

# Multicancer Early Detection

## Evidence from the Discovery Curve

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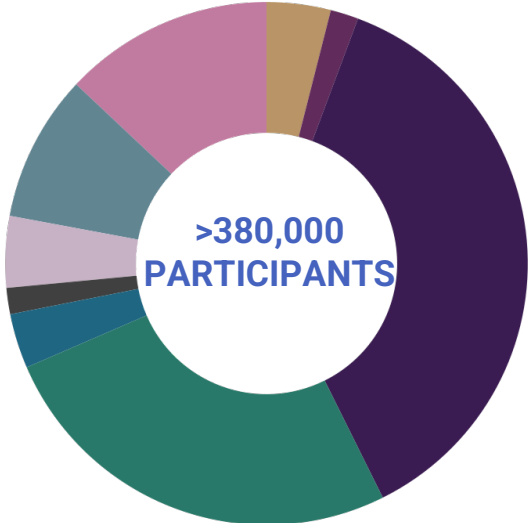
Distinguished Scientist, GRAIL, Inc

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Cleveland Clinic Lerner College of Medicine

# GRAIL Clinical Development Program

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

1	<b>CCGA</b> (n=15,254)	<b>Develop and validate a cell-free DNA-based MCEd test</b> <i>Enrollment: complete, published</i>	<i>Annals of Oncology and Cancer Cell 2020-2023</i>
2	<b>PATHFINDER</b> (n=6,662)	<b>Evaluate clinical implementation and perceptions of MCEd test</b> <i>Enrollment: complete, published</i>	<i>The Lancet 2023</i>
3	<b>SYMPLIFY</b> (n=6,242)	<b>Assess MCEd test in individuals with signs/symptoms of cancer</b> <i>Enrollment: complete, published</i>	<i>Lancet Oncology 2023</i>
4	<b>NHS-GALLERI</b> (n≈142,321)	<b>Assess clinical utility of MCEd for population screening in the UK</b> <i>Enrollment: complete</i>	
5	<b>STRIVE</b> (n=99,481)	<b>Exploration of cancer signal detection in women</b> <i>Enrollment: complete</i>	
6	<b>SUMMIT</b> (n=13,035)	<b>Exploration of cancer signal detection in individuals at high risk of lung cancer</b> <i>Enrollment: complete</i>	
7	<b>REFLECTION</b> (n≈17,000)	<b>Assess experience/clinical outcomes in real-world setting</b> <i>Enrollment: ongoing</i>	
8	<b>PATHFINDER 2</b> (n≈35,000)	<b>Evaluate MCEd test performance in eligible screening population</b> <i>Enrollment: completed</i>	
9	<b>REACH</b> (n≈50,000)	<b>Understand health equity impact of Galleri in a Medicare population</b> <i>Enrollment: ongoing</i>	



# Cancer types detected in Substudy 3 of CCGA

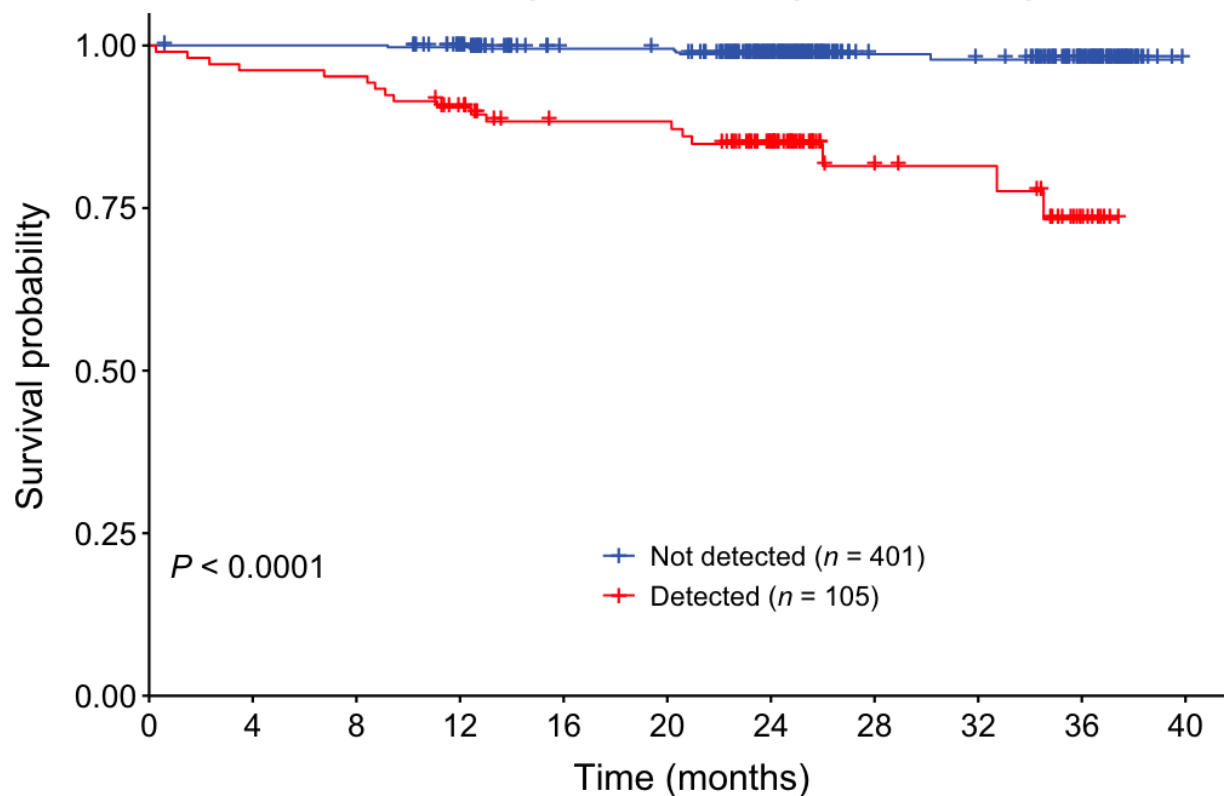
## 45 cancer types lack recommended screening

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

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

# MCEDs Preferentially Detect Aggressive Cancers

**Breast, cervical, colorectal, lung, prostate  
cancers diagnosed through screening**



—	401	400	400	386	356	355	278	119	117	70	0
—	105	101	100	88	77	77	57	23	21	9	0
	Number at risk										

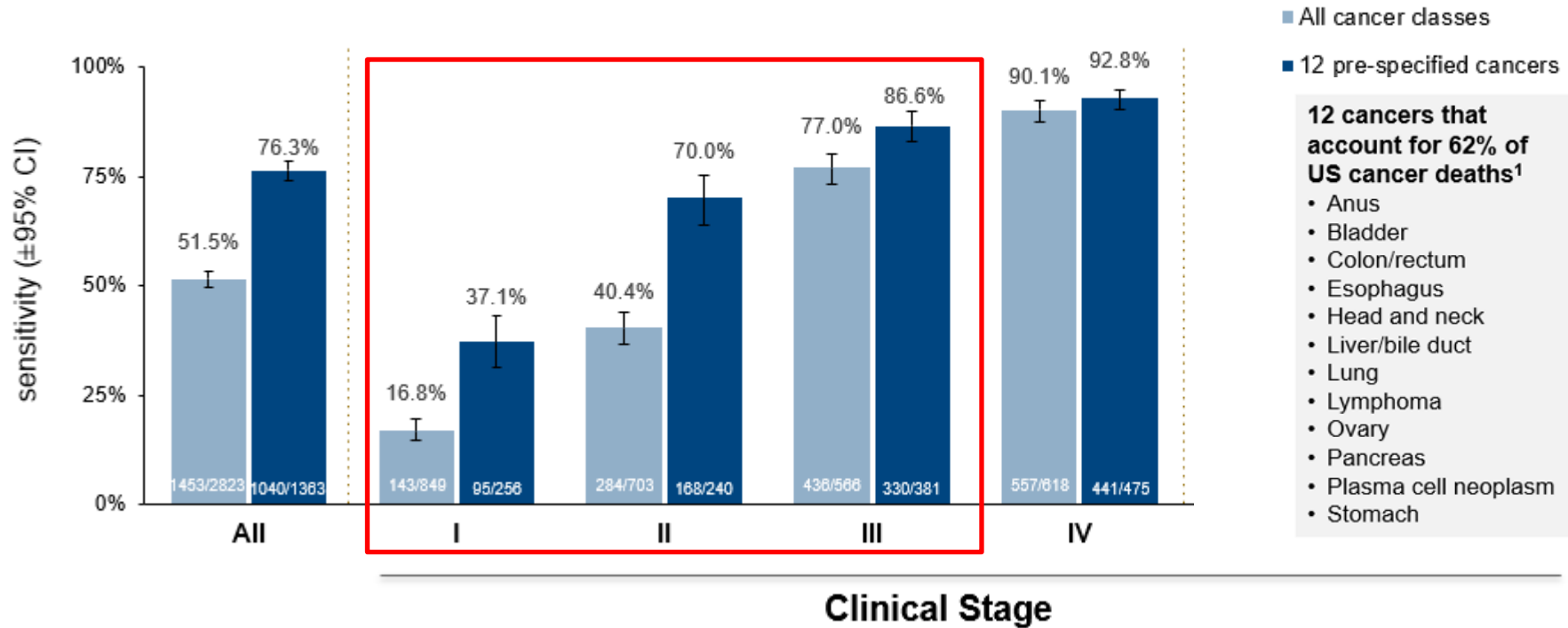
**Shedding of CfDNA is  
Associated with Features of  
Aggressiveness**

- Mitosis rate
- Necrosis
- Depth of invasion
- Angiogenesis
- Tumor blood flow

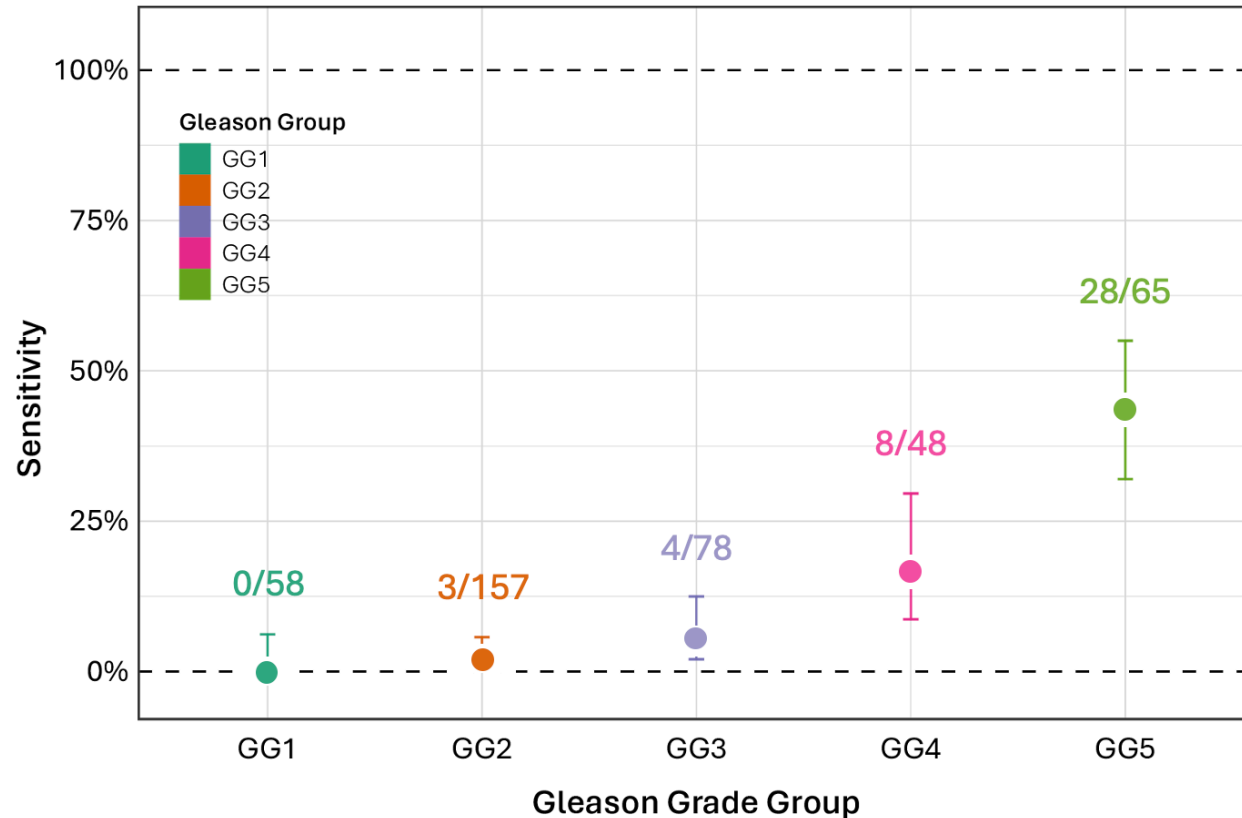
# CCGA3 Results

Sensitivity 67.6% for 12 pre-specified cancers

Sensitivity was higher in these 12 cancers vs overall, particularly in early-stage



# Sensitivity of Prostate Cancer Detection By Grade



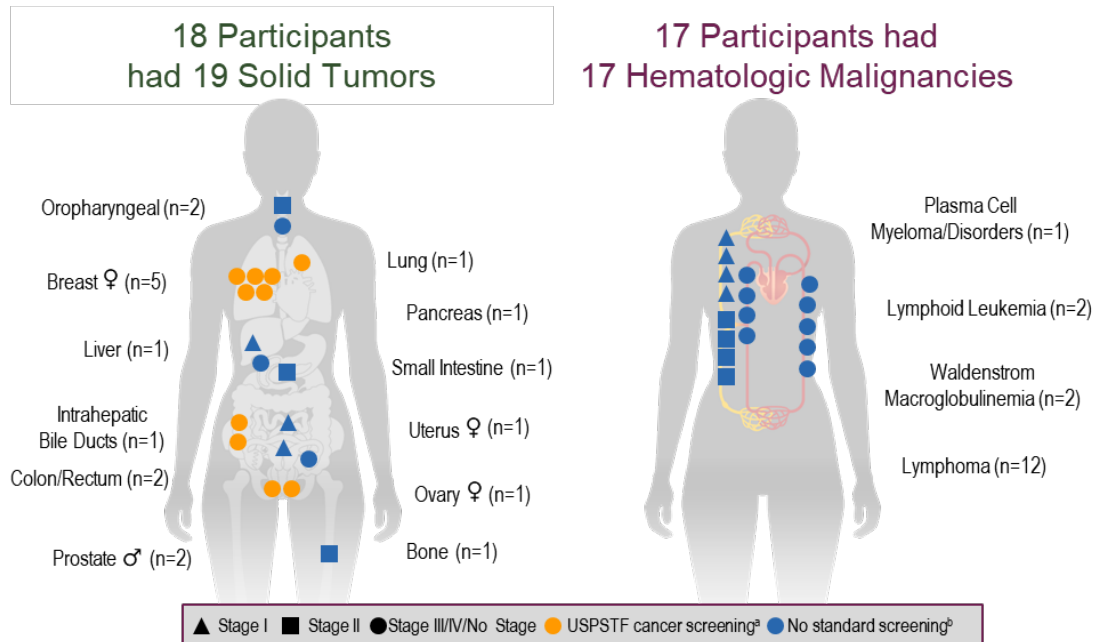
## Substudy 3 of CCGA (N = 420)

Gleason Grade Group	Sensitivity (%)
GG1	0
GG2	1.9
GG3	5.1
GG4	16.7
GG5	43.1

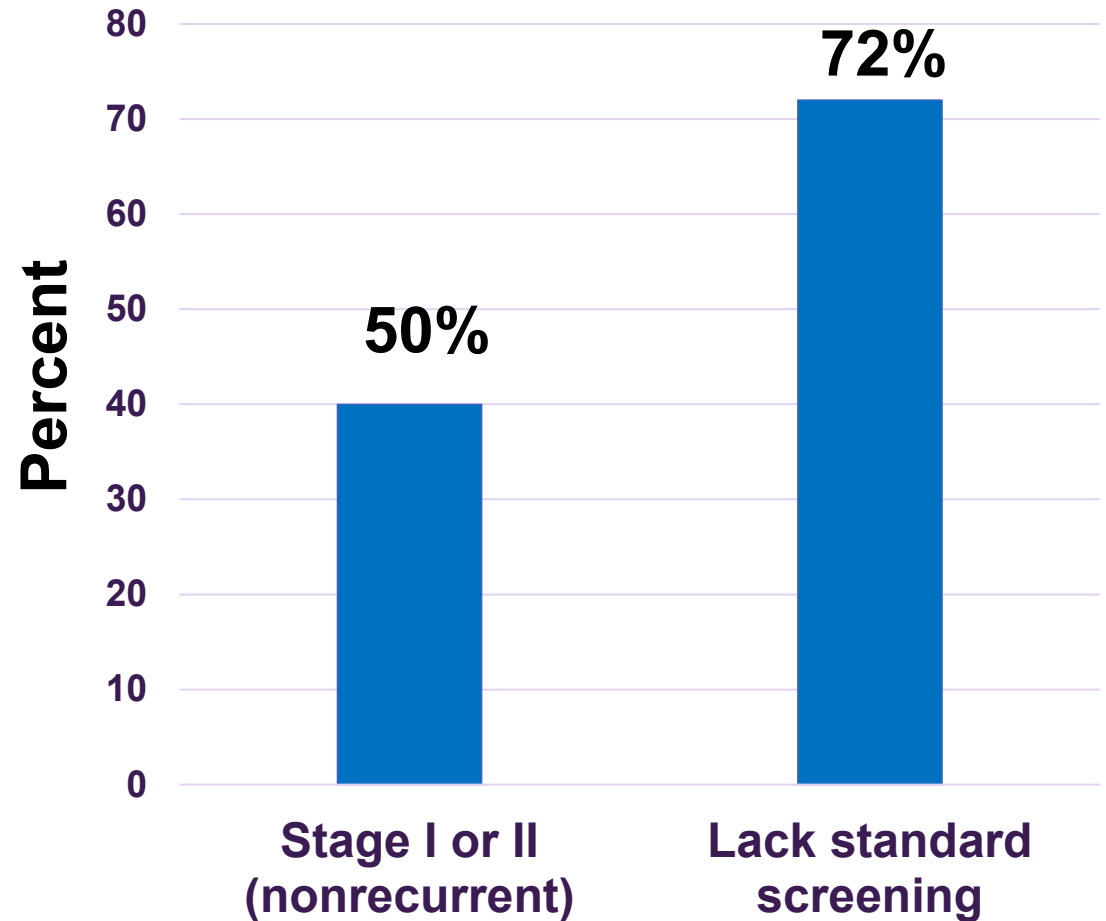
CCGA, Circulating Cell-Free Genome Atlas Study; CSD, cancer signal detected; GG, Gleason grade group.

# PATHFINDER

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



## MCED Detected Cancers



# Consistent Results Across Studies

## Clinical Validation Study (CCGA3)

**0.5%**  
False  
positive rate

**44%**  
Positive predictive value

**89%**  
Localization accuracy

## Confirmatory Intended Use Population Study (PATHFINDER)\*

**0.5%**  
False positive rate

**43%**  
Positive predictive value

**88%**  
Localization accuracy\*\*

Refined test used commercially; \*\*1<sup>st</sup> or 2<sup>nd</sup> location prediction

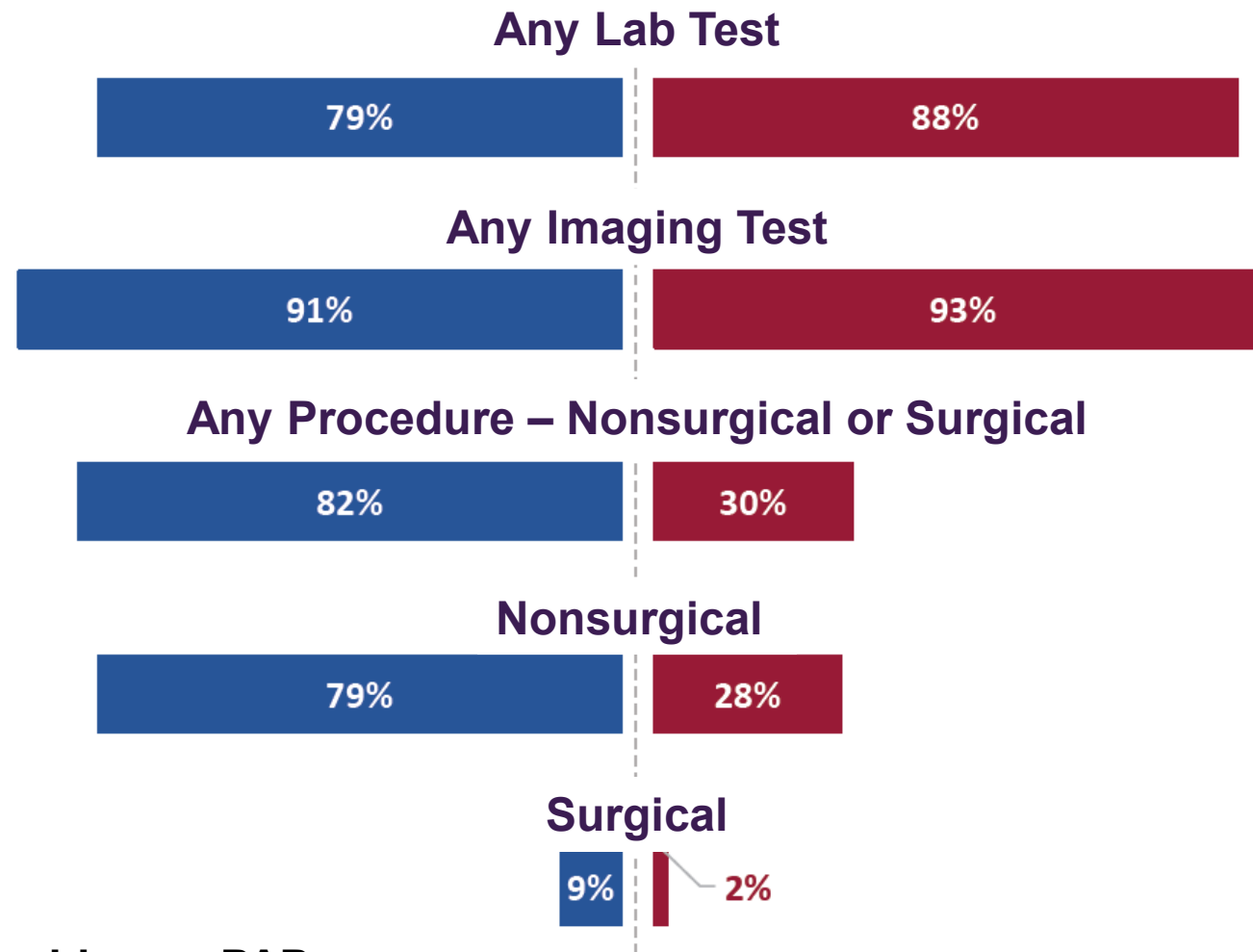
Klein EA, et al. Ann Oncol. 32:1167, 2021  
Schrag et al. Lancet 402:1251, 2023



# Diagnostic Testing in PATHFINDER

**True  
Positives**

**False  
Positives**



**Nonsurgical = endoscopy, biopsy, PAP**

# Time to Diagnostic Resolution in PATHFINDER

**PATHFINDER<sup>2</sup> (n=90)**

**57 days**

**Median** time to diagnostic resolution

*73% of true positives reached resolution in <3 months*



**GITLIN et al<sup>1</sup> (n=)**

**156.2 days**

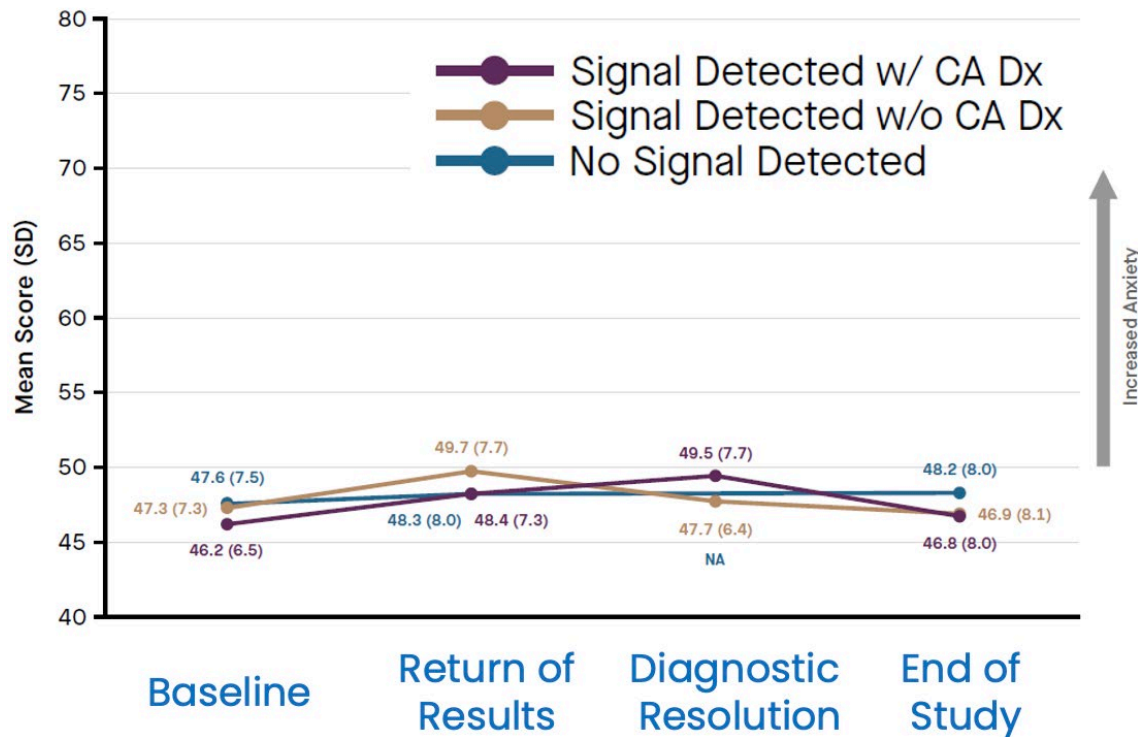
**Mean** time to diagnosis for all cancer patients

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

# Psychosocial Impact in PATHFINDER

## PATHFINDER

### PROMIS Anxiety Scale



Other measures: MICRA, SF-12

RESEARCH

Open Access

Patient-reported outcomes associated with cancer screening: a systematic review

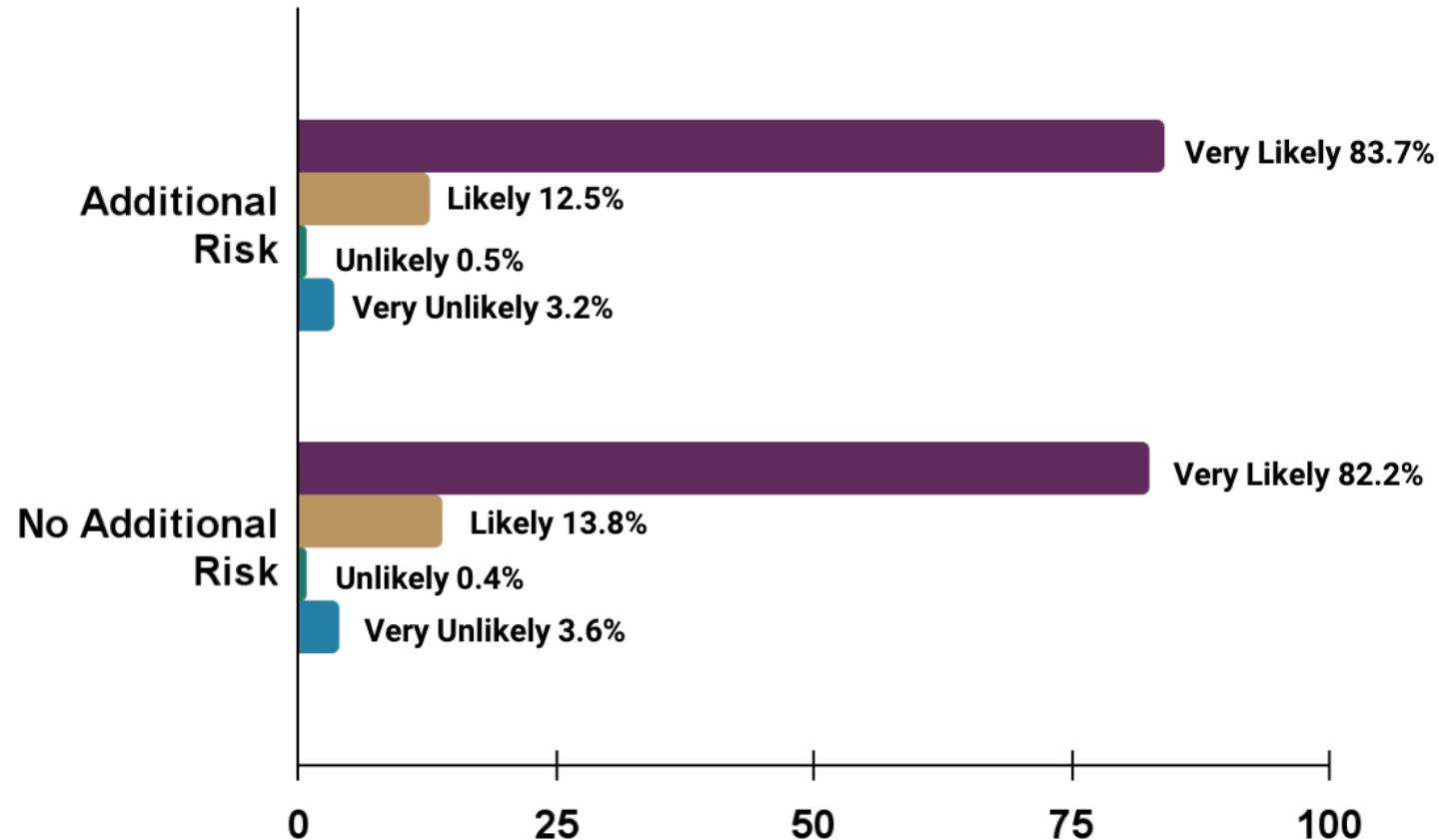
Ashley Kim<sup>1\*</sup>, Karen C. Chung<sup>1</sup>, Christopher Keir<sup>1</sup> and Donald L. Patrick<sup>2</sup>



**12 RCTS & 19 Observational studies of patient reported outcomes**

- Temporary increase in symptoms (anxiety, distress, & worry) @ 2-4 wks
- No long-term psychosocial consequences

# Post-MCED Test Intentions Toward Future Screening in Participants With No Cancer Signal Detected



Additional risk = smoker, germline/hereditary risk, and/or cancer survivor

# Real-World Residual Risk Based on Repeat Testing Data

N = 45



CANCER SIGNAL  
DETECTED



NEGATIVE  
DIAGNOSTIC WORKUP



29%

Persistent CSD on  
retest is associated  
with a **higher risk of  
cancer diagnosis**



CANCER SIGNAL  
DETECTED

Mean f/u 10.3 mo

N = 100



CANCER SIGNAL  
DETECTED



NEGATIVE  
DIAGNOSTIC WORKUP



0%

No cancers have been  
diagnosed in patients  
with **NCSD on Retest**,  
indicating the **residual  
risk of cancer in these  
patients is lower**



NO CANCER SIGNAL  
DETECTED

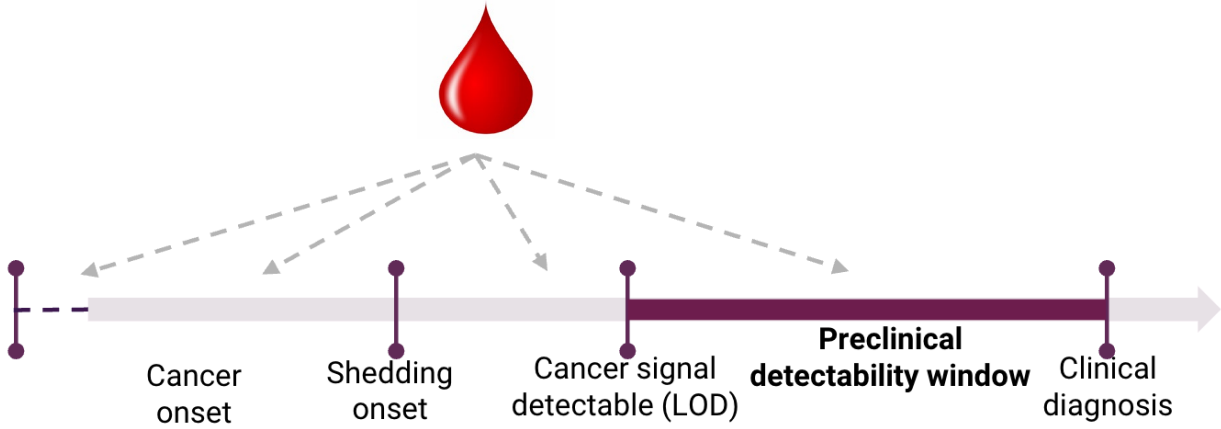
Mean f/u 16.7 mo

Imputed residual risk is a conservative risk estimate that assumes all patients with an unknown clinical status do not have cancer at last follow-up contact, acknowledging that cancer is rare in the general population.

CSD, cancer signal detected; MCEd, multi-cancer early detection; RWE, real-world evidence

Westgate C, et al. Presented at ESMO Annual Meeting; September 2024, Barcelona, Spain

# Preclinical Detectability Window



## ACS CPS-3 Biobank Study

**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

## STRIVE Study

**275 days**  
average time between blood draw and diagnosis among those detected

Prospective, Observational Cohort Design  
Cancer: n=1519, Non-Cancer: n=1616

Vachon et al., ESMO 2024

# RWE with Initial 50k MCED Tests

**32%**

of cases detected  
at stages I/II  
(n=12)\*

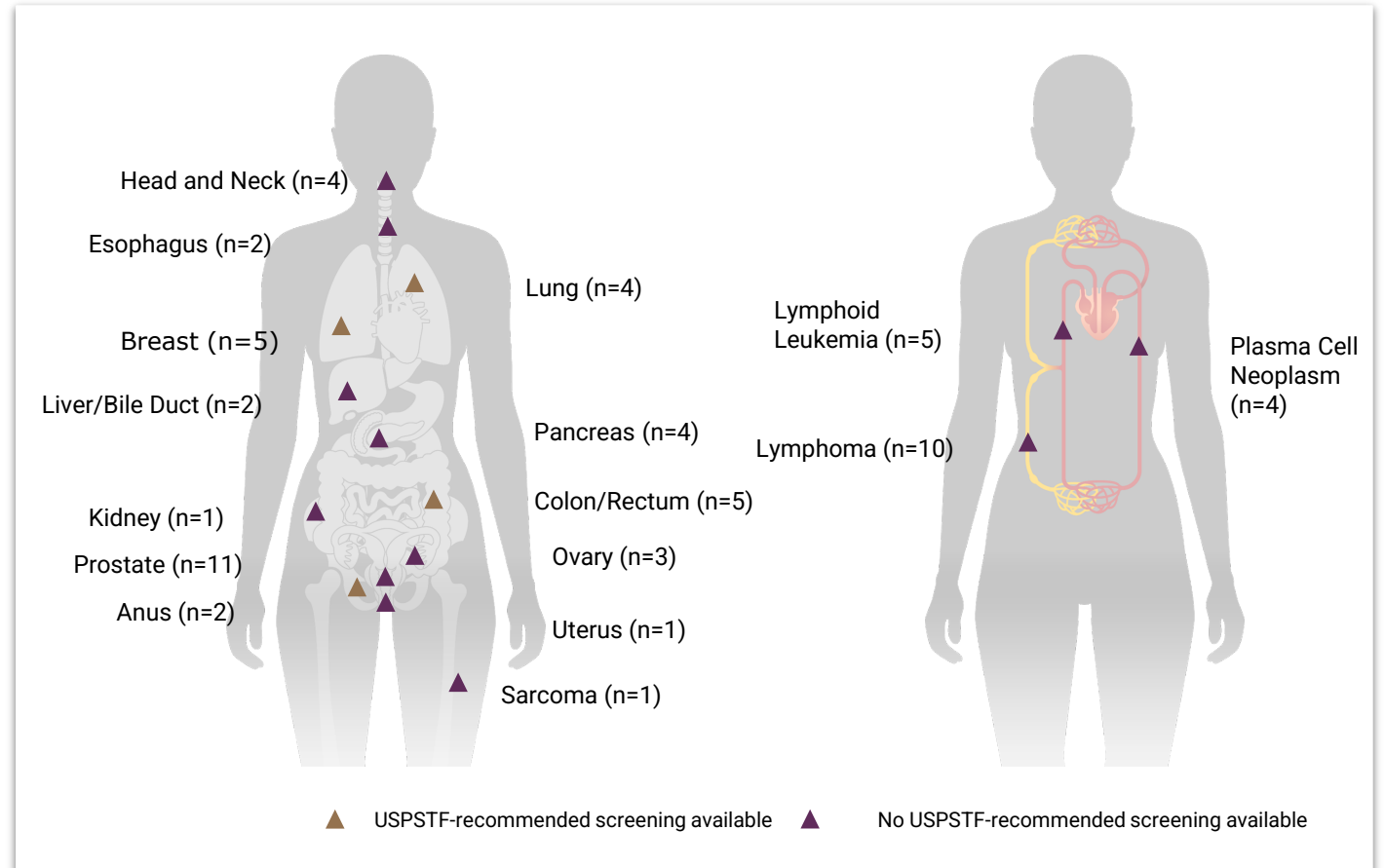
**61%**

of cases detected  
at stages I/II/III  
(n=23)\*

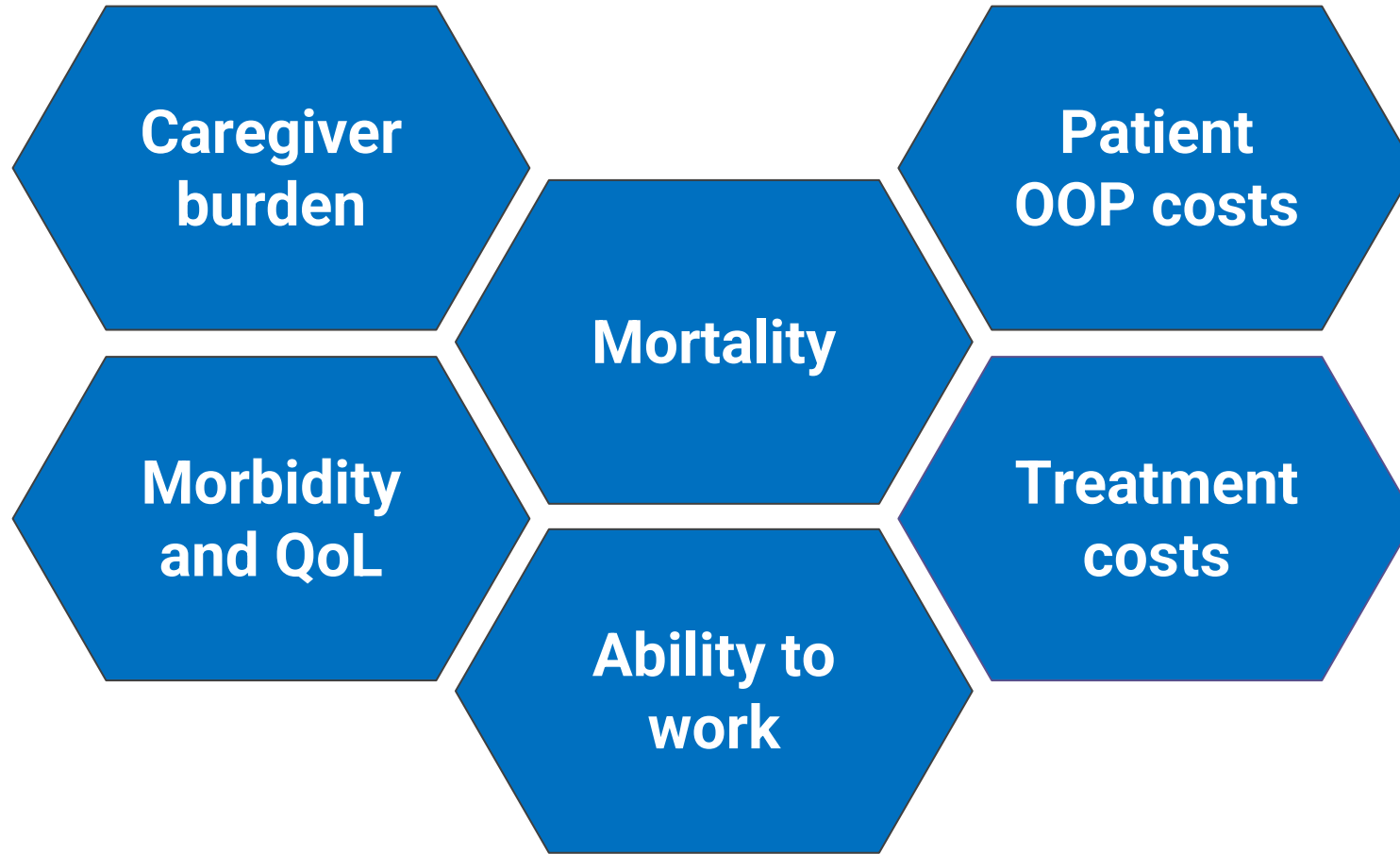
**91%**

CSO prediction accuracy of cases  
with confirmed cancer diagnoses  
(59/65)

Consistent with PATHFINDER (84%) and the Circulating Cell-Free  
Genome Atlas (CCGA) study (89%)



# Total Burden Of Cancer Falls on Many Stakeholders



Its not only about mortality