Multicancer Early Detection

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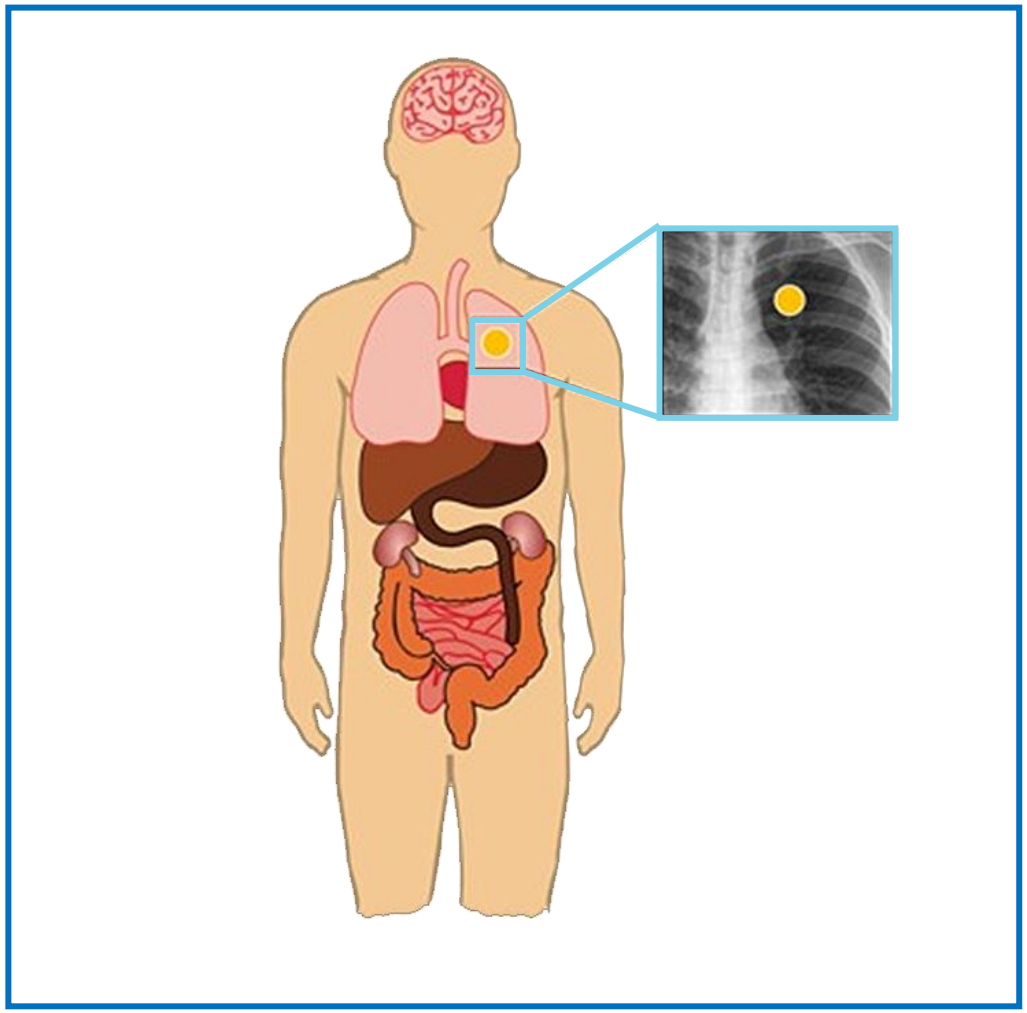
Disclosure:

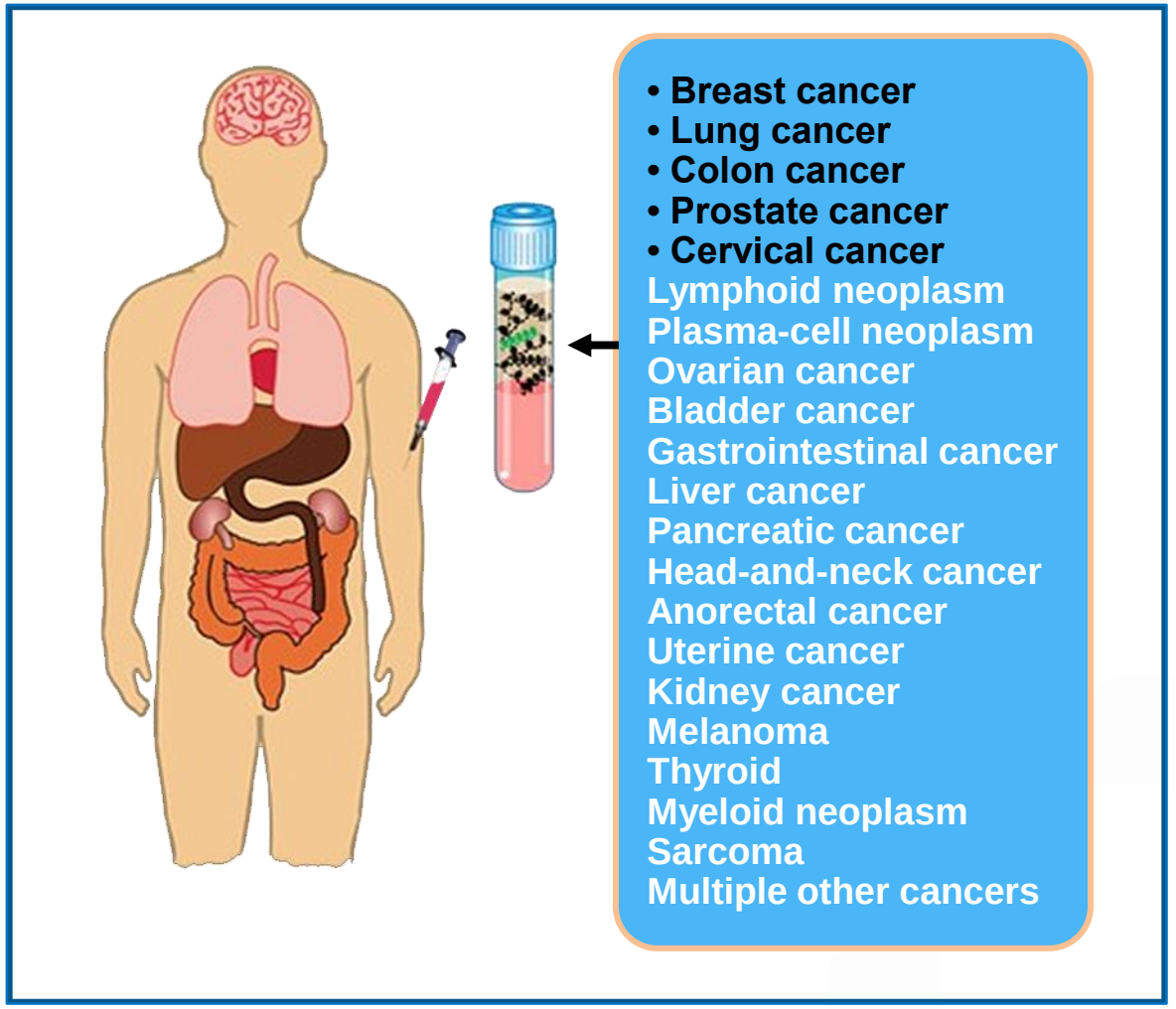
I am a consultant for GRAIL, Inc

Paradigm Shift: Single vs Multi-Cancer Screening

“One test-one cancer” approach

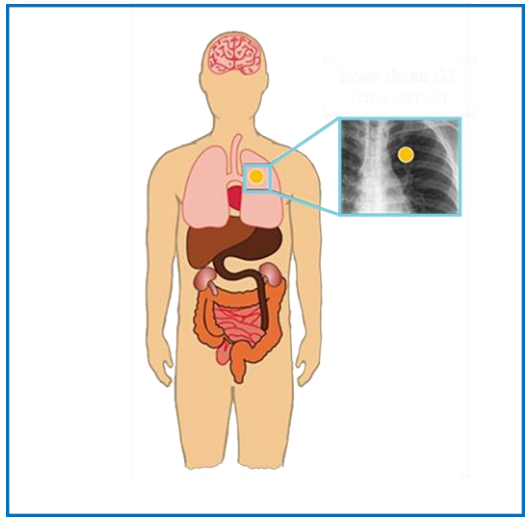


“One test-many cancers” approach based on a shared cancer signal

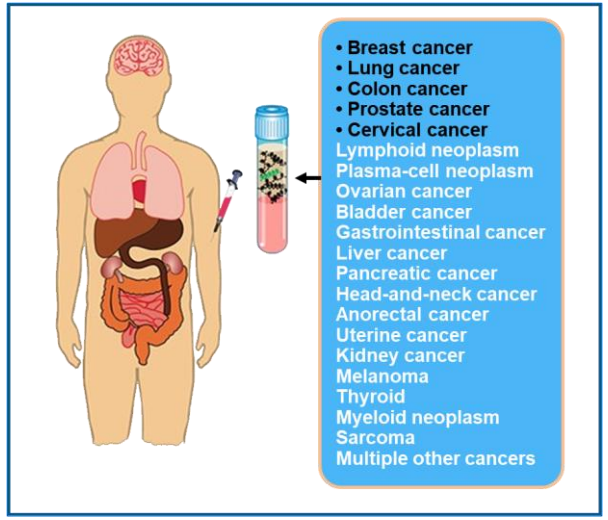


Paradigm Shift

Screening for individual cancers

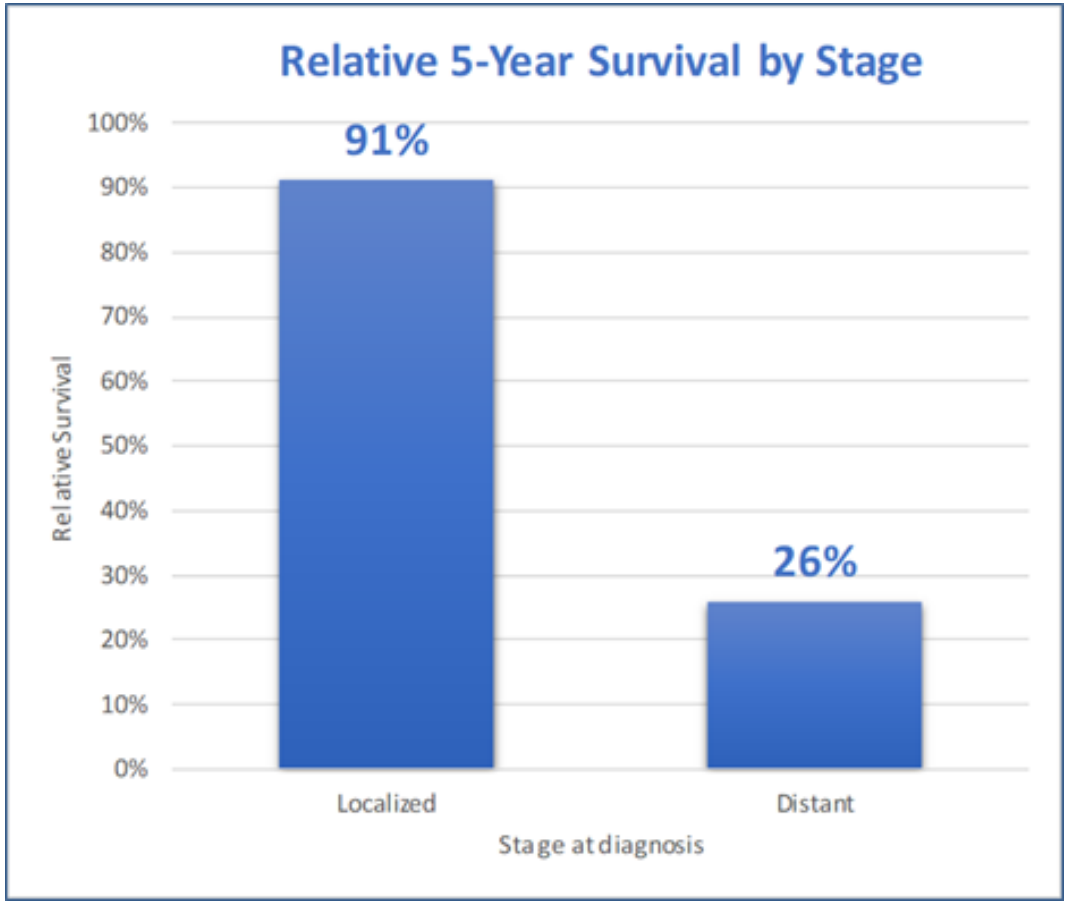


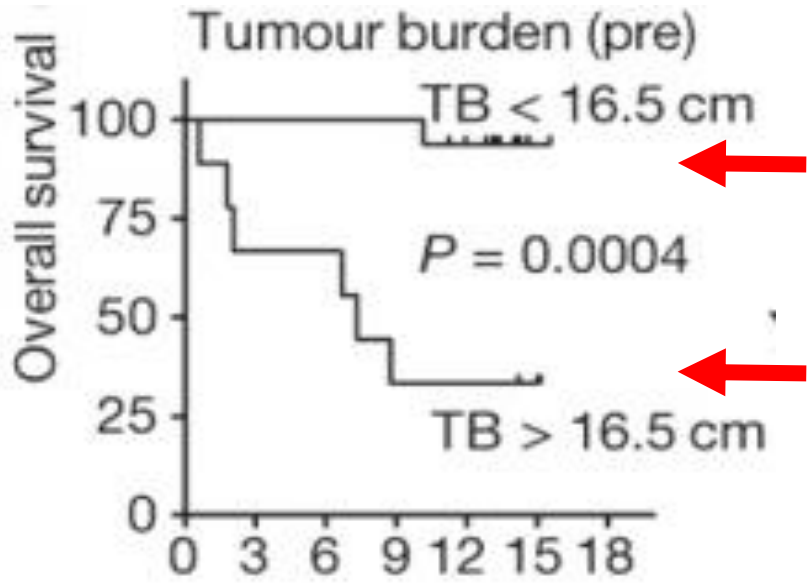
Screening individuals for cancer



- Why is this necessary?
- How is it possible?

Why Early Detection is Important





Low Tumor Burden

High Tumor Burden

USPSTF Recommendations for Cancer Screening

Cancer	Grade	Population	Modality/ Recommendation
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Colorectal	A B	Adults aged 50 to 75 Adults aged 45-49	Regular annual screening, multiple effective methods available
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Mortality

Limitations of Current Screening Paradigm

Compelling Rationale for a Paradigm Shift to Include MCED

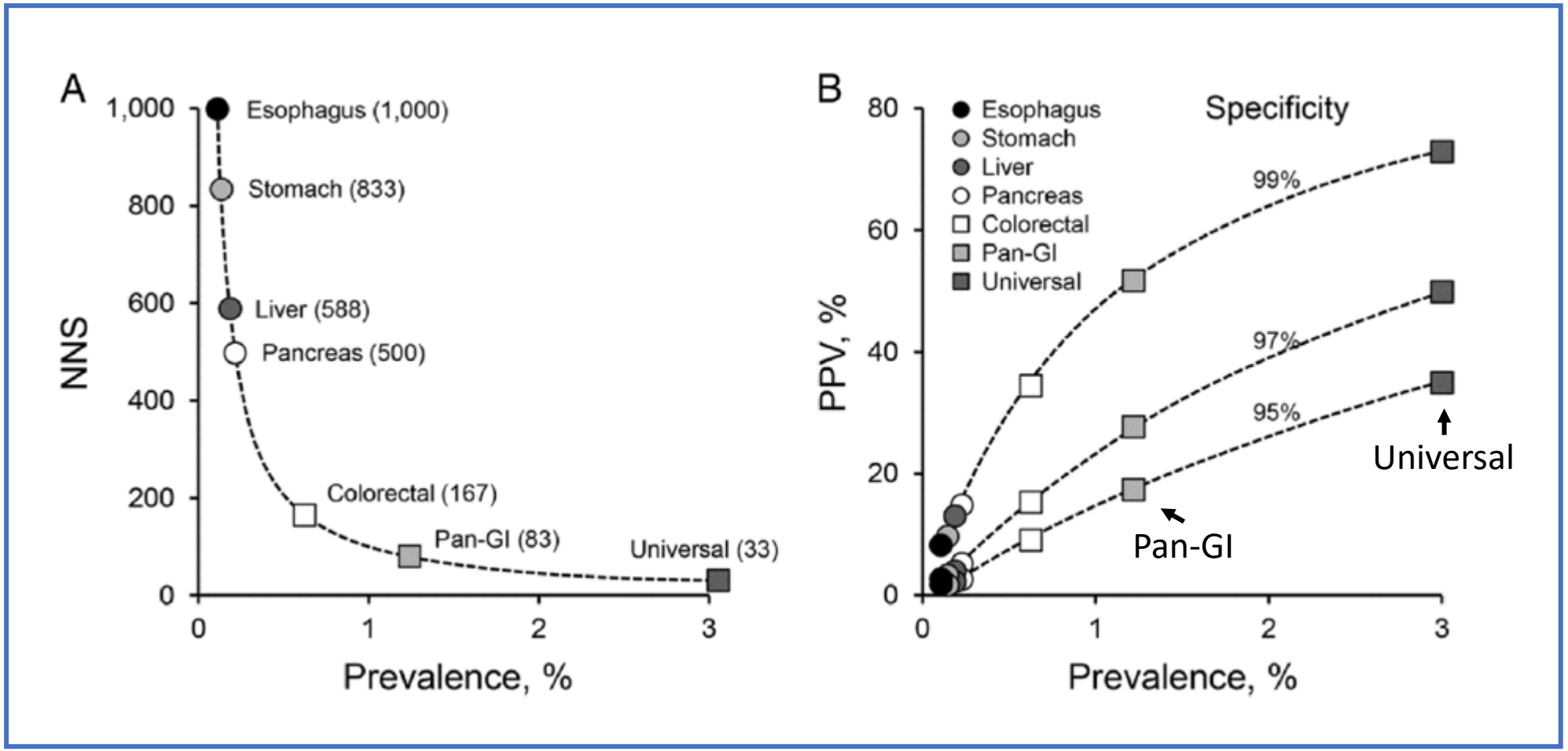
~ 600,000 cancer deaths per year in the US despite current screening

Why?

- **Unscreened cancers account for ~70% of deaths**
- **Adherence rates are sub-optimal (5 [lung] - 80% [cervical])**
- **Patients are more likely to be diagnosed with a different cancer than those targeted by screening**
- **PPV for single cancers is <10%**
- **Cumulative false positive rates are high (40-50%)**

Universal Cancer Screening Improves Efficiency

Effect on NNS & PPV



Ahlquist, NPJ Precision Oncol 2:23, 2018

The Value of MCED at the Population Level

Advantages	Practical Effects
Detects cancers not currently screened for	Increased overall Cancer Detection Rate
Improves efficiency of screening	
Shifts diagnosis to earlier stages	

MCED is not about finding a particular cancer type
MCED should not be compared to tests that screen for individual cancers

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Improves efficiency of screening	Improved PPV = Reduced NNS Reduced false positive rate
Shifts diagnosis to earlier stages	Lower burden of treatment Improved cure rate

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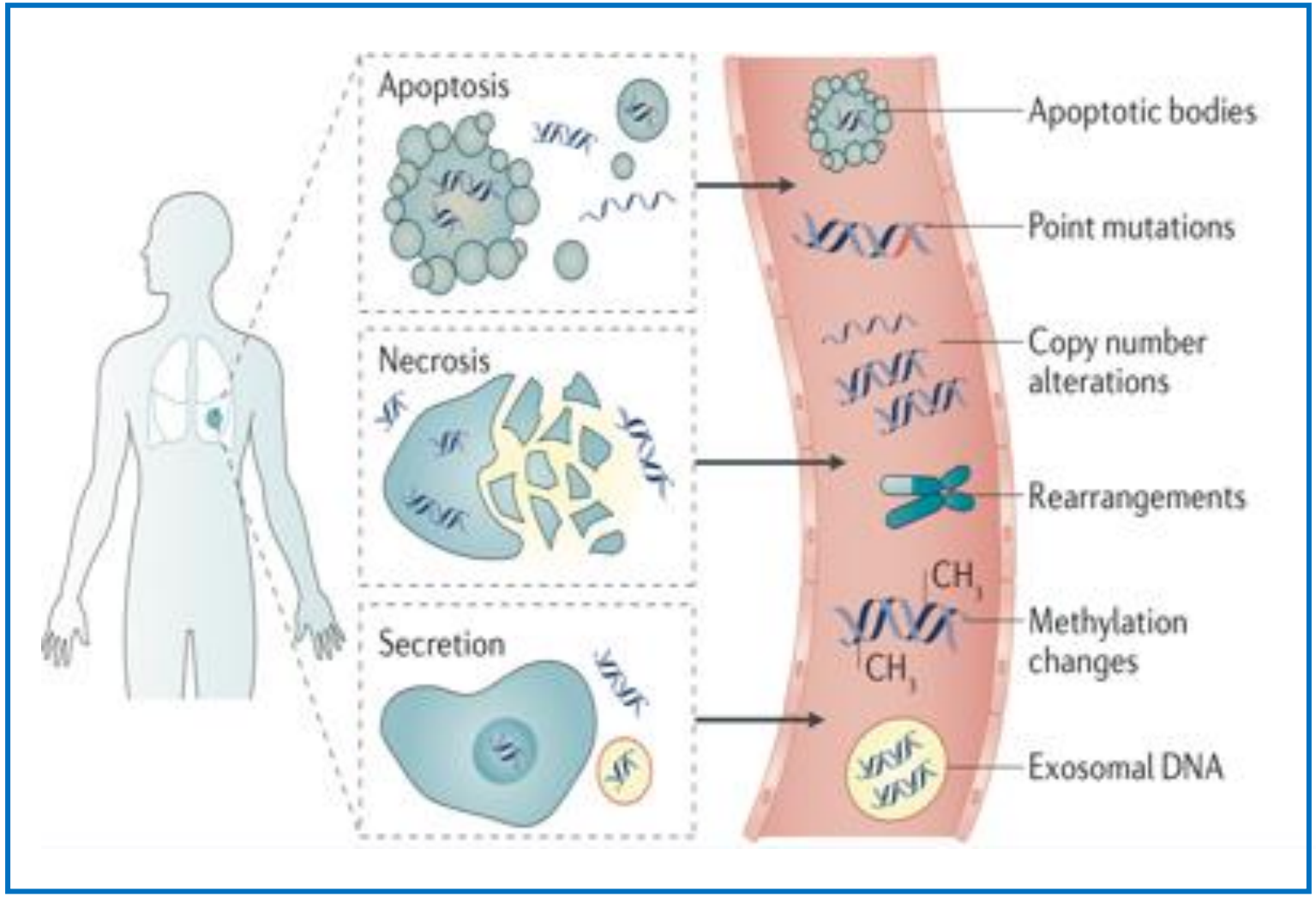
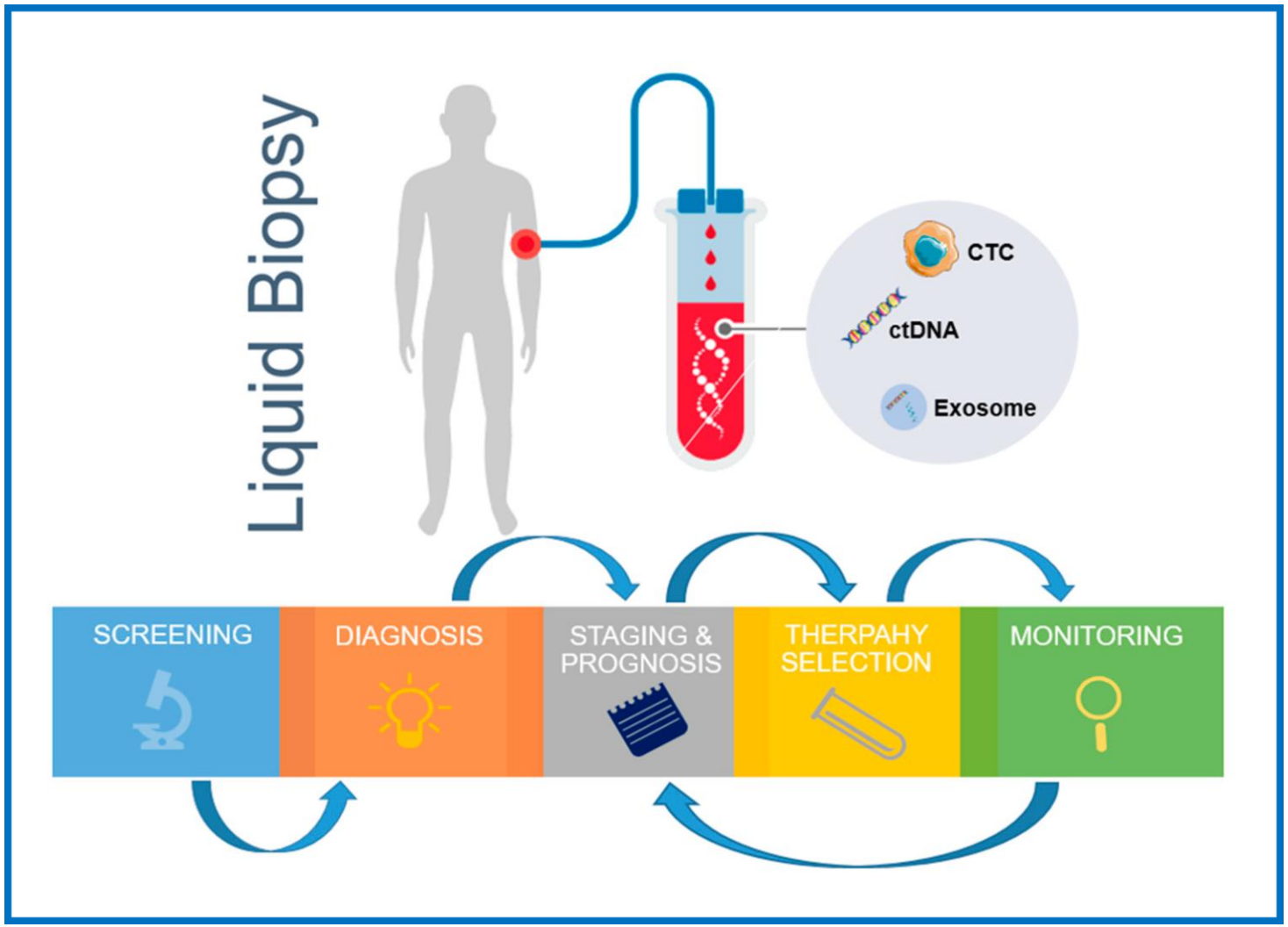
Liquid Biopsy



Liquid Biopsy
Uses in Cancer Care



Cancer Signals in Blood

- Methylation
- Mutations
- Chromosomal copy number alterations
- Fragmentomics
- Proteins
- miRNA
- Microvesicles
- Multi-Analyte

*** Circulating Cell-Free Genome Atlas Study**

Jamashidi et al., Cancer Cell 2022 (in press)

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Which is the Best Approach?

***CCGA1 compared WGS, Targeted Mutation, and Methylation head-to-head**

Methylation was best for Limit of Detection (LOD) & Cancer Site of Origin (CSO)

*** Circulating Cell-Free Genome Atlas Study**

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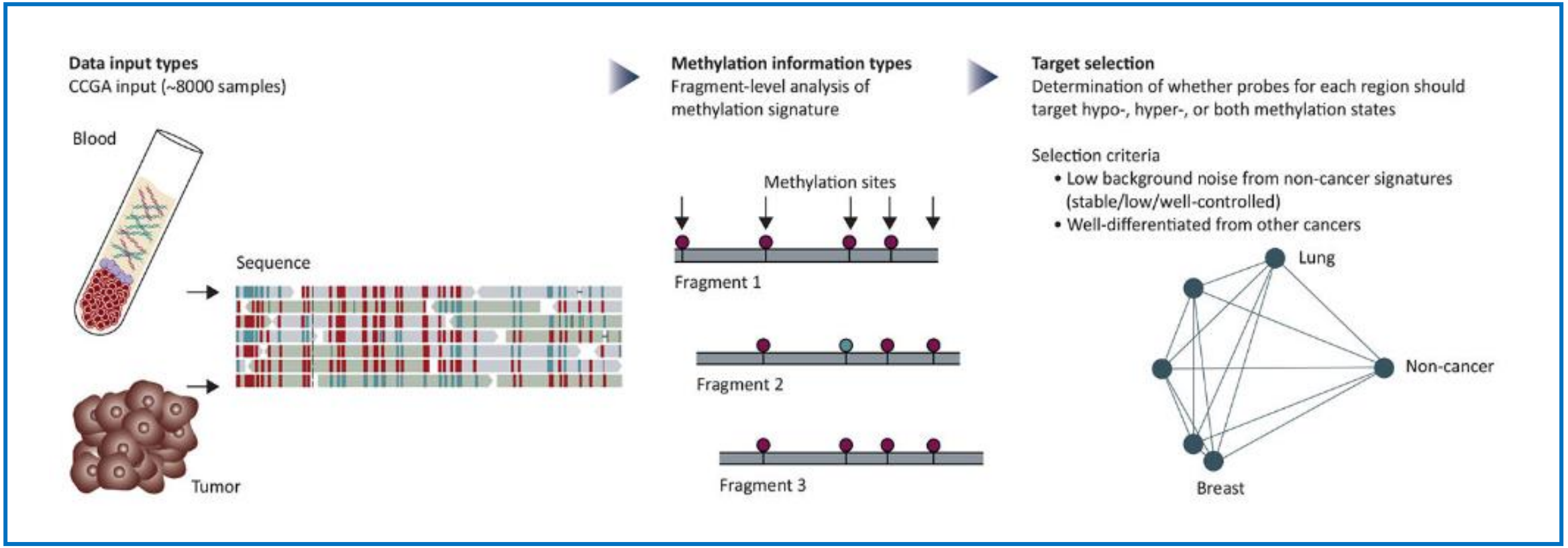
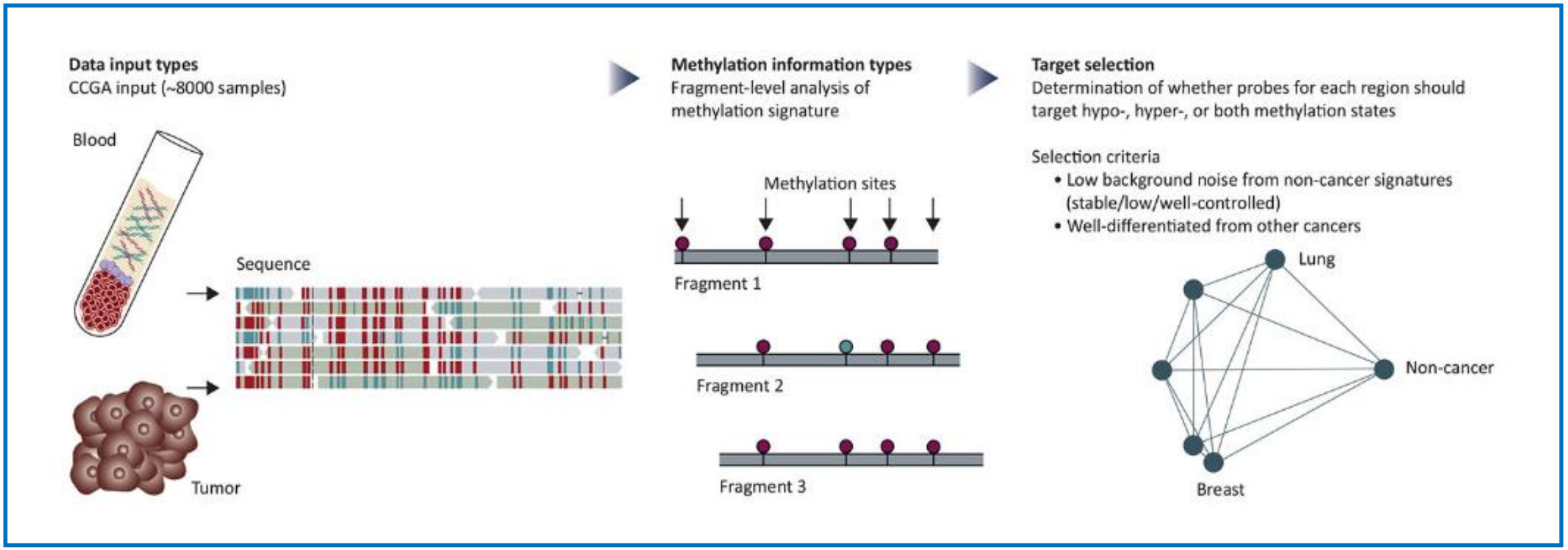
Biology of cfDNA-Based Cancer Detection



Liu et al., Ann Oncol. 31:745, 2020; Cristiano et al., Nature 570:385, 2019

Biology of cfDNA-Based Cancer Detection



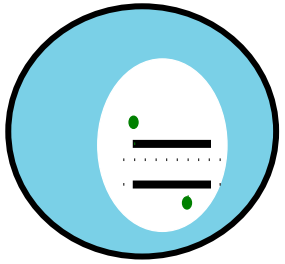
Algorithm Outputs

1. Cancer present – yes/no
2. Predicted cancer origin

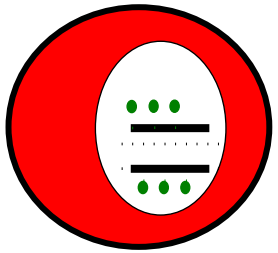
Liu et al., Ann Oncol. 31:745, 2020; Cristiano et al., Nature 570:385, 2019

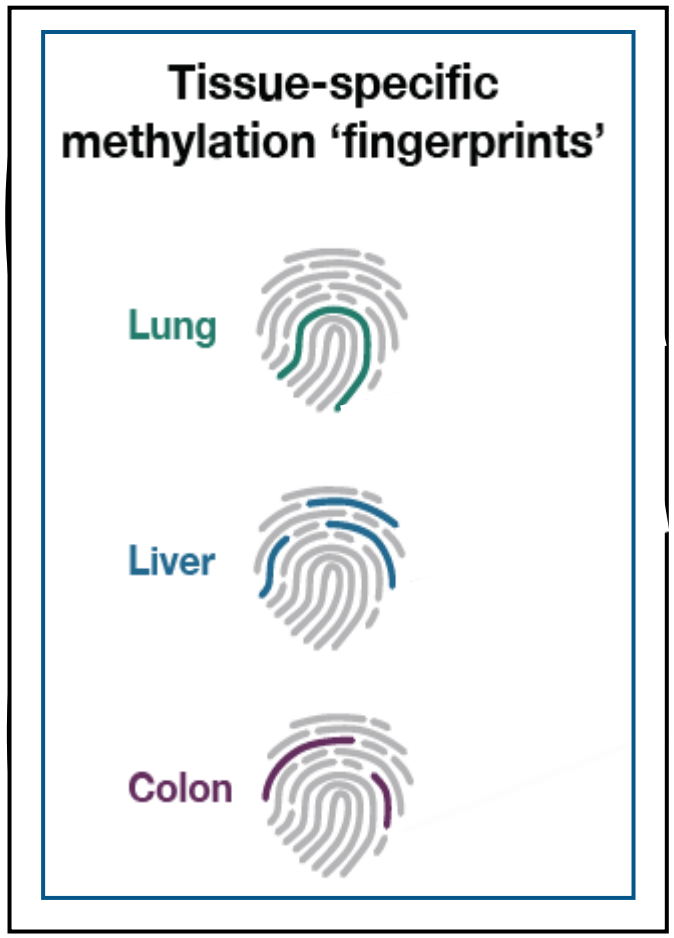
Clinical Site of Origin Prediction

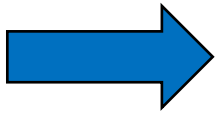
Normal cell

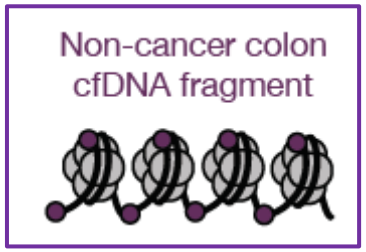


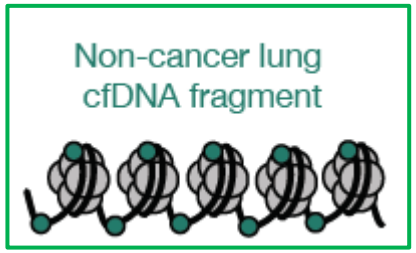
Cancer cell

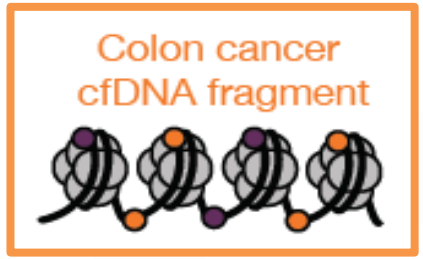




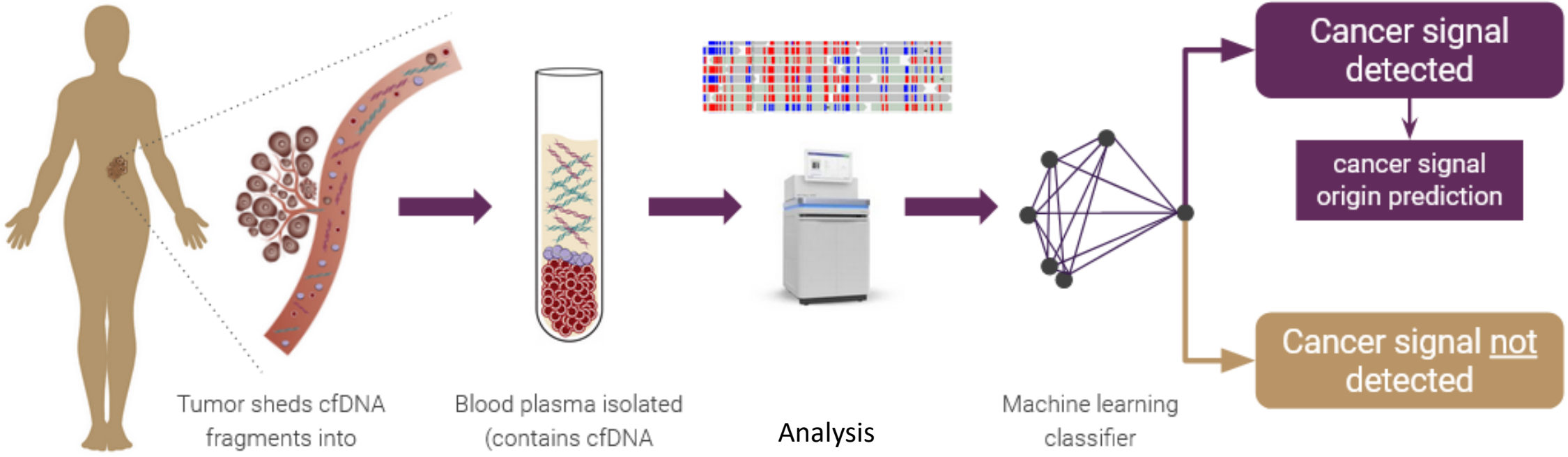








MCED Clinical Workflow



Results Report

Results

Cancer Signal Detected

The Galleri® test detected DNA methylation signals associated with cancer in the analyzed cell-free DNA obtained from the patient's sample.
Detection of a cancer signal is not a diagnosis of cancer. Diagnostic evaluation for cancer should be conducted.

Top Predicted Signal Origins to Guide Diagnostic Evaluation

Head & Neck

Signal Origin(s) Score

This chart displays the top score(s) of Cancer Signal Origins predicted by the Galleri test. The size of each bar represents confidence in predicting cell or tissue origin of detected cancer signal: long bar reflects higher confidence and short bar reflects lower confidence in cancer signal origin. This chart does not provide an indication of the overall likelihood of cancer.

Cancer signals are organized into 21 Cancer Signal Origins, which are listed in the Method section. For more information, please visit www.galleri.com/test-report.

Included sub-categories of the predicted origins:

- **Head & Neck:** Oropharynx, Hypopharynx, Nasopharynx, Larynx, Lip and Oral Cavity (including Oral Tongue), Nasal Cavity, Paranasal Sinuses, Major Salivary Glands
- **Lung:** Lung, Bronchus

Circulating Cell-Free Genome Atlas (CCGA) Study

Prospective, observational, longitudinal, case-control study

15,254 participants
with and without cancer
—
142 sites

Blood samples
(from all participants)

Tissue samples
(cancer only)

Follow-up for 5 years
(vital status and cancer status)

Liu et al., Ann of Oncology 32(9) 2021

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CCGA1
Discovery & Assay Development
(N = 2800)

CCGA2
Assay Refinement
(N = 4487)

CCGA3
Validation of Targeted Methylation Assay
(N = 5309)

Liu et al., Ann of Oncology 32(9) 2021

CCGA3 Results

	Cancer (n=2823)	Non-cancer (n=1254)	Total (n=4077)
Test Positive	1453	6	1459
Test Negative	1370	1248	2618

Specificity:
99.5%
(95% CI: 99.0–99.8%)

↓

0.5%
false-positive rate

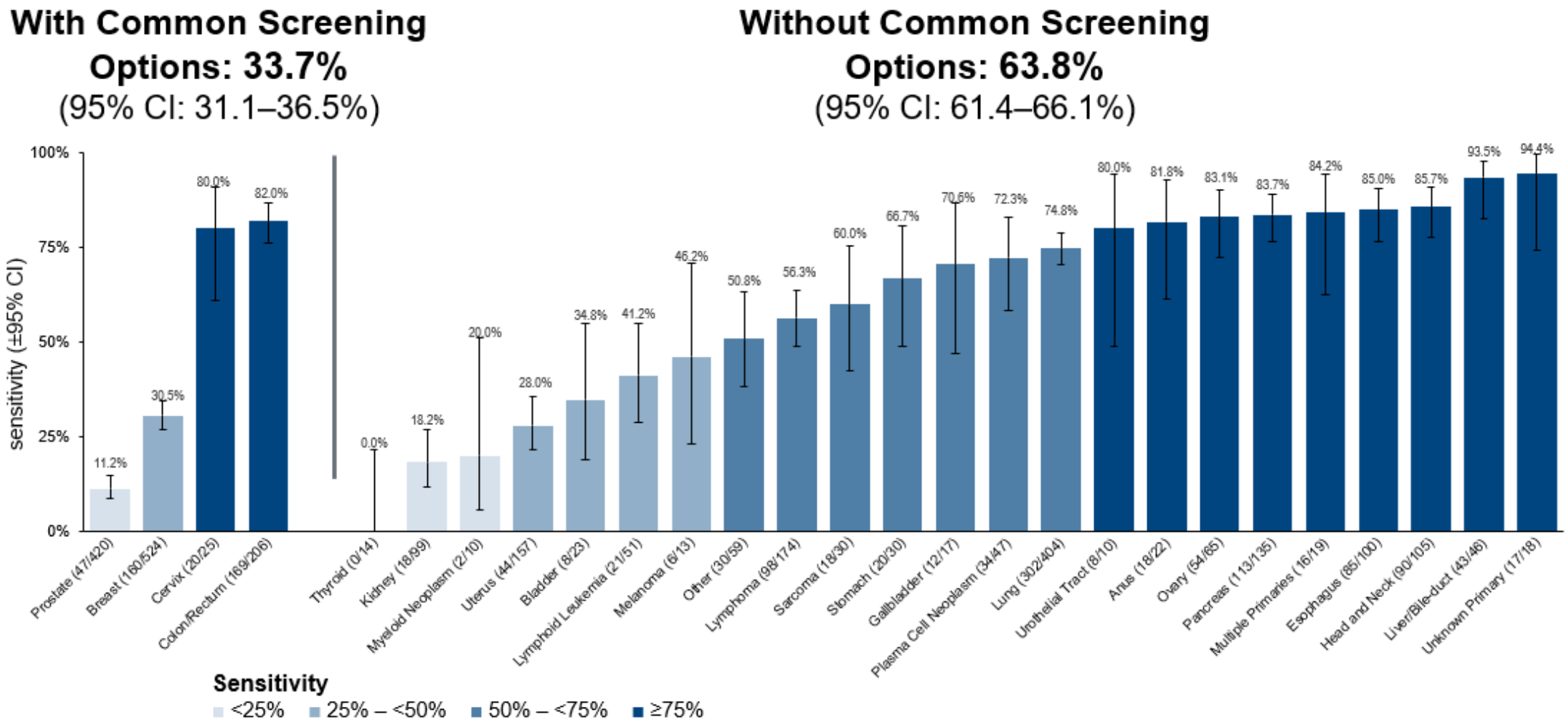
Sensitivity:
51.5%
(95% CI: 49.6–53.3%)

↓

Signal origin prediction accuracy : 88.7%
(95% CI: 87.0–90.2%)

Klein et al, Ann Oncol 32:1167, 2021

CCGA3 Results



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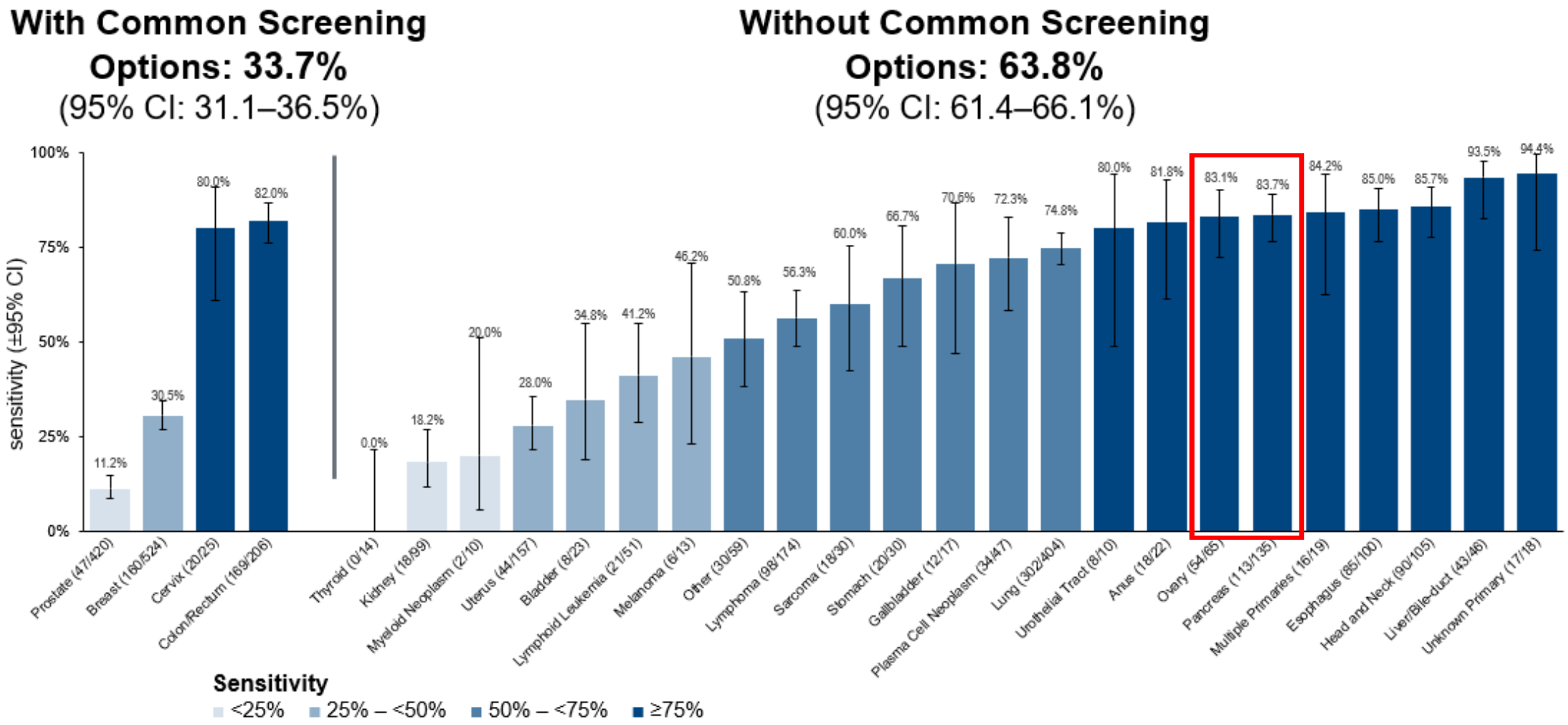

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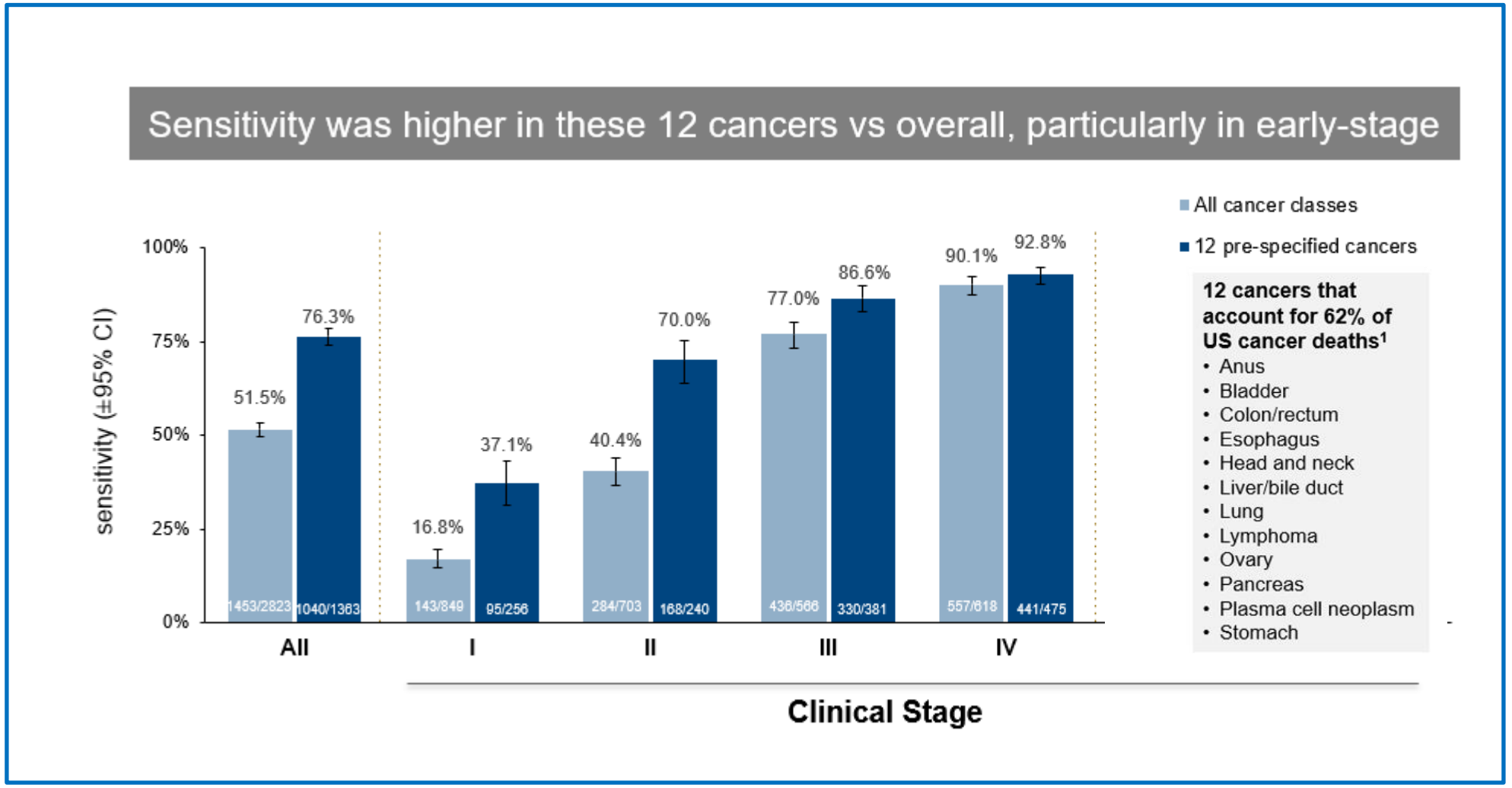

Sensitivity 67.6% for 12 pre-specified cancers

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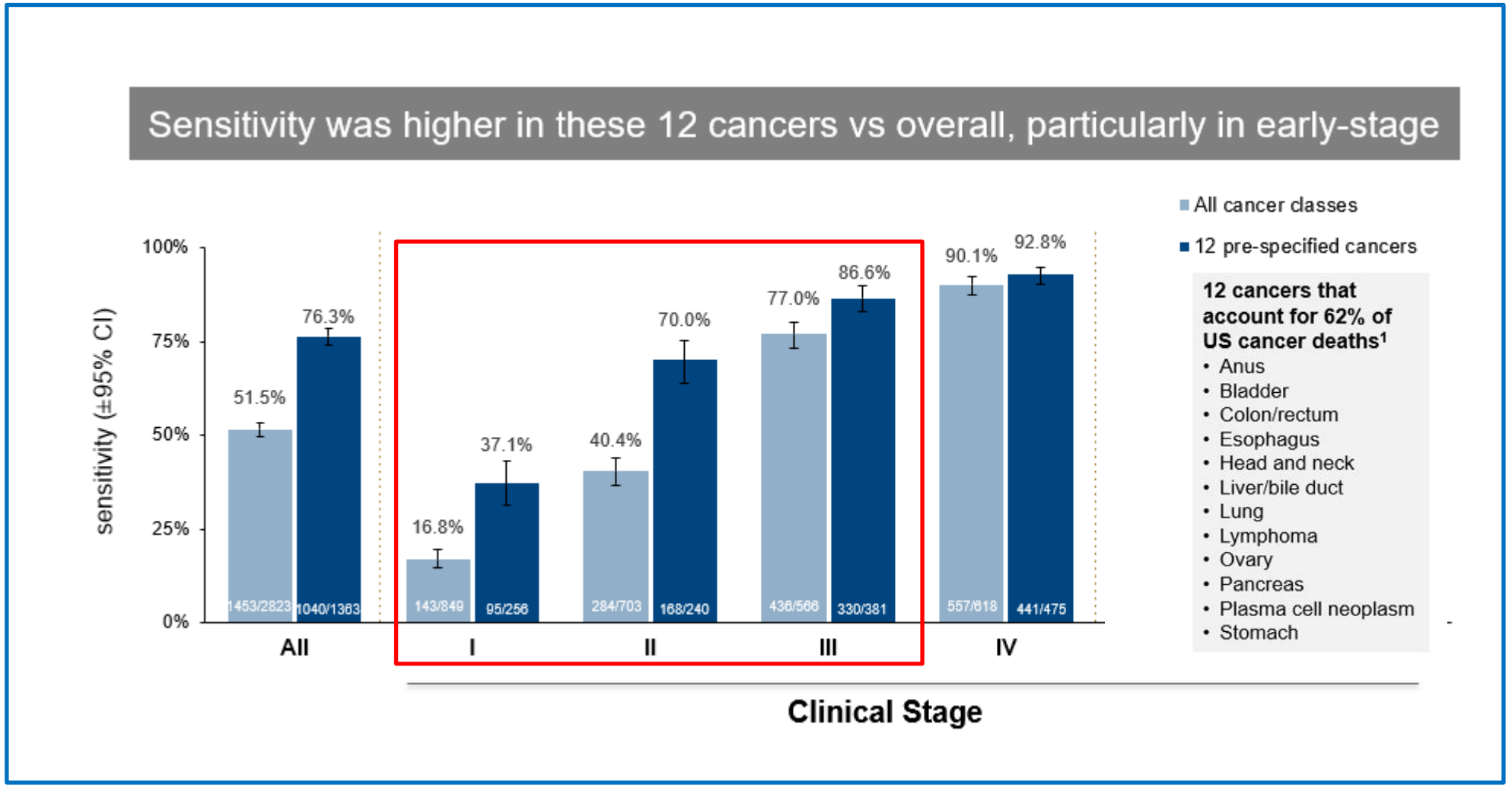

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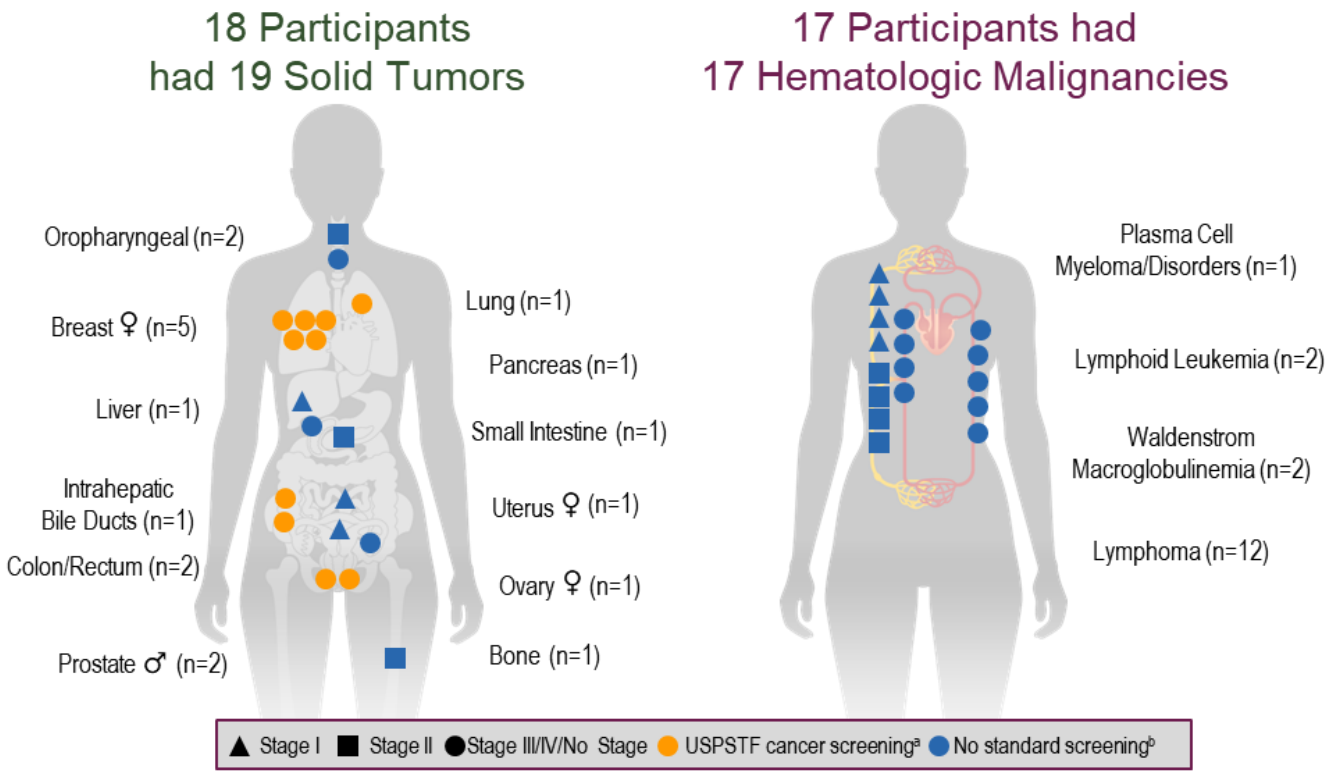
Pathfinder Study

Results returned to provider and participant

Pathfinder Study

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



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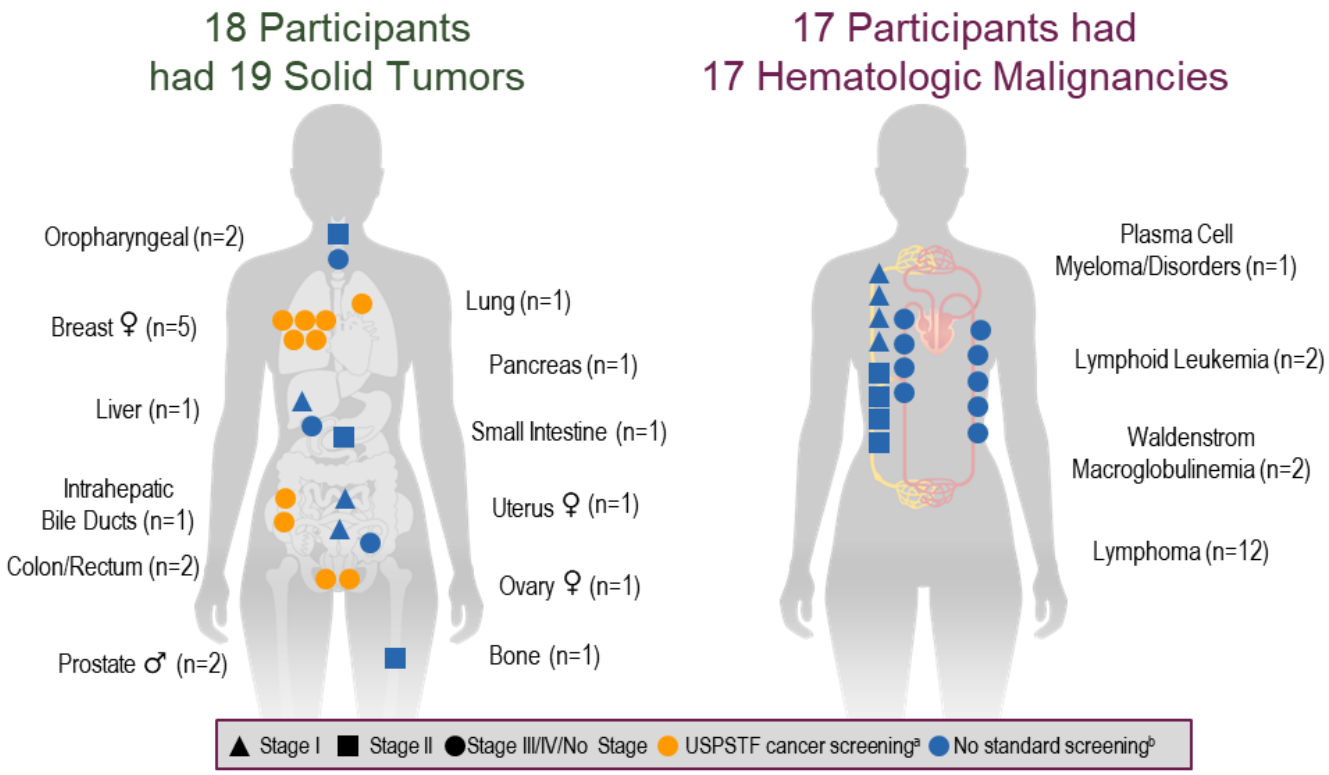
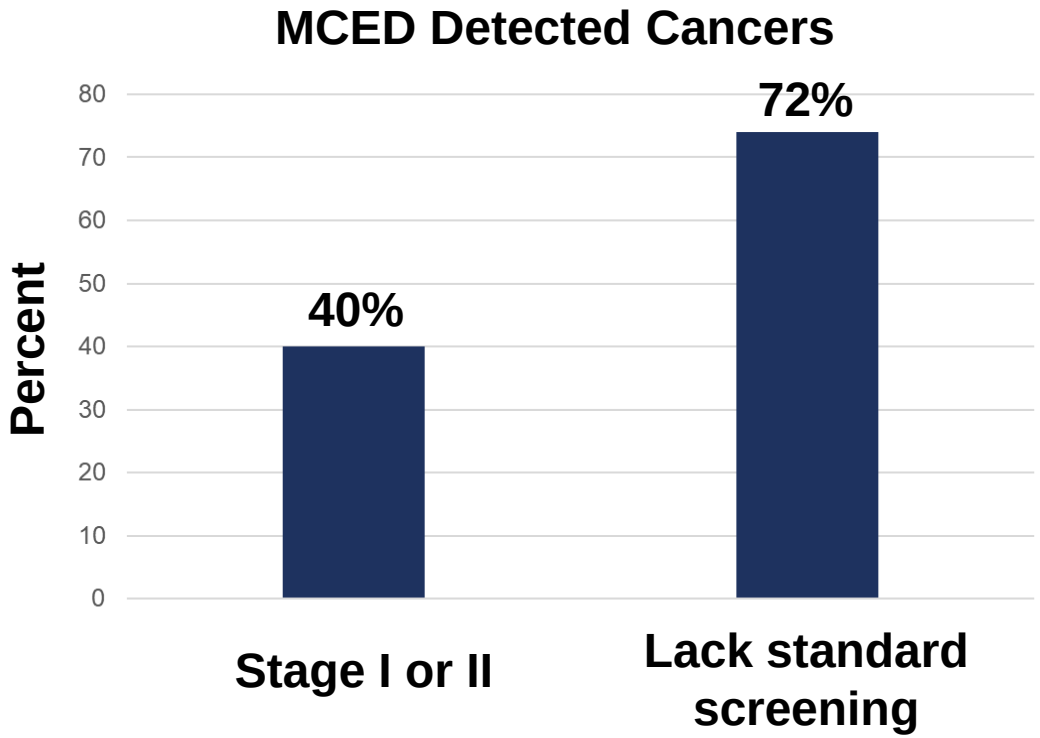
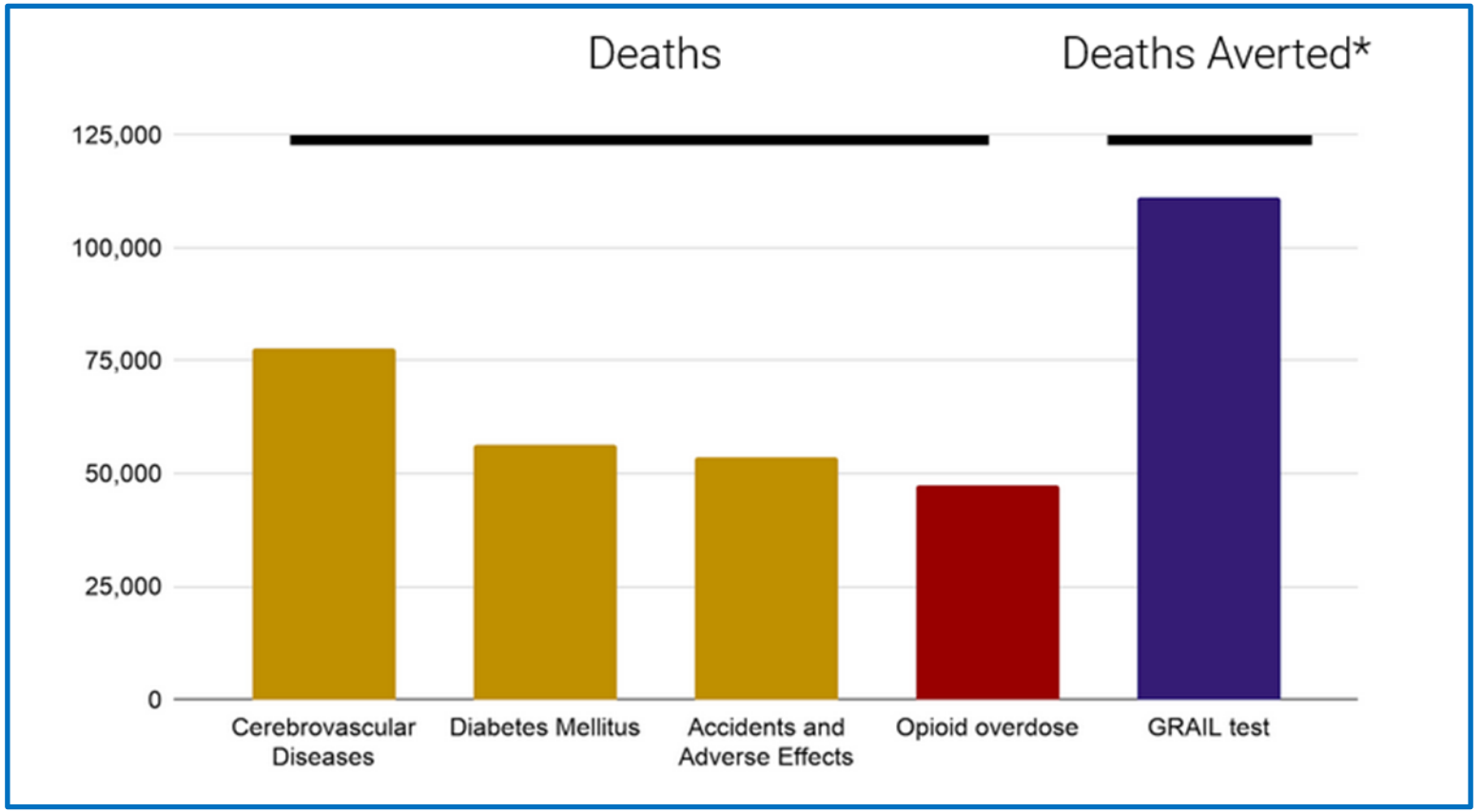




Potential for Earlier Detection to Save Lives
Modeled Data from SEER and CCGA



26% Reduction in Cancer Mortality

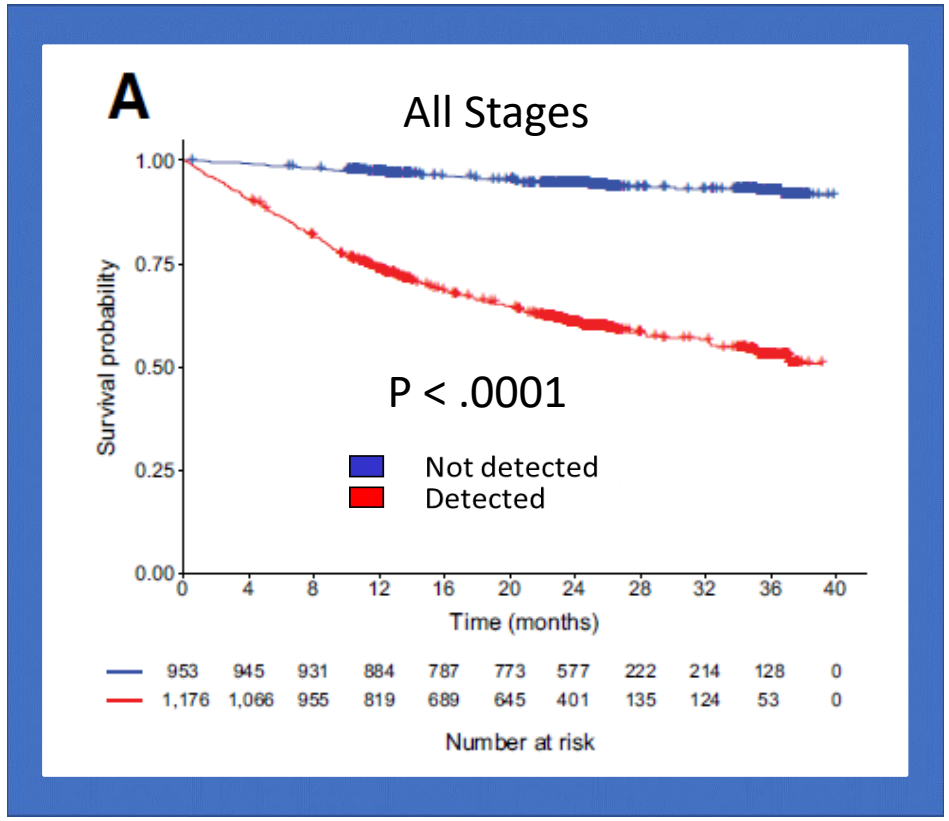
Hubbell E, et al. Cancer Epidemiol Biomarkers Prev., 2020

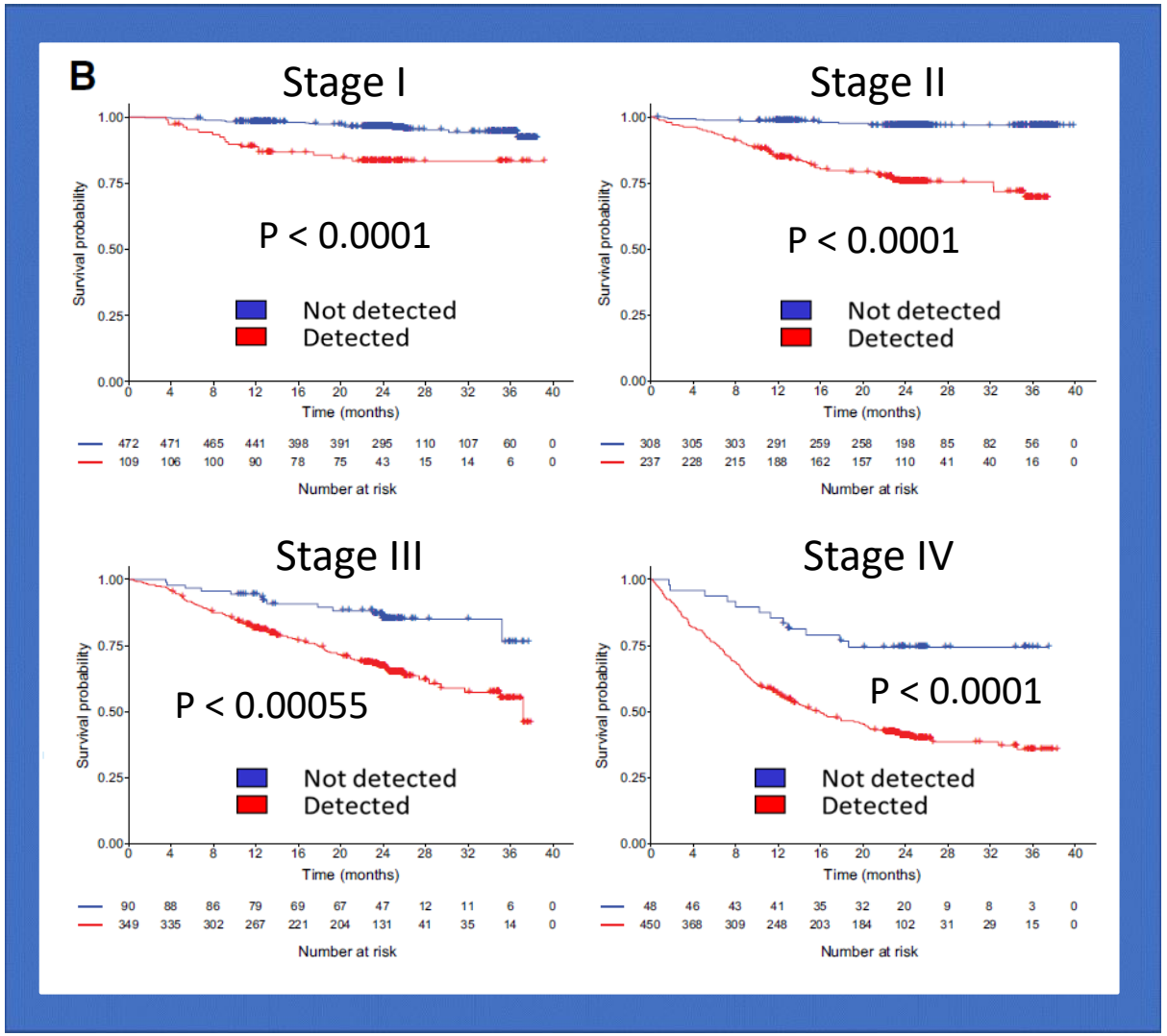
MCED Challenges

- **Overdiagnosis**
- **False Positives**
- **Cost**

Do MCEDs Overdetect Nonlethal Cancers?

Not detected
Detected

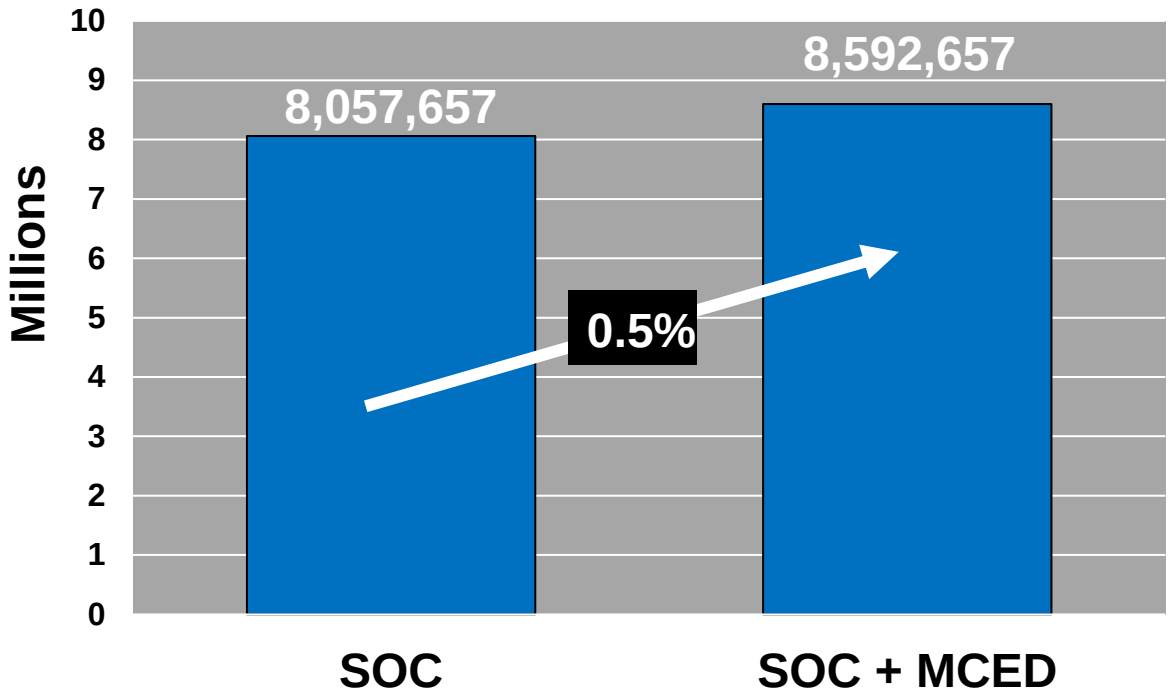




Chen et al., Clin Cancer Res 27:422, 2021

False Positives

Eligible for screening (ages 50-79): 107M



Hackshaw et al., Brit J Cancer (2021) 125:1432 – 1442

Pathfinder, Schrag et al., ESMO (2022)

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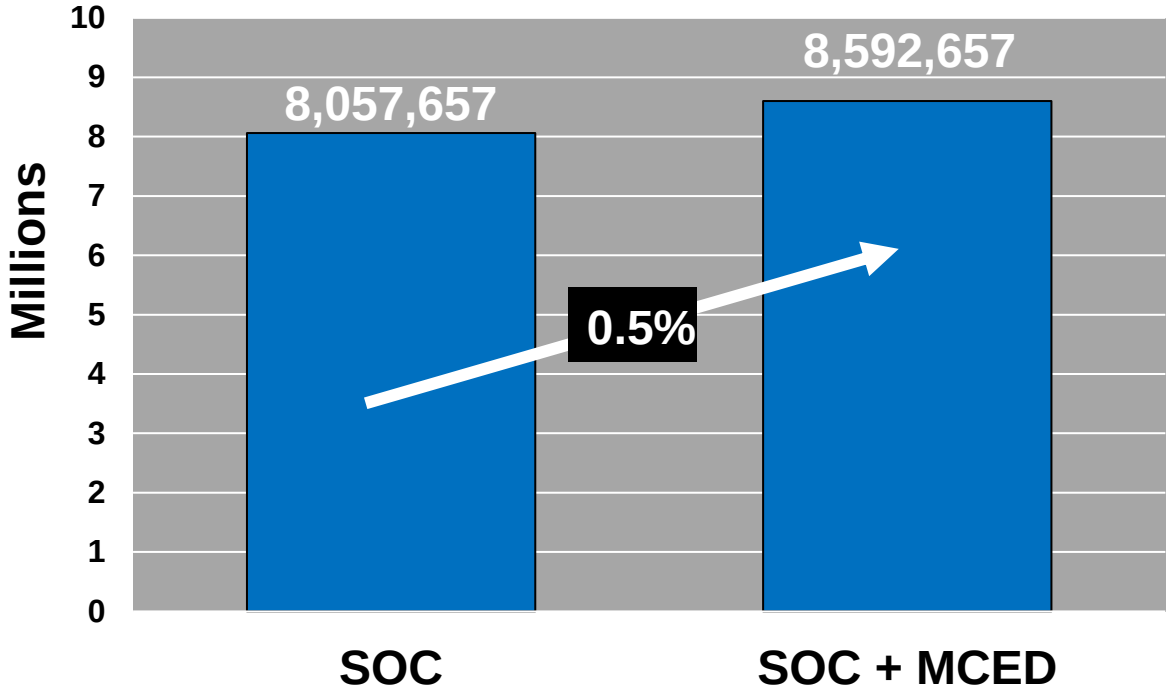

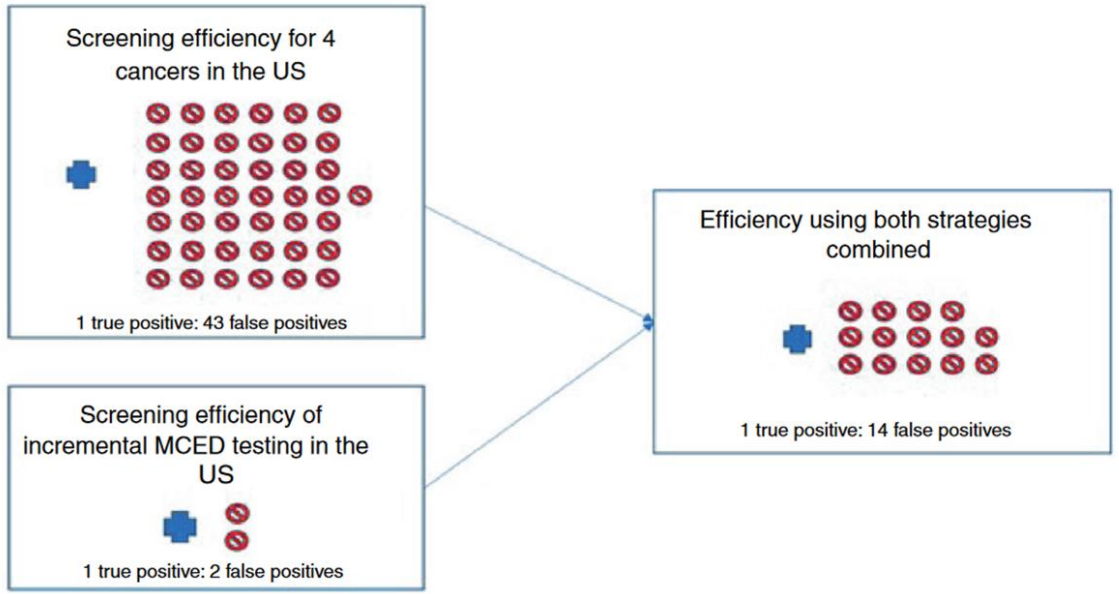

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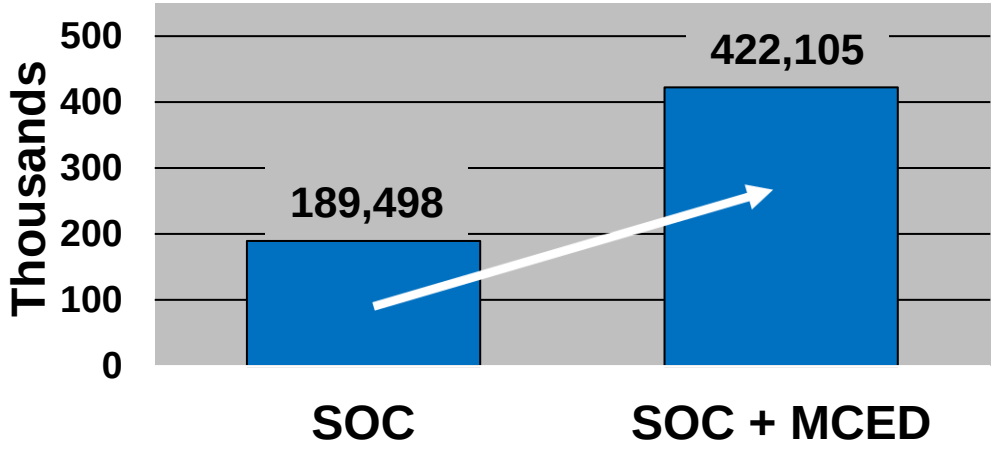
Cost

Current SOC cost: $16.9B
MCED cost: $3B

Number of Cancers Detected



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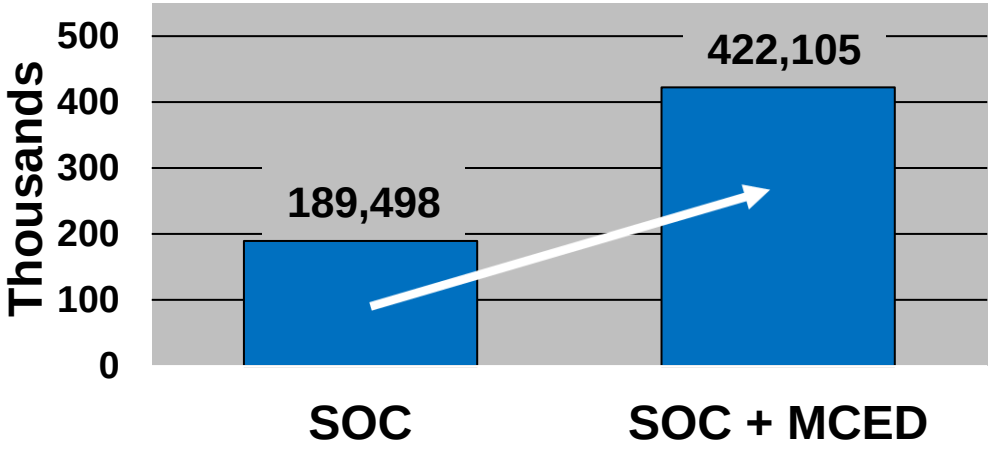
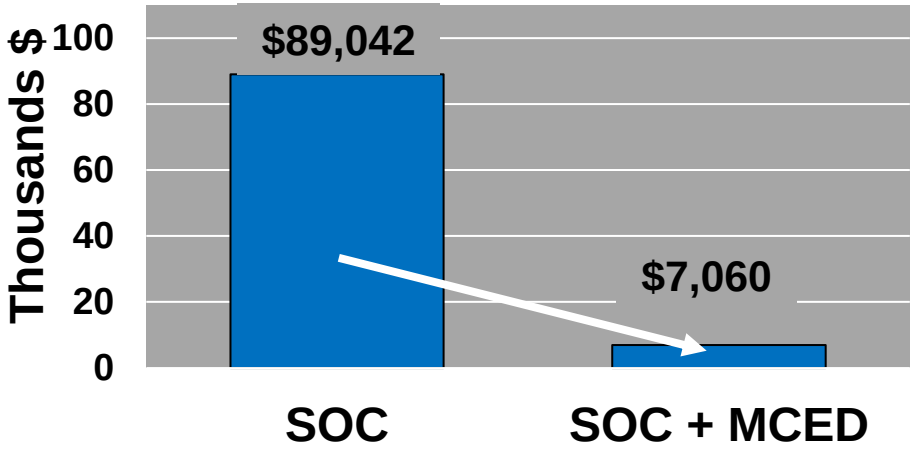


Cost per Cancer Detected



2.2X increase in CDR results in a 12.6X reduction in cost

Eligible to be screened ~107M (aged 50 – 79)

Hackshaw et al., Brit J Cancer (2021) 125:1432 – 1442

Intended Use

- Adjunct to current screening tests
- In the short term
  - Higher risk of cancer
    - Smokers
    - Strong family history
    - Known genetic carrier or syndrome (BRCA, others)
    - Prior history of cancer
    - Pediatric cancer survivors
    - Immunosuppressed
    - Worried well
- In the long term
  - General population – adults over 50

Despite this

USPSTF Recommendations for Cancer Screening

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Cervical	A	Women aged 21 to 65	Regular screening (3–5 years) using cervical cytology and/or HPV tests
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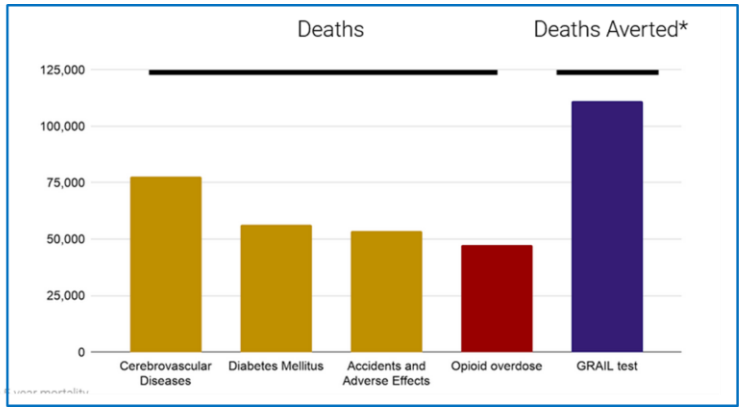
To achieve this

Adding MCED has the potential...



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