Blood-Based Screening for Cancer Detection

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COI Disclosure

- Freenome – UPMC/Dr. Schoen study site for PREEMPT clinical trial
- Research Collaboration with Johns Hopkins

ctDNA: Circulating Tumor DNA

- As cancer cells turn over, release DNA into adjacent media
- Blood, stool, urine, pancreatic juice, cysts, cervical mucous, CSF, saliva, bronchial, etc.
- ctDNA – searching for somatic mutations within driver genes that are responsible for clonal growth

Targets in Blood Beyond ctDNA

- Epigenetic changes (methylation)
- Proteins
- Fragmentomics

cfDNA vs. ctDNA

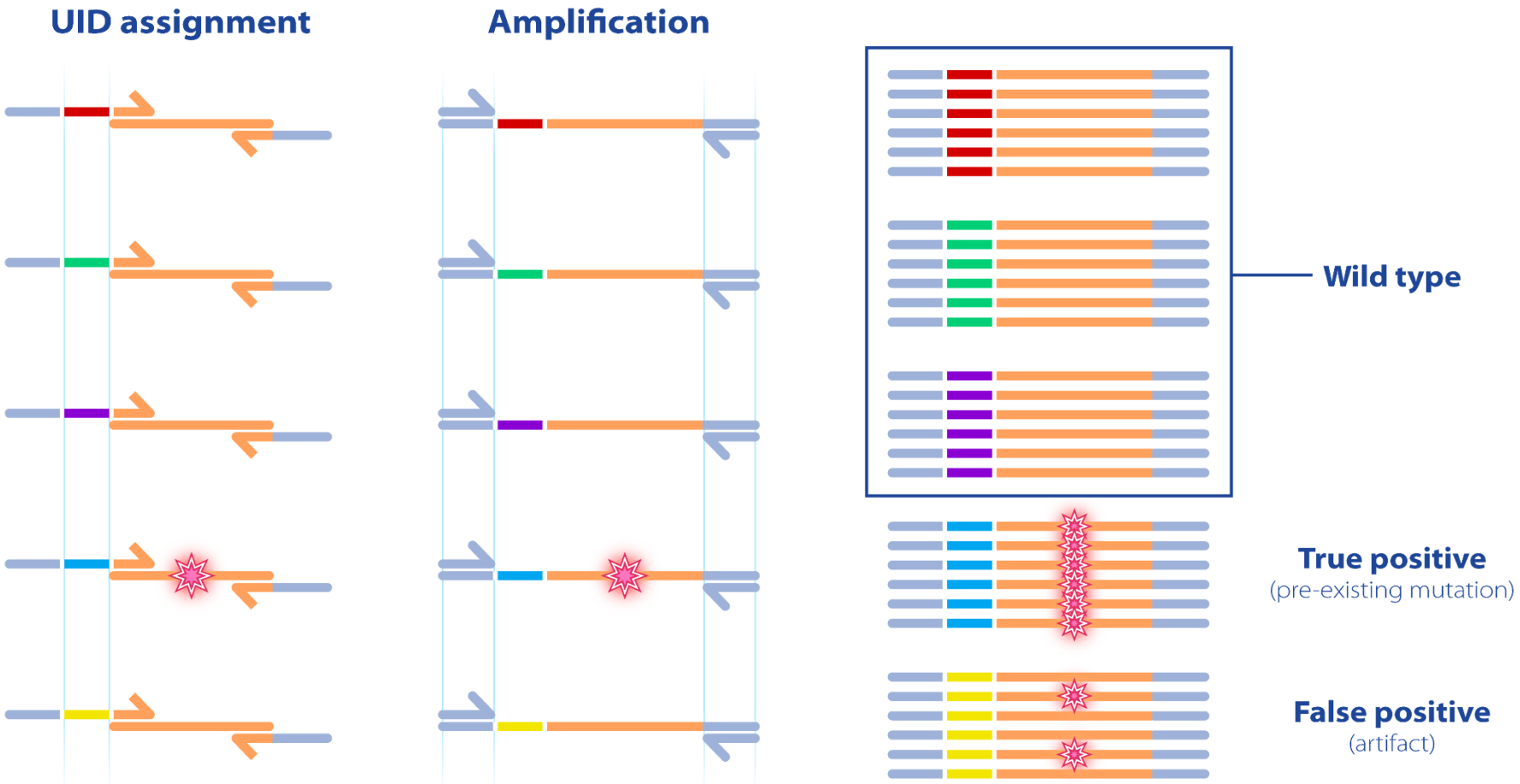
- Vast majority of cfDNA is from hematopoietic cells.
- Release arises from apoptosis
- We don’t understand etiology of level/amount – not necessarily proportional to tumor size/stage (though generally so), varies by tumor site

Challenges for ctDNA as a Biomarker

1. Sensitivity – can be <1 mutant molecule/ml of plasma: requires large volume plasma for testing
2. Specificity – other sources of mutant DNA must be excluded, e.g., CHIP – clonal hematopoiesis of indeterminate potential
3. Tissue of origin: Mutations not specific to one type of cancer: Find a mutation: Where is it coming from?

Digital Genomics

Conceptual Elements of Molecular Barcoding



UID – Unique IDentifier

Cohen J. Can Epi Biomark 2020

Pan-Cancer vs Single Cancer?

It is better to develop a test that seeks to identify multiple cancers?

Or, should we focus on a blood test for a single cancer of interest, e.g., colorectal cancer?

Pan-Cancer Testing

Grail: targeted methylation: detecting >50 cancer types

Challenges/Benefits to Pan-Cancer Testing

1. Specificity: Concern for unintended consequences of false positive test
2. Search for more cancers means higher population prevalence, leads to higher PPV
3. Each cancer has its own idiosyncrasies – is screening efficacious?, work up burden, variable sensitivity – ctDNA is highly sensitive for liver, ovary, not so for breast cancer

Colorectal Cancer

Specificity not an issue: false positive test that leads to CS not much of a concern

Blood Based Screening

Pan Cancer

No

- Grail (1.1B): targete ethylation
- Thrive/Exact (2.1B): ctDN

Yes

Colorectal Cancer

- Freenome (260M): multior
- Guardant (550M): ctDNA, methylation, fragmentomics

Fits within framework for multiphase approach for evaluating new tests?

CRC focused Blood Based "Registration" Trials

1. Freenome - "Preempt" (N=24K)
2. Guardant: "Eclipse" trial - Lunar2 Assay – (N=10K)

Blood-based CRC Trials: Prevention?

- How will blood tests be at detecting advanced adenomas?
- In PLCO trial: 2/3’rds mortality benefit estimated to be due to prevention (reduction in incidence) as opposed to early detection of CA

Douroudi M. Cancer 2017:123:4815

DETECT-A

Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing

i. Can a multi-cancer blood test detect CA?

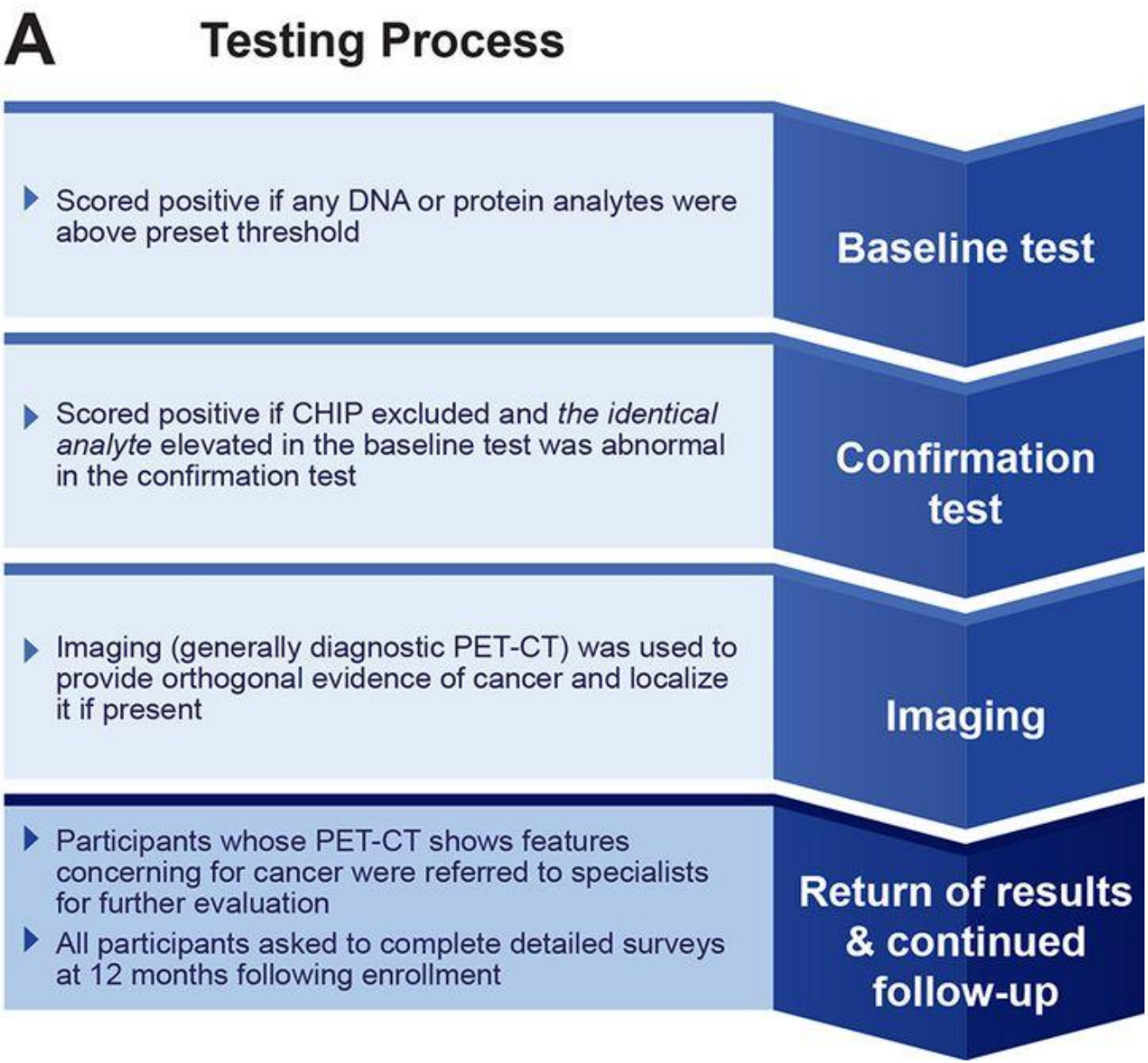
ii. Can test intervene/affect CA progression?

iii. Can it not interfere with SOC screening?

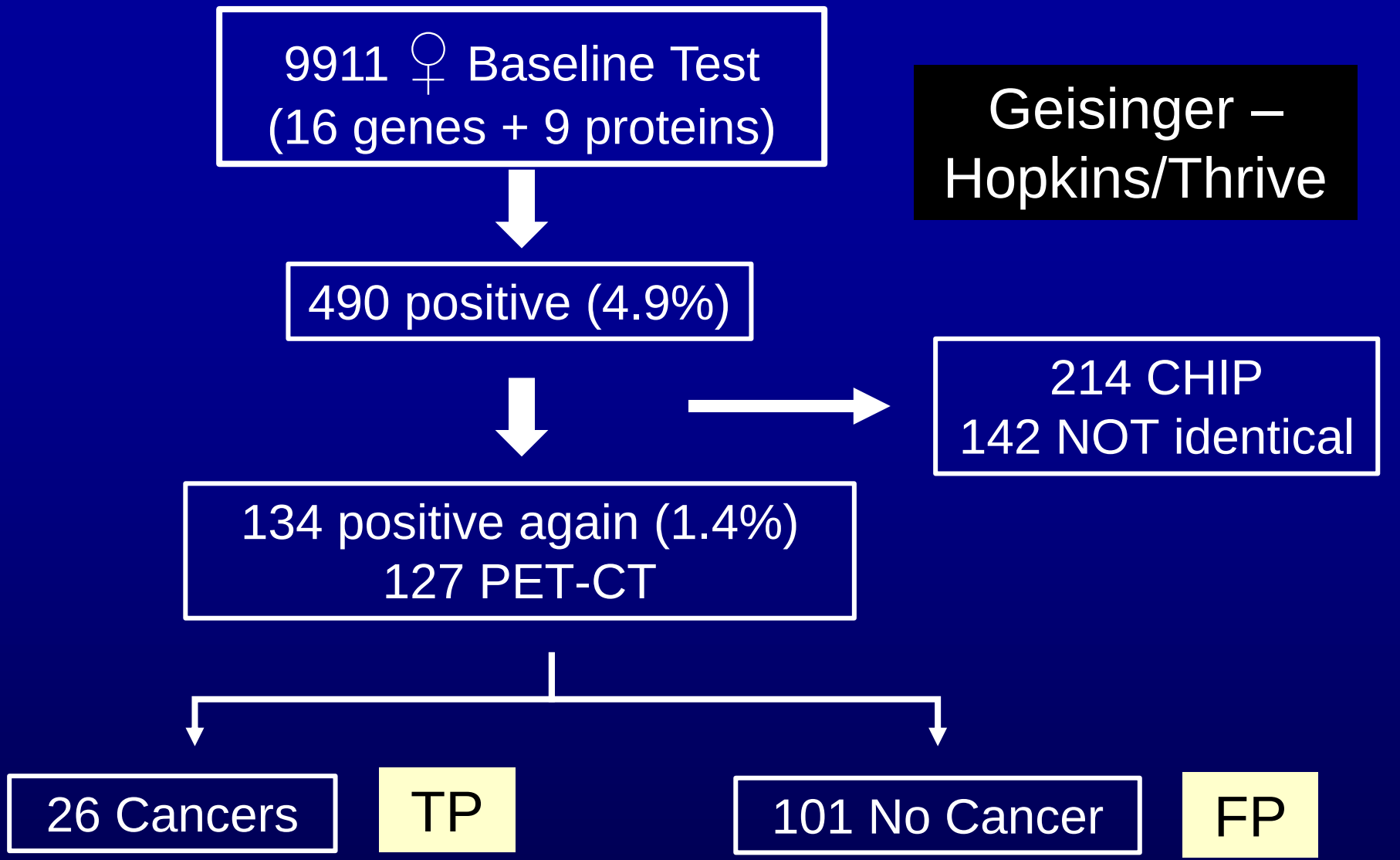
iv. Can it performed safely without incurring a lot of futile or dangerous work-up?

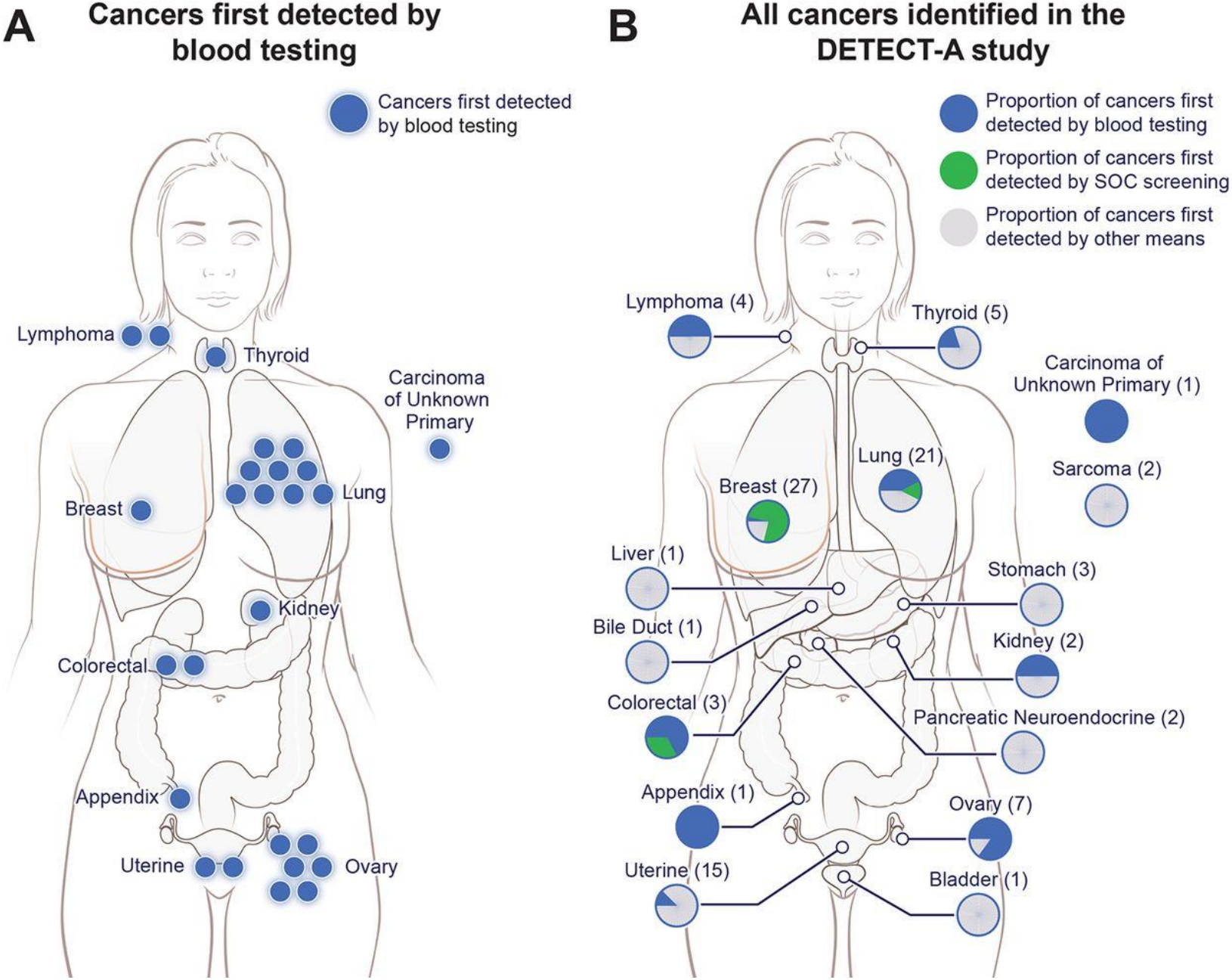
Anne Marie Lennon et al. Science 2020

DETECT-A process and rationale



Anne Marie Lennon et al. Science 2020;science.abb9601


9911 ♀ Baseline Test
(16 genes + 9 proteins)
Geisinger – Hopkins/Thrive
490 positive (4.9%)
214 CHIP
142 NOT identical
134 positive again (1.4%)
127 PET-CT
26 Cancers
TP
101 No Cancer
FP
24 Cancers detected by SOC
46 Cancers detected by neither
26/96 = 27%

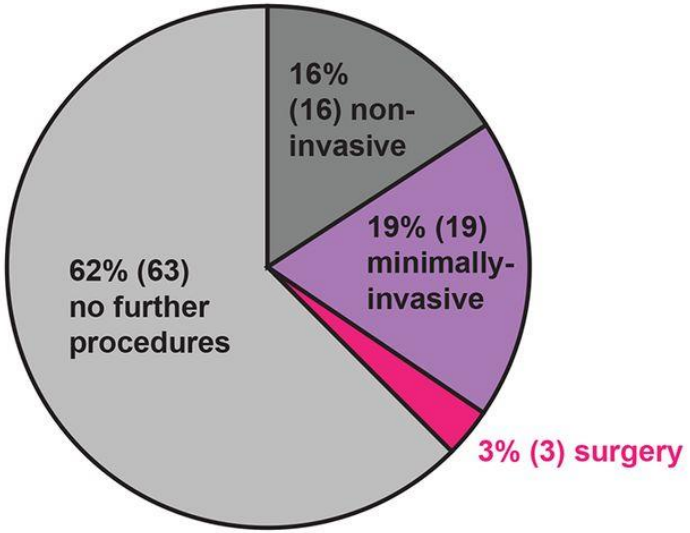

A
Cancers first detected by blood testing
Cancers first detected by blood testing
Lymphoma
Thyroid
Carcinoma of Unknown Primary
Lung
Breast
Kidney
Colorectal
Appendix
Uterine
Ovary
B
All cancers identified in the DETECT-A study
Proportion of cancers first detected by blood testing
Proportion of cancers first detected by SOC screening
Proportion of cancers first detected by other means
Lymphoma (4)
Thyroid (5)
Carcinoma of Unknown Primary (1)
Lung (21)
Sarcoma (2)
Breast (27)
Liver (1)
Stomach (3)
Bile Duct (1)
Kidney (2)
Colorectal (3)
Pancreatic Neuroendocrine (2)
Appendix (1)
Ovary (7)
Uterine (15)
Bladder (1)

Stage of Cancers Detected by Blood Screening

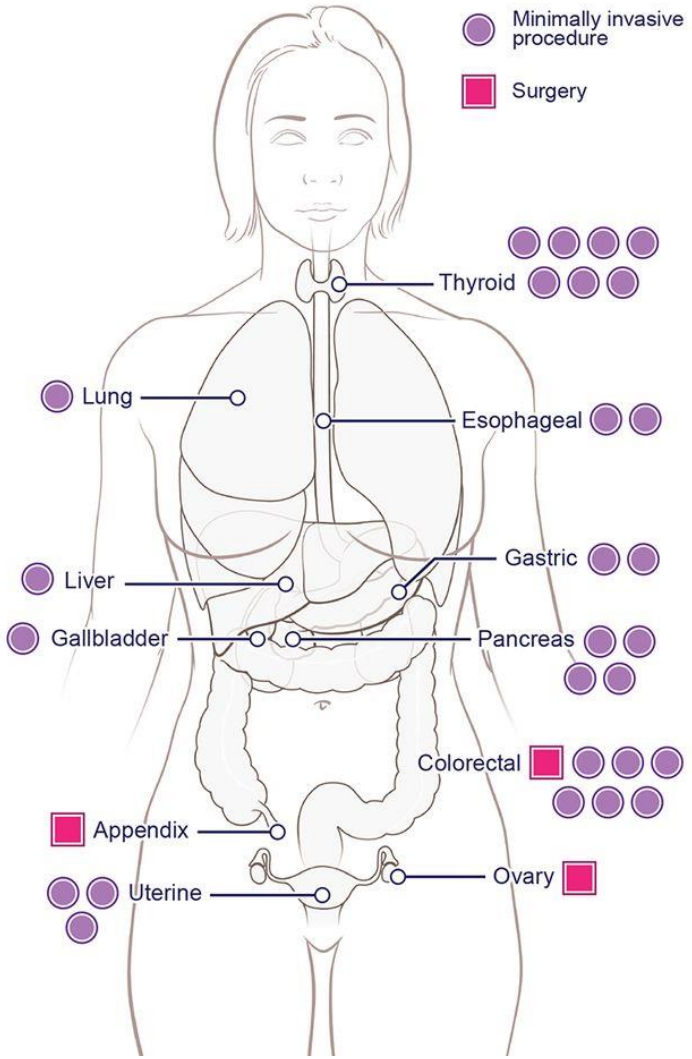
Stage	#
I	5
II	3
III	8
IV	9
Pending	1

The False Positive Burden in #101 Without Cancer

A Diagnostic outcome following PET-CT in 101 participants without cancer



B All minimally-invasive and surgical procedures in 22 participants without cancer



Non-invasive: Xray, CT, USG

Min invasive: EGD, hysteroscopy

Surgery: HGD in colon, mucinous cystadenoma ovary, in situ CA appendix

DETECT-A

- Can a multi-cancer blood test detect CA?

YES

- Can test intervene/affect CA progression?

Suggestive – No Control Group

- Can it not interfere with SOC screening?

YES

- Can it be performed safely without incurring a lot of futile or dangerous work-up?

YES

DETECT-A: Observations

- Even with high specificity (>99%), the low prevalence of cancer means that most positive pan-cancer blood tests will be FALSE POSITIVES
- Sensitivity – 46/96 (48%) cancers not detectable by blood test nor SOC screening

Conclusions

- Blood based biomarkers could potentially screen unscreened
- Potential for multi-cancer detection
- We are in early stages in determining efficacy