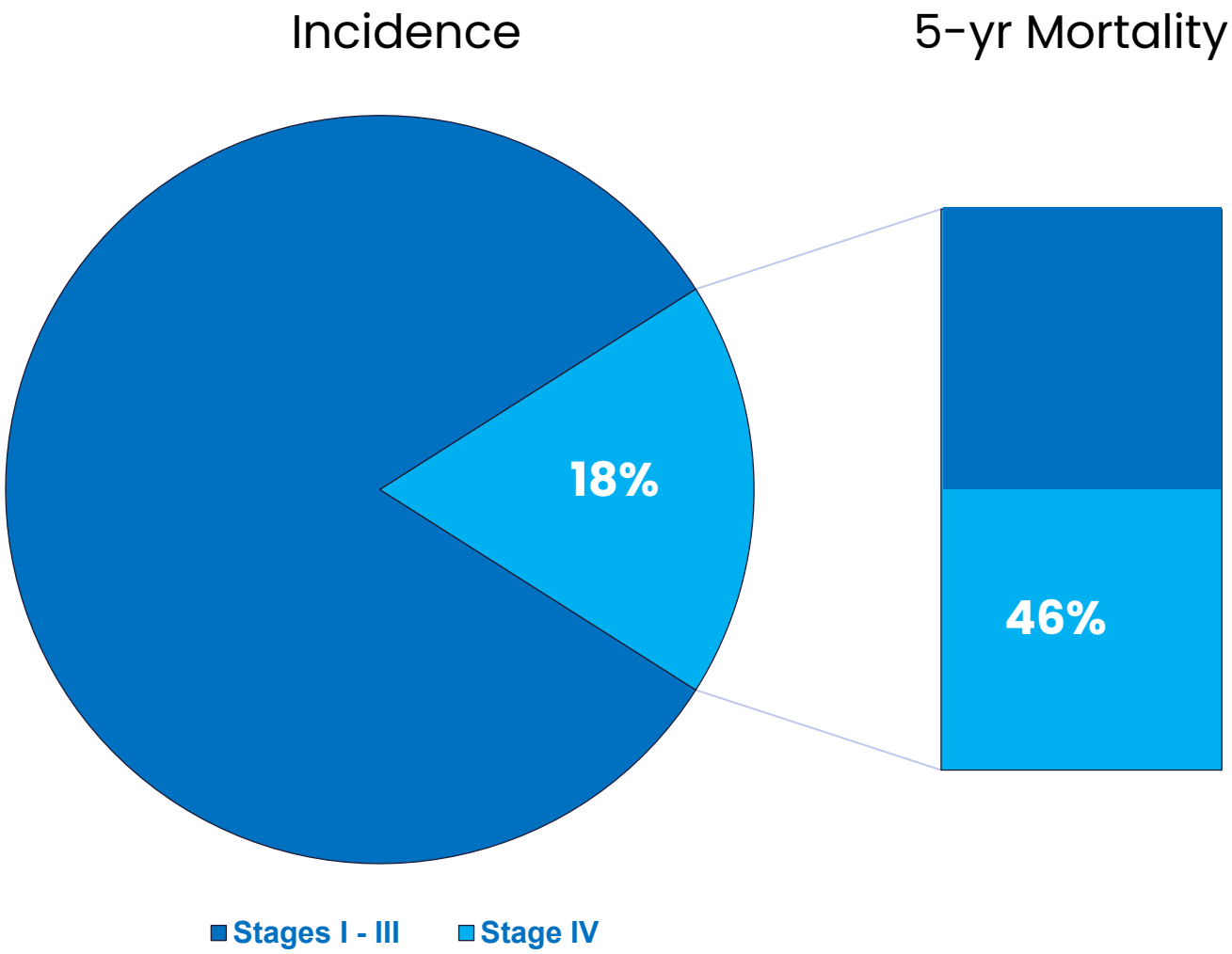
Expected Stage-Shift in Incident Cancers by Adding the Galleri test to SoC, based on Modeled Data



Based on modeled data of GRAIL's MCED test in elevated risk population age 50–79 years.

Hubbell E et al. Cancer Epidemiol Biomarkers Prev. 2021;30:460-468

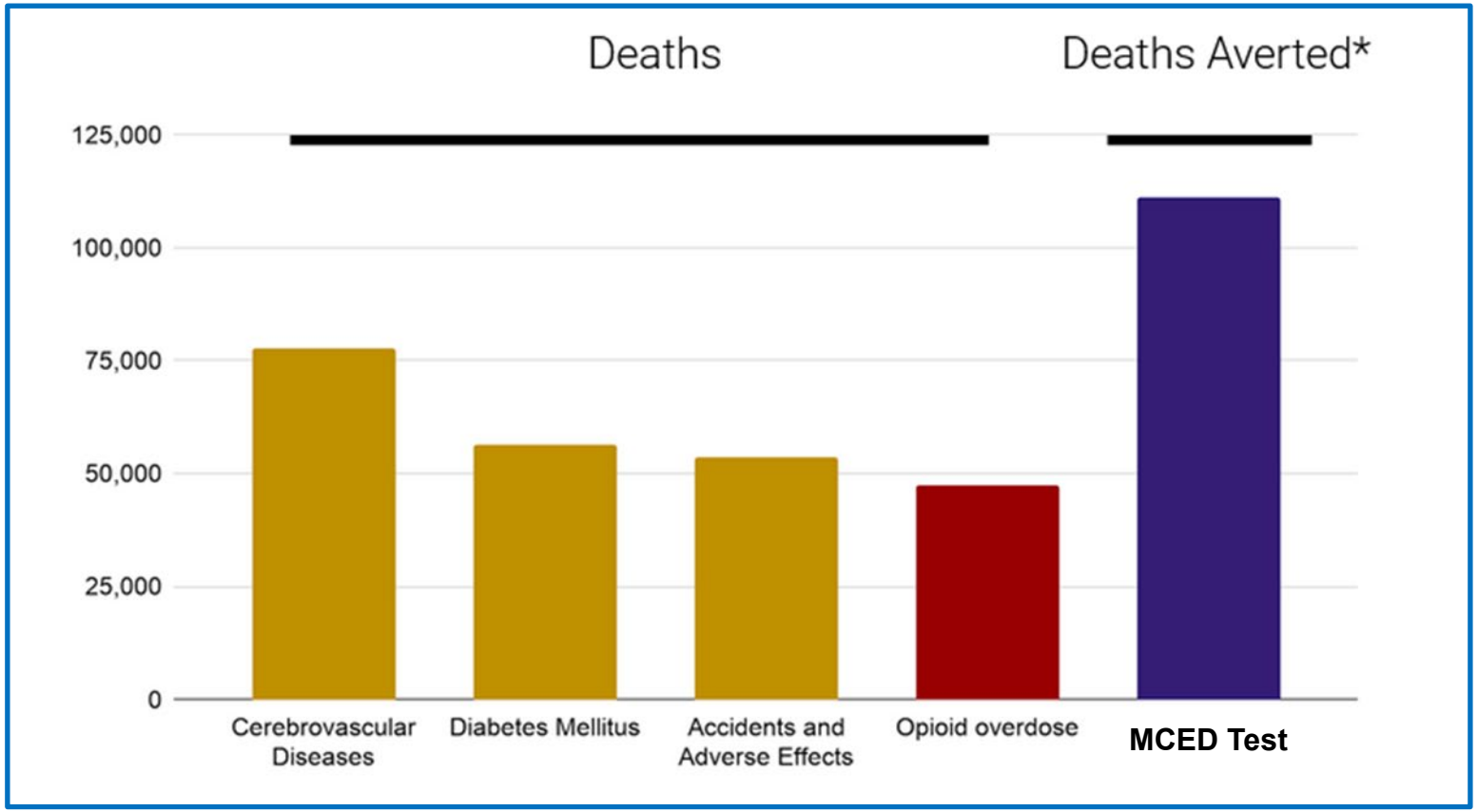
Stage IV Cancers Account for an Outsized Proportion of Cancer Deaths



Source: SEER, adults aged 50-79, 2006-2015

Clarke et al.: Cancer Epidemiol Biomarkers Prev. 2020 29:895-902

Potential for Earlier Detection to Save Lives
Modeled Data from SEER and CCGA

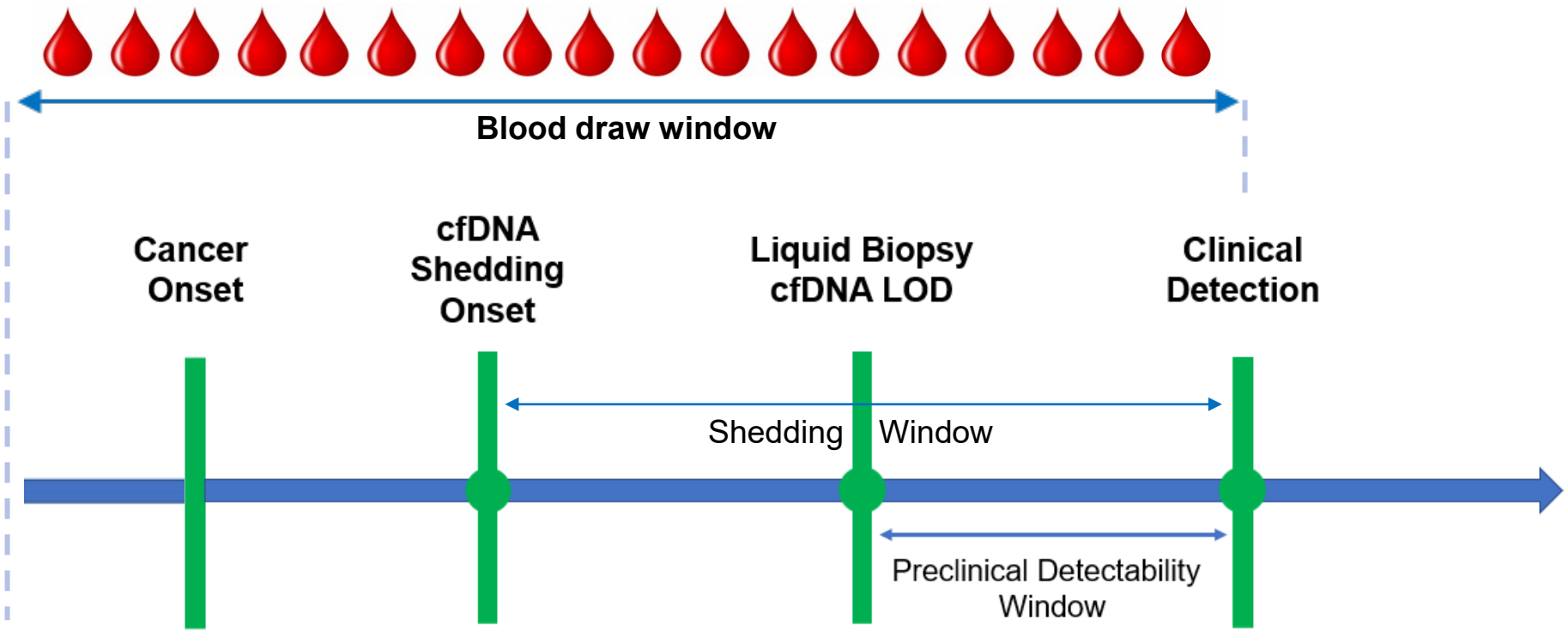


26% Reduction in Cancer Mortality

Hubbell E, et al. Cancer Epidemiol Biomarkers Prev., 2020

Methylated DNA Biomarkers and Incident Cancer in the American Cancer Society (ACS) Cancer Prevention Study-3 (CPS-3) Cohort

Supports 1-year screening interval



323 days

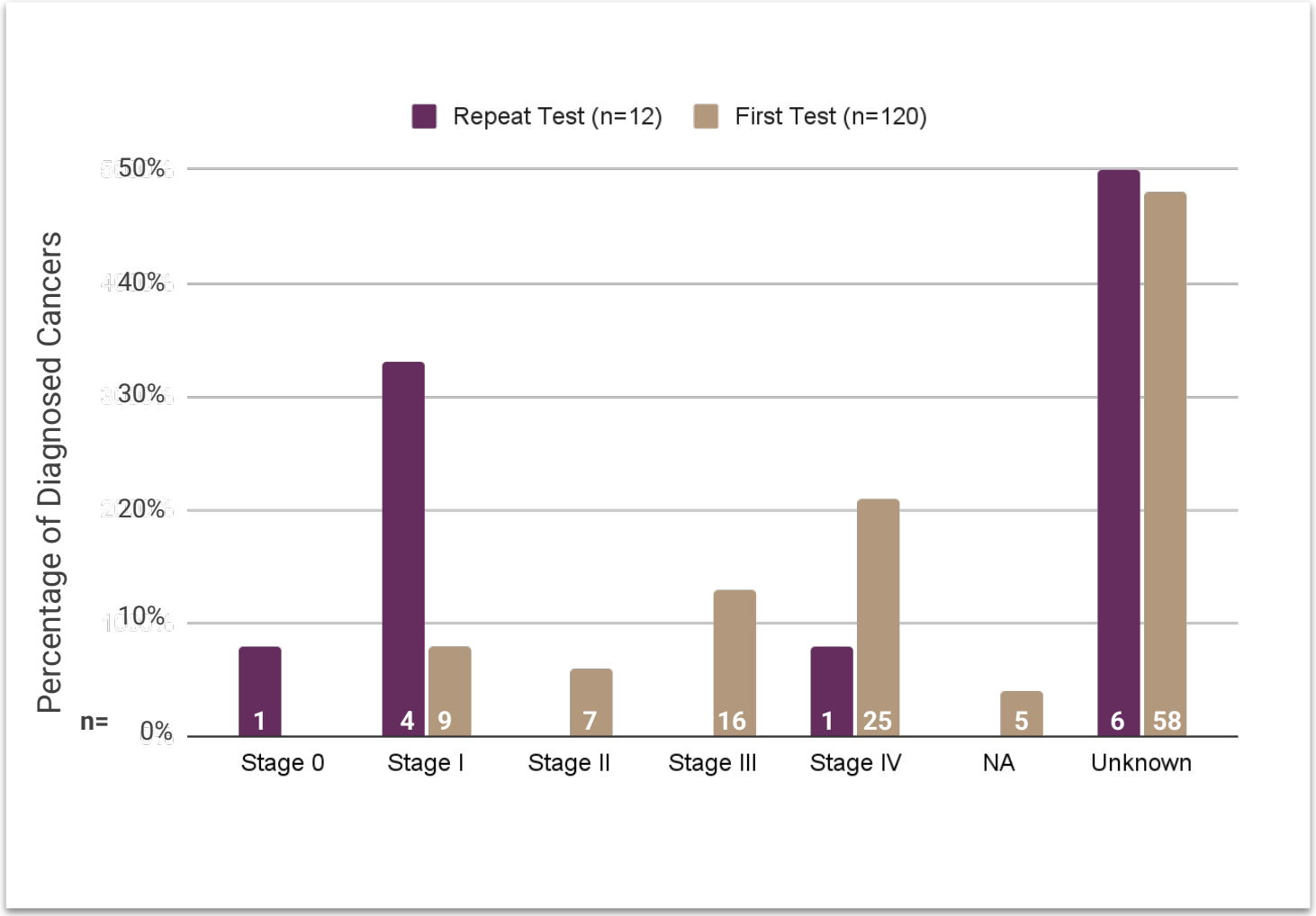
average time between blood draw and diagnosis among those detected

Cohort sampling design
1:1 cancer:noncancer (N = 1,425 each)
Total eligible N = 245,171

Patel et al., ASCO 2023

High Percentage of Stage I Diagnoses With Repeat Testing

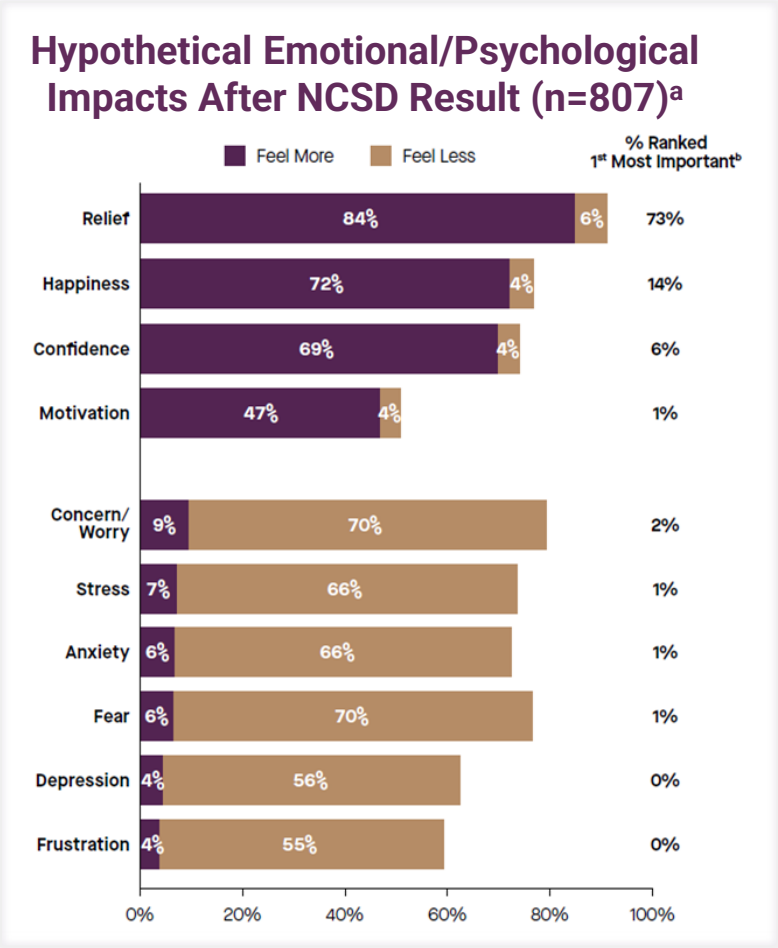
Repeat testing may improve early detection of multiple cancer types, including those currently without USPSTF-recommended screening[a,b]



[a]N values shown at bottom of each column. [b]NA, not applicable or no AJCC/Rai stage expected. Patients for whom the practice has not reported cancer staging are captured as Unknown.

Abrams R, et al. Presented at American Association for Cancer Research (AACR) Annual Meeting April 5-10, 2024.

Projected Increased Relief, Happiness, and Confidence After an NCSD MCED Test Result: General Population



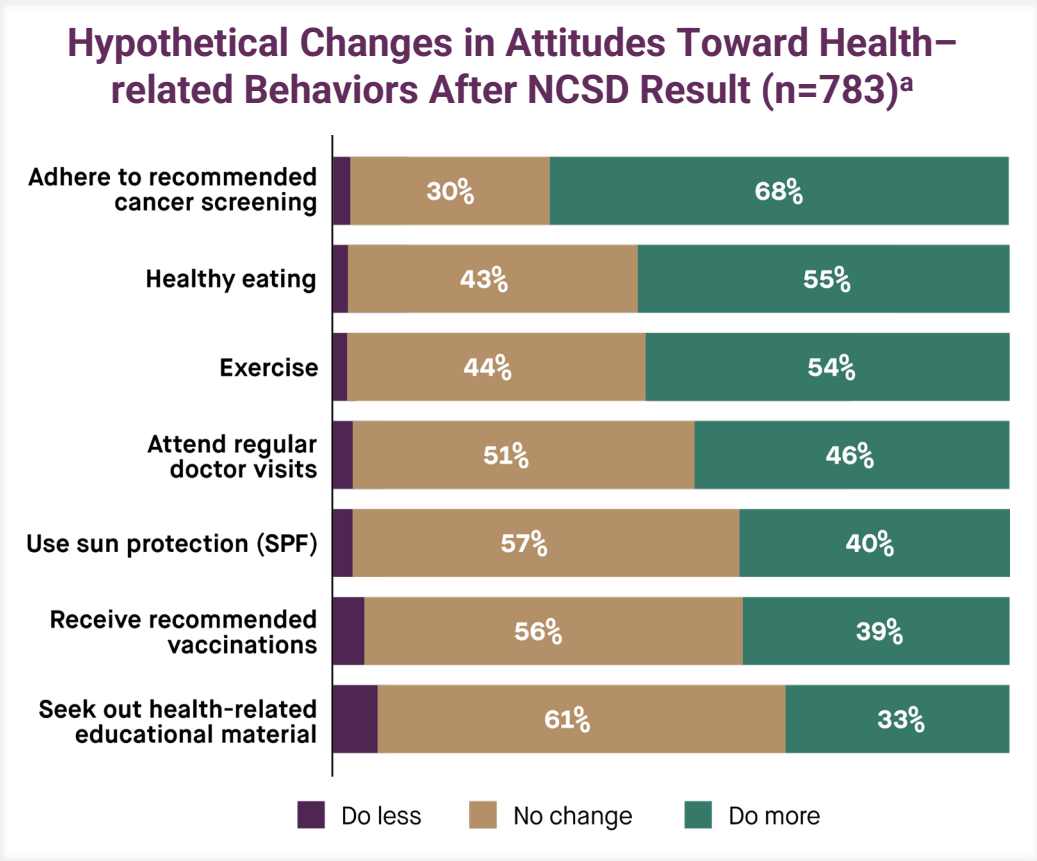
Relief was the most important emotional or psychological impact

Participants anticipated feeling more relief, happiness, confidence, and motivation

Participants anticipated feeling less concern/worry, stress, anxiety, fear, depression, and frustration

[a]The subset of 1073 participants who indicated that they would anticipate an emotional/psychological impact from receiving an NCSD result, ie, participants were asked about specific changes only if they anticipated an overall impact.
[b]Rankings were asked only of participants who selected 2 or more emotional/psychological impacts.
Patrick DL, et al. Poster presented at ASCO 2024; May 31–June 4, Chicago, IL.

Impacts of NCSD MCED Test Result Include Positive Changes in Health-Related Behaviors: General Population



Majority (73%) of participants would maintain or improve their health-related behaviors

Most participants were very-to-extremely certain of increasing health-related behaviors, including adherence to recommended cancer screening and eating healthy

[a]The subset of 1073 participants who indicated that they would make a change to their health-related behaviors due to receiving an NCSD result, ie, participants were asked about specific changes only if they anticipated an overall impact.

Patrick DL, et al. Poster presented at ASCO 2024; May 31–June 4, Chicago, IL.

Despite this

USPSTF Recommendations for Cancer Screening

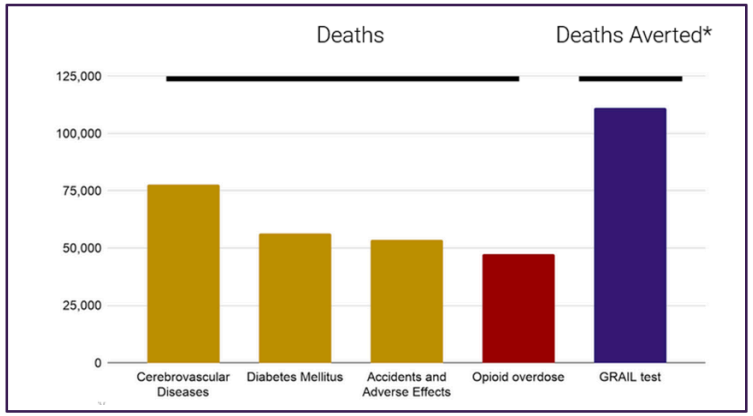
Cancer	Grade	Population	Modality/ Recommendation
Cervical	A	Women aged 21 to 65	Regular screening (3–5 years) using cervical cytology and/or HPV tests
Colorectal	A B	Adults aged 50 to 75 Adults aged 45-49	Regular annual screening, multiple effective methods available
Breast	B C	Women aged 50 to 74 Women aged 40 to 49	Biennial screening mammography
Lung	B	Adults aged 55–80, with history of smoking	Annual low-dose computed tomography (LDCT) screening
Prostate	C	Men aged 55 to 69	Periodic PSA screening on case-by-case basis

Mortality

> 600,000 people die of cancer every year In the US

To achieve this

Adding MCED has the potential...



26% Reduction in Cancer Mortality

Stage IA Ovarian Clear Cell Carcinoma

Pathological Diagnosis Confirmed at 28 Days Following MCED Test Results

Characteristics

- Female
- 67
- No specific risk factors noted beyond age-associated risk and maternal history of multiple myeloma

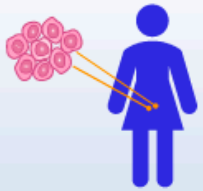
Blood Draw

Day 1

MCED test report returned

Cancer Signal Detected

CSO Prediction
CSO1=Uterus
CSO2=Ovary



Pelvic Ultrasound and CT Scan

Day 10

- 8.5x8.7cm mass of suspected uterine origin.
- Subsequent CT scan confirmed vascular pelvic mass arising from left ovary.

Diagnosis

Day 28

- Surgical pathology showed a stage pT1AN0M0 ovarian clear cell carcinoma.

Surgery

Day 28

- Total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, and peritoneal biopsy and washing.

Treatment

Day 64

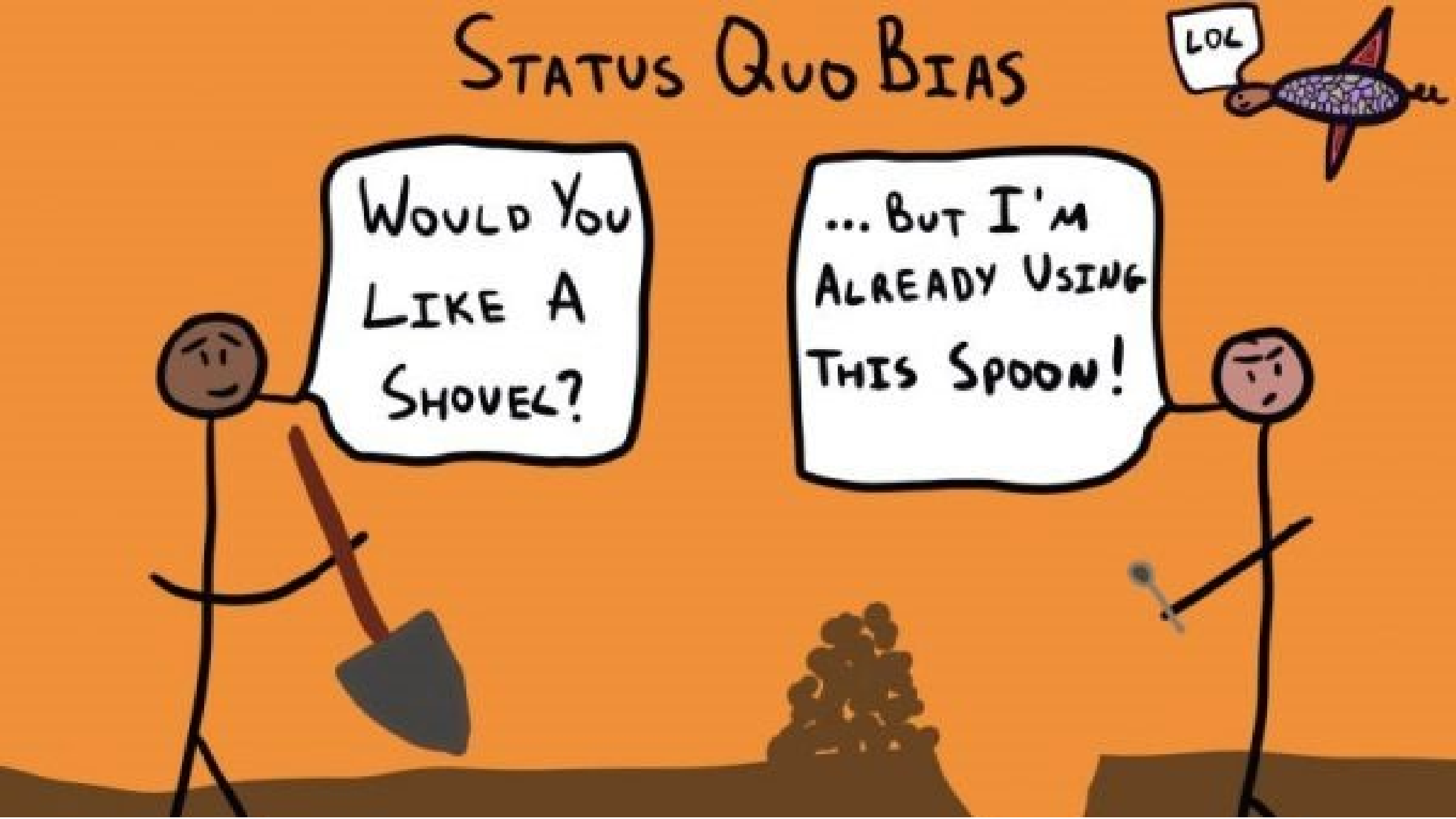
- Treatment with 6 cycles of adjuvant chemotherapy (carboplatin and taxol) initiated.

Current Status

NED 21 Months

- A 6-month follow up CT scan was negative, and individual remains asymptomatic with **no clinical evidence of disease after 21 months of follow up.**

Vittone et al., NPJ Precision Oncology 8:91, 2024


STATUS QUO BIAS
WOULD YOU LIKE A SHOVEL?
...BUT I'M ALREADY USING THIS SPOON!
LOL