A Case for Multi Cancer Testing

EDRN Steering Committee– July 1st

Ken Kinzler for
The Ludwig Center at Johns Hopkins
and The DETECT A Study Group

LUDWIG CANCER RESEARCH
Johns Hopkins

Disclosures

- Thrive Earlier Detection –Equity, Consultant Fee
- Symex –Consultant Fee
- PGDx –Equity
- Eisai, Inc. –Consultant Fee
- CAGE Pharma –Equity
- Neophore –Equity

NON FDA Approved Use of Drugs or Products Referenced in this Presentation - NONE

Kenneth W. Kinzler Ph.D.

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The Case for Earlier Detection

- Prevention is most efficient.
- Primary prevention can not prevent all cancers.
- Outcomes are better for earlier stage cancers for every cancer type.
- Treatments work better with less disease burden.
- As life expectancy increases, the incidence and impact of cancer will increase.
- If we don't find cancers early, we will never develop effective management strategies.

The Case for Multi-Cancer Blood Test

- Many mutations and molecular changes are shared across tumor types.
- Even classic markers are not cancer specific.
- Blood samples a variety of tumor types effectively.
- Better performance for patients (one test).
- Easier to get meaningful performance (PPV)

Challenges to Earlier Detection

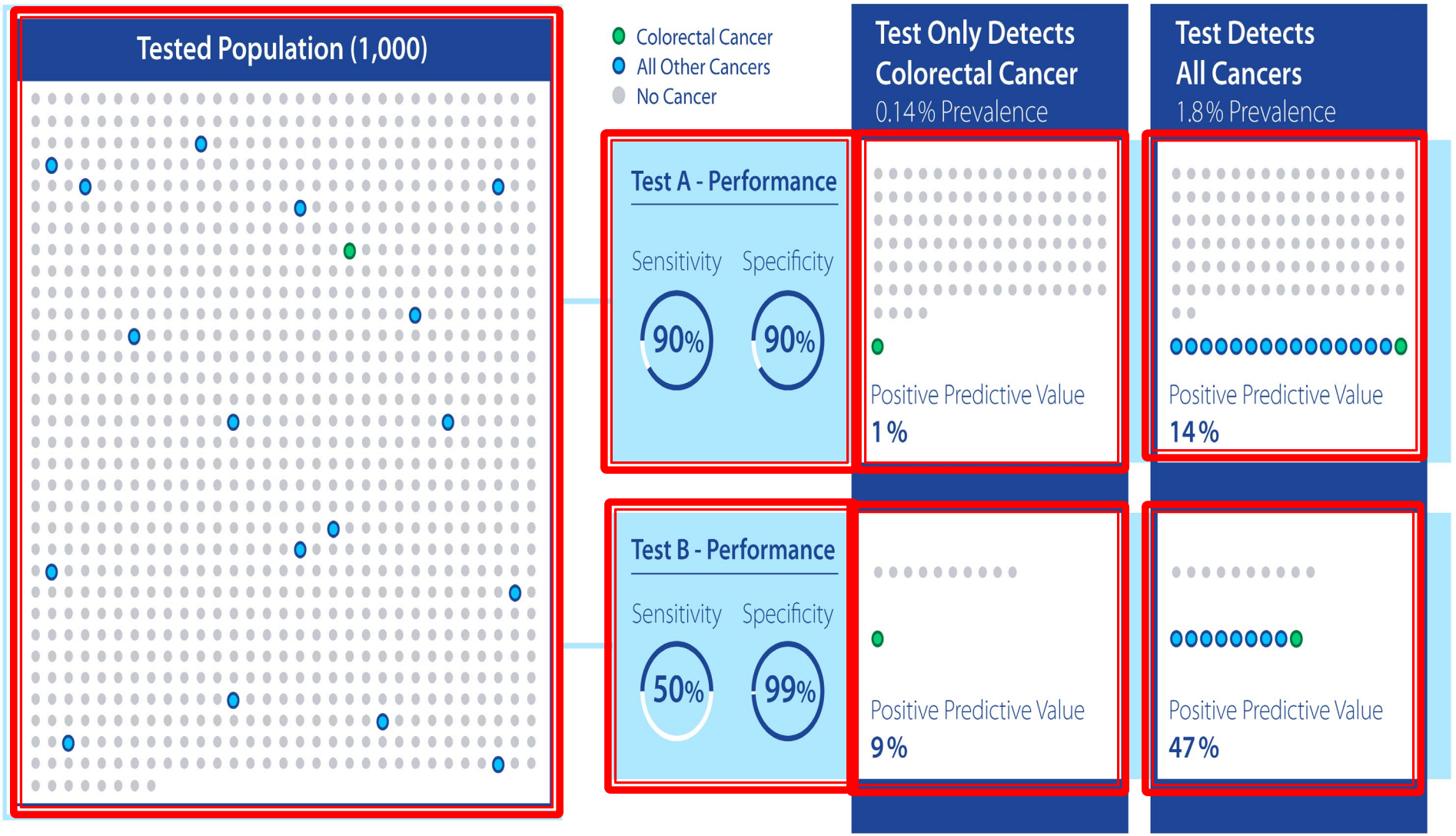
- Psychosocial – Society and individuals tend to give priority to reactive rather than proactive solutions.
- Economical – Needs to be cost effective to administer across the population.
- Practical – Needs to be readily deliverable across the population.

Challenges to Earlier Detection

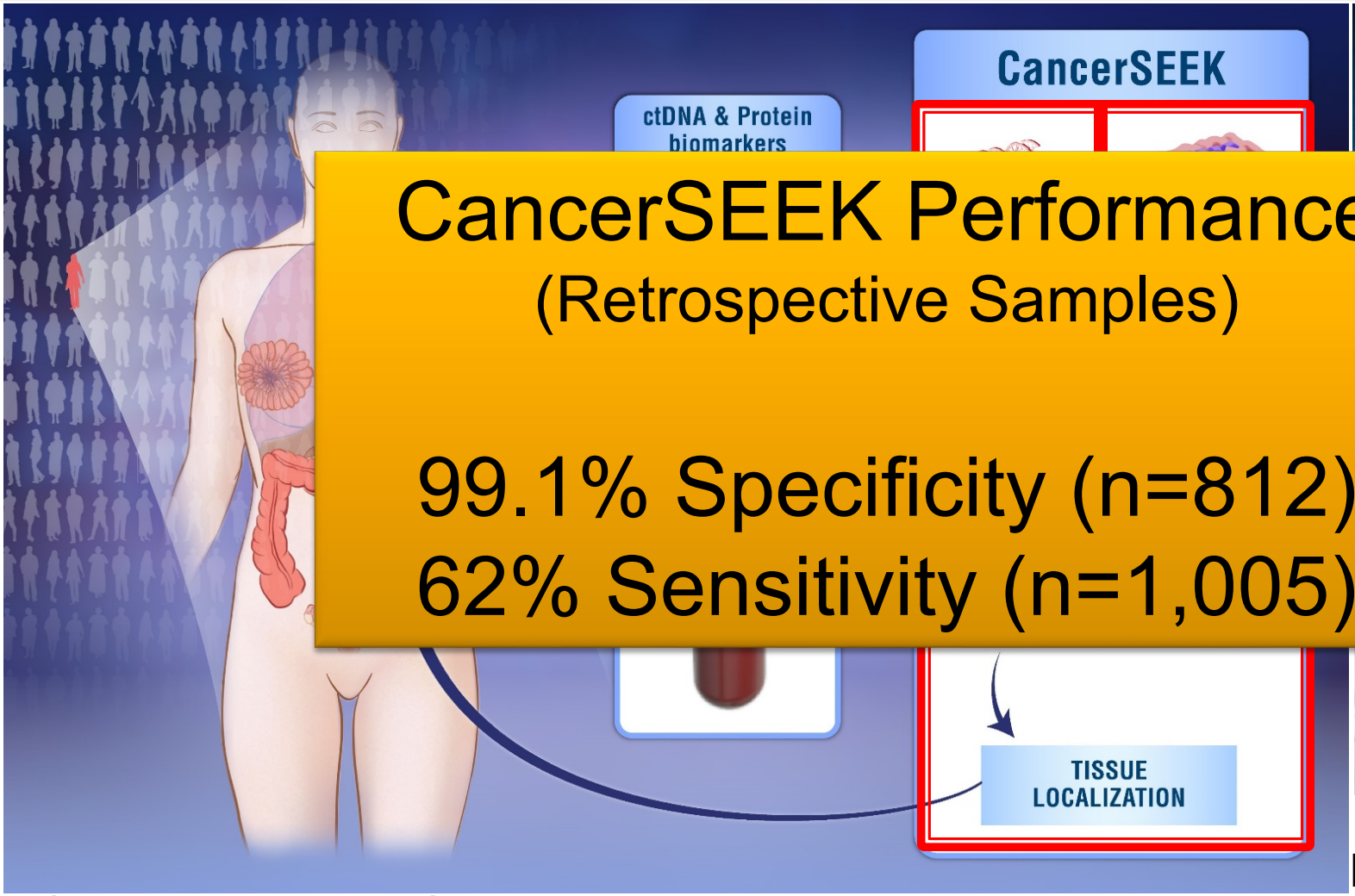
- Clinical – Effective Management Strategies

A practical cancer screening approach begins with a **Convenient Sample** and a **Specific Cancer Biomarker**.

Specificity and PPV

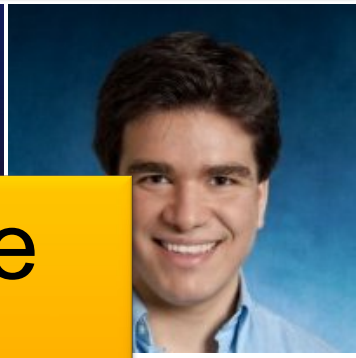


CancerSEEK Blood Test



CancerSEEK Performance
(Retrospective Samples)

99.1% Specificity (n=812)
62% Sensitivity (n=1,005)



h Cohen

Nick Papadopoulos

Cohen *et al.*, **Science** 359:926-30 2018

Multi-Cancer Blood Tests are Here

Cristiano *et al*., **Nature** 570:385-89, 2019

Genome–wide cell–free DNA fragmentation in patients with cancer

Stephen Cristiano[1,2,15], Alessandro Leal[1,15], Jillian Phallen[1,15], Jacob Fiksel[1,2,15], Vilmos Adleff[1], Daniel C. Bruhm[1], Sarah Østrup Jensen[3], Jamie E. Medina[1], Carolyn Hruban[1], James R. White[1], Doreen N. Palsgrove[1], Noushin Niknafs[1], Valsamo Anagnostou[1], Patrick Forde[1], Jarushka Naidoo[1], Kristen Marrone[1], Julie Brahmer[1], Brian D. Woodward[4], Hatim Husain[4], Karlijn L. van Rooijen[5], Mai–Britt Worm Ørntoft[3], Anders Husted Madsen[6], Cornelis J. H. van de Velde[7], Marcel Verheij[8], Annemieke Cats[9], Cornelis J. A. Punt[10], Geraldine R. Vink[5], Nicole C. T. van Grieken[11], Miriam Koopman[5], Remond J. A. Fijneman[12], Julia S. Johansen[13], Hans Jørgen Nielsen[14], Gerrit A. Meijer[12], Claus Lindbjerg Andersen[3], Robert B. Scharpf[1,2]* & Victor E. Velculescu[1]*

Liu *et al*., **Annals of Oncology**, in press, 2020

Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA

M. C. Liu[1†], G. R. Oxnard[2†], E. A. Klein[3], C. Swanton[4,5], M. V. Seiden[6*] & on behalf of the CCGA Consortium[‡]

Douville *et al*., **PNAS** 117:1858-63, 2020

Assessing aneuploidy with repetitive element sequencing

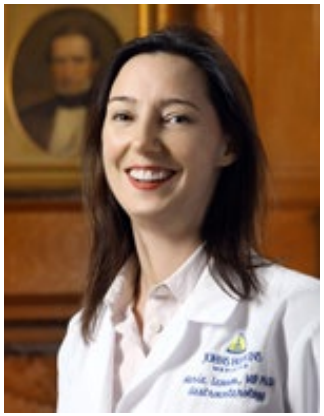
What we need to know to safely and effectively implement?

Prospective Interventional Studies to Address…

- Can a multi-cancer blood test prospectively detect cancer in individuals whose cancer was not previously detected by other means?
- Can such a test be used to intervene in the tumor progression, leading to therapy with intent to cure?
- Can such a test be incorporated into routine clinical care and not discourage participants from engaging in SOC screening?
- Can such a test be performed safely, without incurring a large number of futile, invasive follow-up tests based on the test results?

The DETECT-A Study: Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing

Lennon *et al*., **Science**, in press, 2020



Anne Marie O'Broin Lennon

Nick Papadopoulos

Science

RESEARCH ARTICLES

Cite as: A. M. Lennon *et al.*, *Science* 10.1126/science.abb9601 (2020).

Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention

Anne Marie Lennon[1,4,10*], Adam H. Buchanan[11*], Isaac Kinde[12*], Andrew Warren[12,13*], Ashley Honushefsky[11*], Ariella T. Cohain[12], David H. Ledbetter[11], Fred Sanfilippo[14], Kathleen Sheridan[11], Dillenia Rosica[11], Christian S. Adonizio[11,16], Hee Jung Hwang[12], Kamel Lahouel[1,6], Joshua D. Cohen[1,2,3,4,5], Christopher Douville[1,3], Aalpen A. Patel[11], Leonardo N. Hagmann[12], David D. Rolston[11], Nirav Malani[12], Shibin Zhou[1,3,4], Chetan Bettegowda[1,3,8], David L. Diehl[11], Bobbi Urban[12], Christopher D. Still[11], Lisa Kann[12], Julie I. Woods[11], Zachary M. Salvati[11], Joseph Vadakara[11], Rosemary Leeming[11], Prianka Bhattacharya[11], Carroll Walter[11], Alex Parker[12], Christoph Lengauer[12,13], Alison Klein[1,4,15], Cristian Tomasetti[1,6,7], Elliot K. Fishman[1,4,10], Ralph H. Hruban[1,4,9], Kenneth W. Kinzler[1,3,4†], Bert Vogelstein[1,2,3,4†], Nickolas Papadopoulos[1,3,4,9†]

The DETECT-A Team

The Marcus Foundation, Inc.

NCI / EDRN

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LUDWIG CANCER RESEARCH

CURE PANCREATIC CANCER
LUSTGARTEN FOUNDATION

10,000 Women in the DETECT Study

Adam H. Buchanan
David Ledbetter
and the team from
Geisinger

Thrive.
Earlier Detection

Elliot Fishman
Cristian Tomasetti
Ralph Hruban
Bert Vogelstein

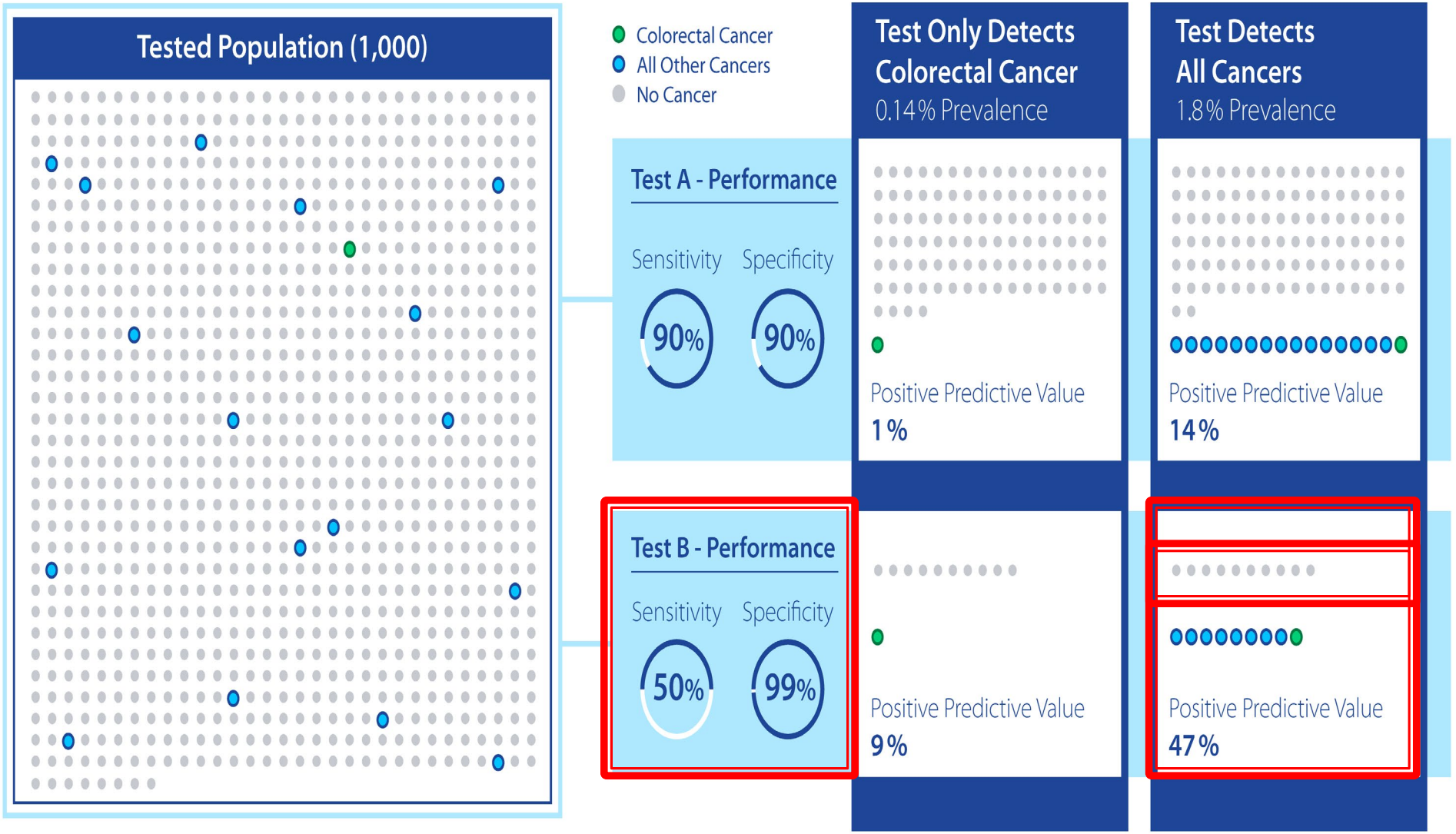
and the Hopkins Team

JOHNS HOPKINS UNIVERSITY

DETECT-A Blood Test

- Multi-Analyte: DNA and Protein
- Efficient and cost-effective: 2,001 bases covering regions of 16 commonly mutated genes and 9 proteins known to be linked to cancer
- An early version (2016-2017) of CancerSEEK
  - Threshold based, no machine learning
  - Does not include improvements in test characteristics developed for CancerSEEK (Cohen *et al.*, 2018; Douville *et al.*, 2020)

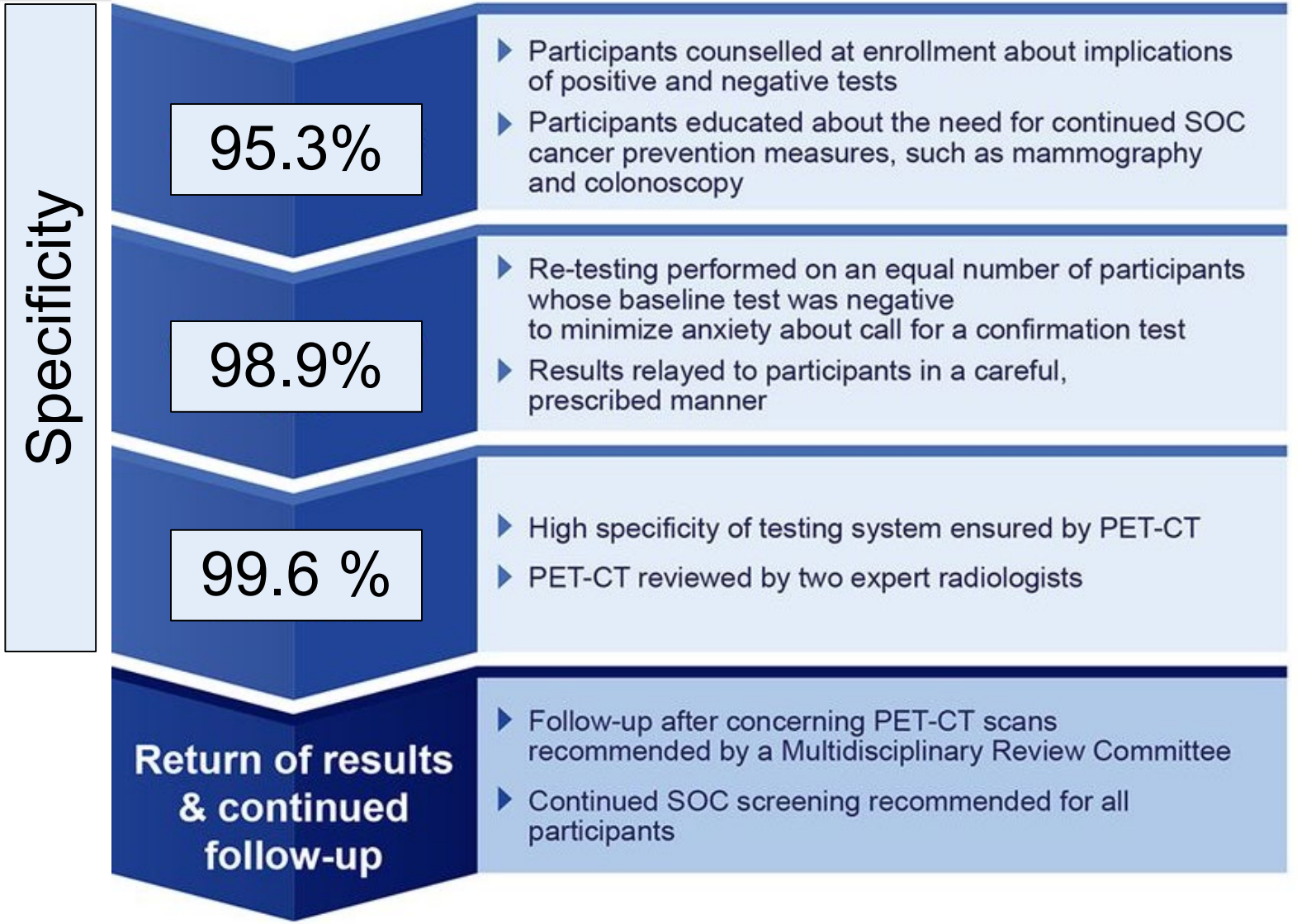
Localization of Tumor



DETECT-A:
PET-CT for Tumor Localization

- Advantages of PET CT with Contrast
  - Diagnostic PET-CT is routinely used in clinical practice and is FDA-cleared for detecting, localizing, staging and diagnosing tumors
  - Orthogonal confirmation of the blood testing
  - Single Uniform Diagnostic Pathway
  - It provides information beyond tissue localization (e.g., left vs right lung, proximal or distal colon, metastatic or not)
  - Reduction of unnecessary follow-ups

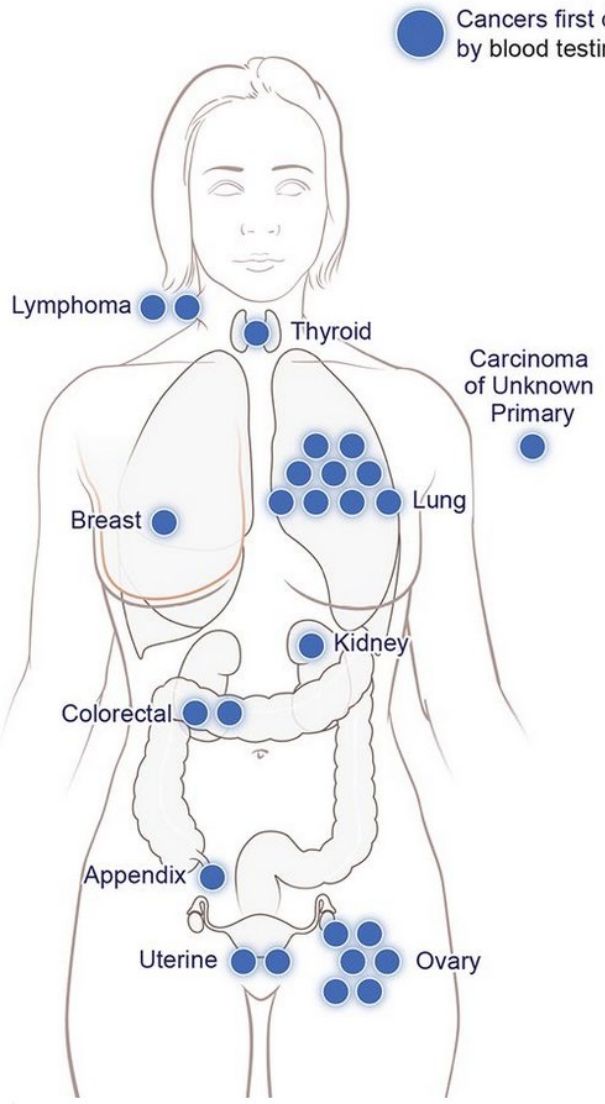
DETECT-A Design Safety Features



DETECT-A : Population

- 10,000 women 65 – 75
  - Enriched for ovarian cancer
- Only exclusion criterion (current or previous known cancer)
  - Less advanced and smaller cancers than in case-control studies
  - Multiple co-morbidities
- All enrolled through Geisinger Health System (18 sites)
  - Access to EMR
  - Minimize loss to follow-up
- 10,006 enrolled, 95 excluded, 9911 Baseline Tested

Can a multi-cancer blood test prospectively detect cancer in individuals whose cancer was not previously detected by other means?

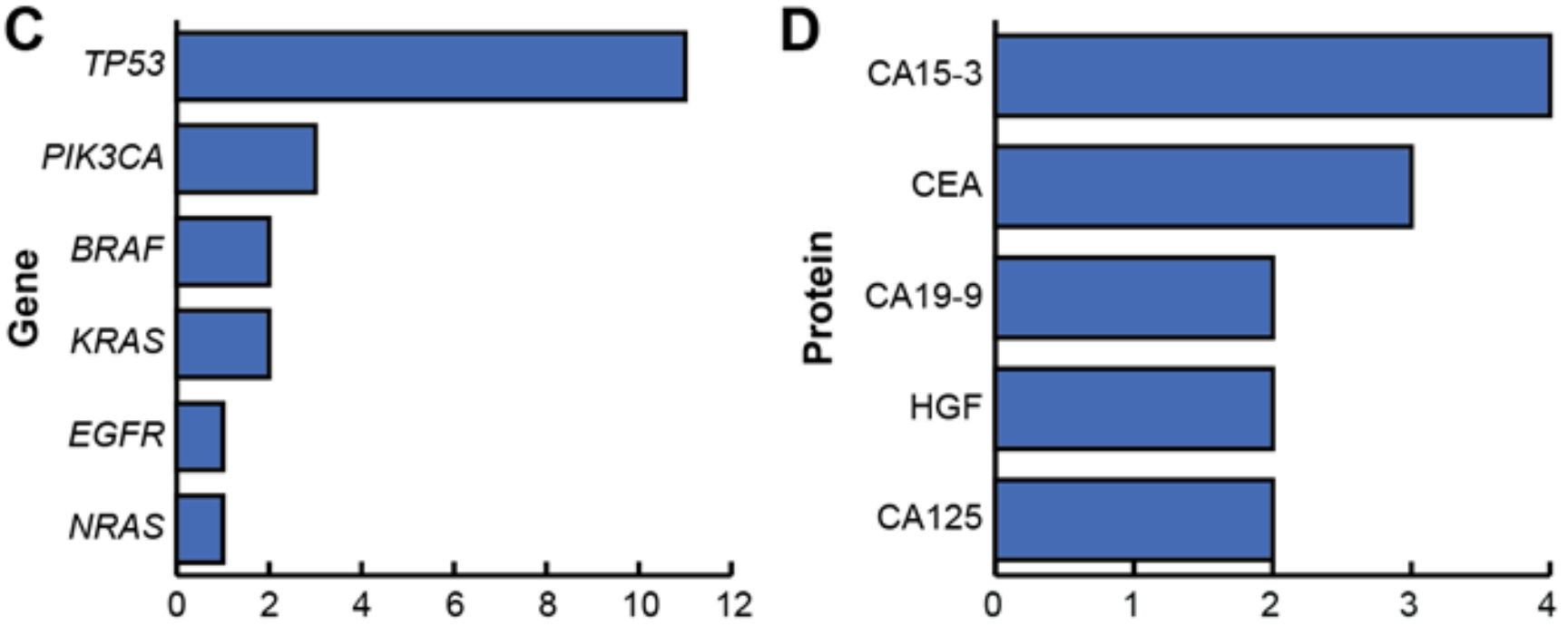


- 26 Cancers
- 10 Cancer Types
- Blood Test PPV = 19%
- Plus imaging PPV = 41%
- 58% detected by mutations

Analyte Performance

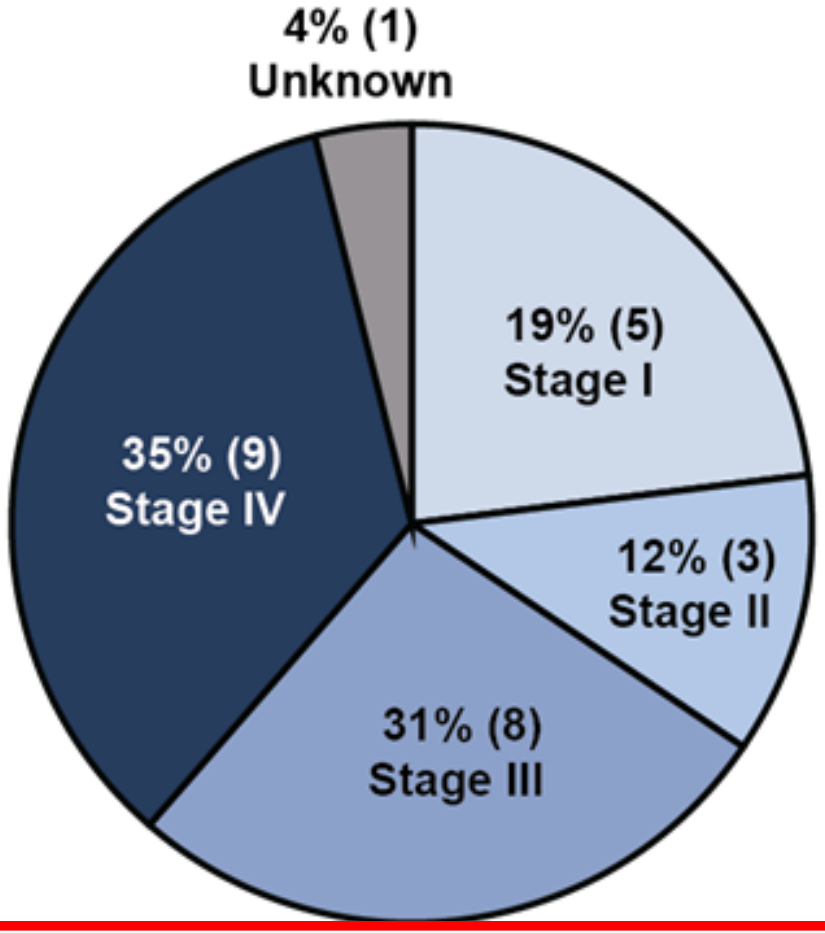
ctDNA

Protein



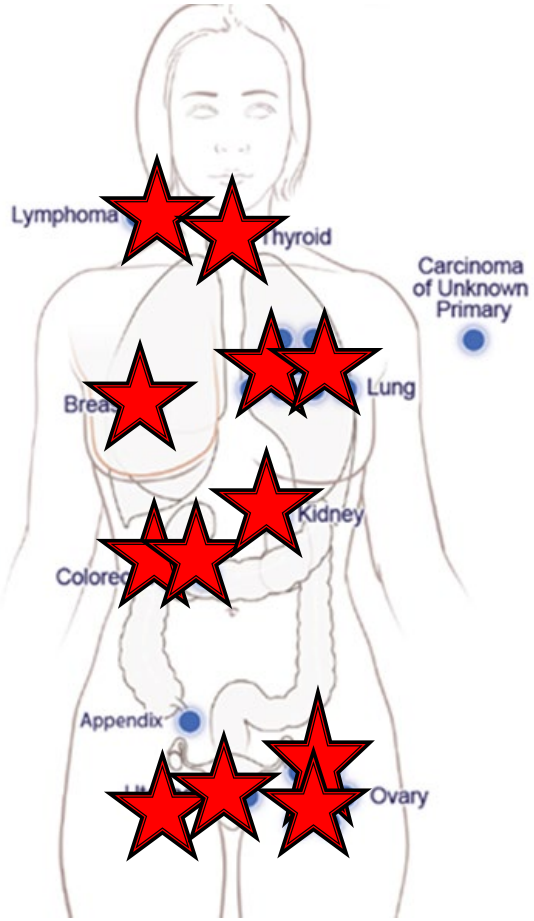
Number of times observed in 26 participants with cancer first detected by blood testing

Can a multi-cancer blood test be used to intervene in tumor progression, leading to therapy with intent to cure?



64% (16/25) Localized or Regional

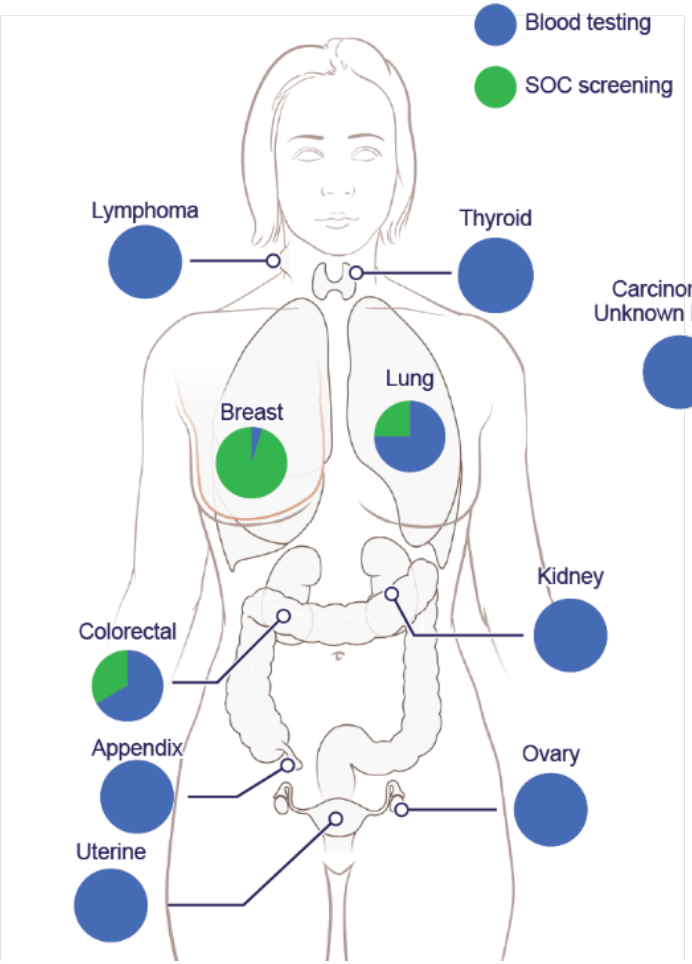
Can a multi-cancer blood test be used to intervene in tumor progression, leading to therapy with intent to cure?



12 Curative Intent Surgeries

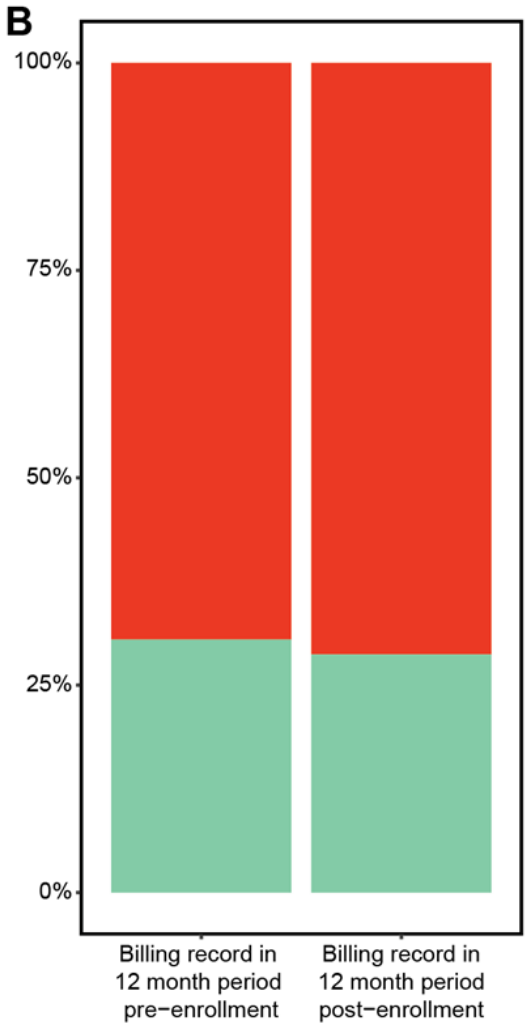
Can a multi-cancer blood test be incorporated into routine clinical care and not discourage participants from engaging in SOC screening?

Screen Detected Cancer



It **doubled** the number of cancers detected by standard-of-care screening alone.

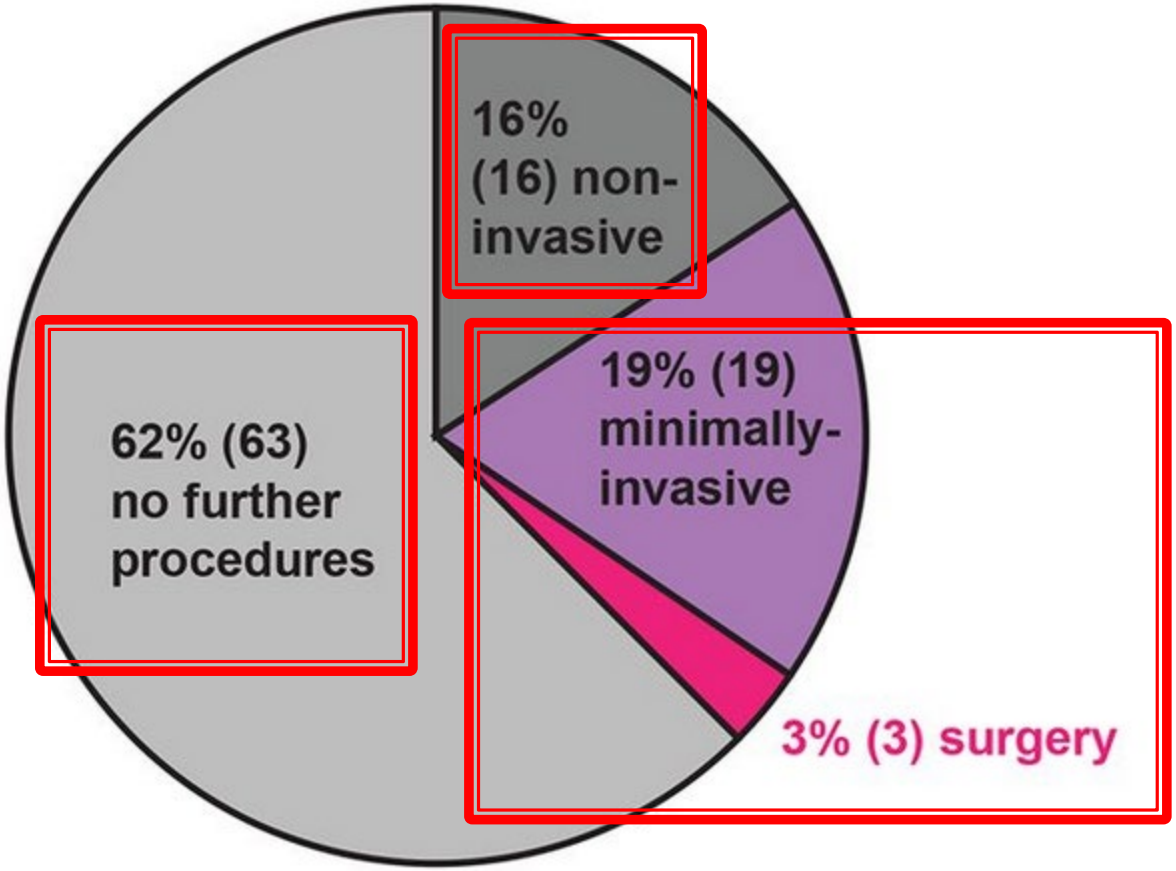
Can a multi-cancer test be incorporated into routine clinical care and not discourage participants from engaging in SOC screening?



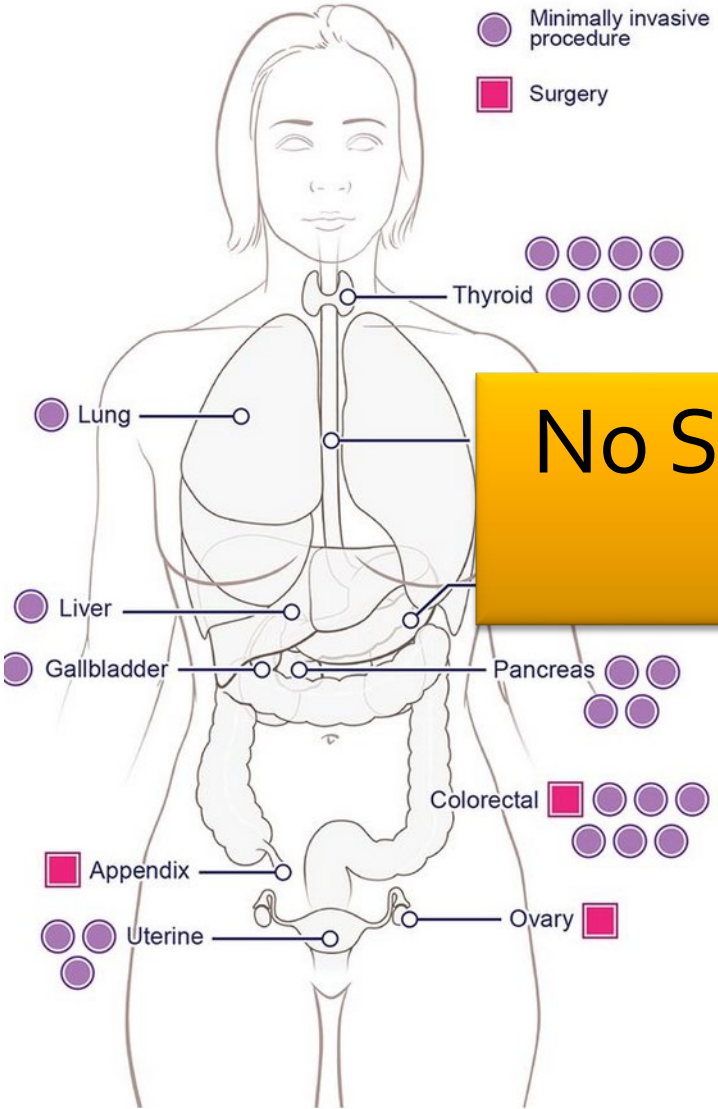
It did not discourage standard-of-care screening in the DETECT-A participants.

Can a multi-cancer blood test be performed safely, without incurring a large number of futile, invasive follow-up tests based on the test results?

Diagnostic Outcome of PET-CT in 101 (1.0%) participants without cancer



Can a multi-cancer test be performed safely, without incurring a large number of futile, invasive follow-up tests based on the test results?



All minimally-invasive and surgical procedures performed on the 22 (0.22%) participants without cancer.

No Serious Adverse Events

- iduals with positive
  ancer
- Large colonic polyps with high-grade dysplasia which could not be removed endoscopically
- In situ carcinoma of the appendix
- 10 cm ovarian lesion that was ultimately found to be a mucinous cystadenoma

Cancers in the DETECT-A Cohort

- 96 cancers (0.9%)
- Sensitivity
  - 25% with SOC screening
  - 27% with blood test screening
  - 31% with blood test for cancers without SOC
  - 52% with SOC and blood test

Conclusions

- The findings suggest that a multi-cancer blood test can …
  - identified cancers in individuals not previously known to have cancer (cancers of 10 organ were detected)
  - enable treatment with intent to cure in at least a subset of individuals (64% of detected cancer were local or regional)
  - be additive and complementary to SOC screening (blood testing doubled the screen detected cancers)
  - detect cancers with high specificity with imaging (99.6% and 40.6% PPV) or without (98.9%, 19.4% PPV)
  - PET-CT is an efficient and effective method for tumor localization

- These findings help inform and provide a model for the design of future randomized trials to establish clinical utility, cost effectiveness, and benefit-to-risk ratio of future tests.

Future of Screening: Multi-Fluid, Multi-Analyte, Multi-Cancer

Multi-Analyte Assays

Multi-Fluid Analysis

Thanks You!

Questions?

EDRN Steering Committee Meeting

DETECT-A: Futile Radiation Exposure