Noninvasive Multi-Cancer Screening Using Liquid Biopsy

Screening Workshop

March 2-3rd, 2020

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The Sidney Kimmel Comprehensive Cancer Center

The Johns Hopkins School of Medicine

Disclosures

- Shareholder: PGDx, Thrive, NeoPhore, CagePharma
- BOD: Thrive.

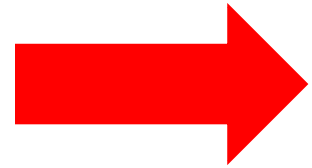
- In the past consulted for Sysmex_Inostics and received honorarium from MERCK for a talk

- Sysmex, PGDx, Thrive, ThermoFisher and other companies have licensed technologies from Johns Hopkins University, on which NP is an inventor. These licenses and relationships are associated with royalty payments to NP. The terms of these arrangements are being managed by Johns Hopkins University in accordance with its conflict of interest policies.

Paradigm Shift

Single Site

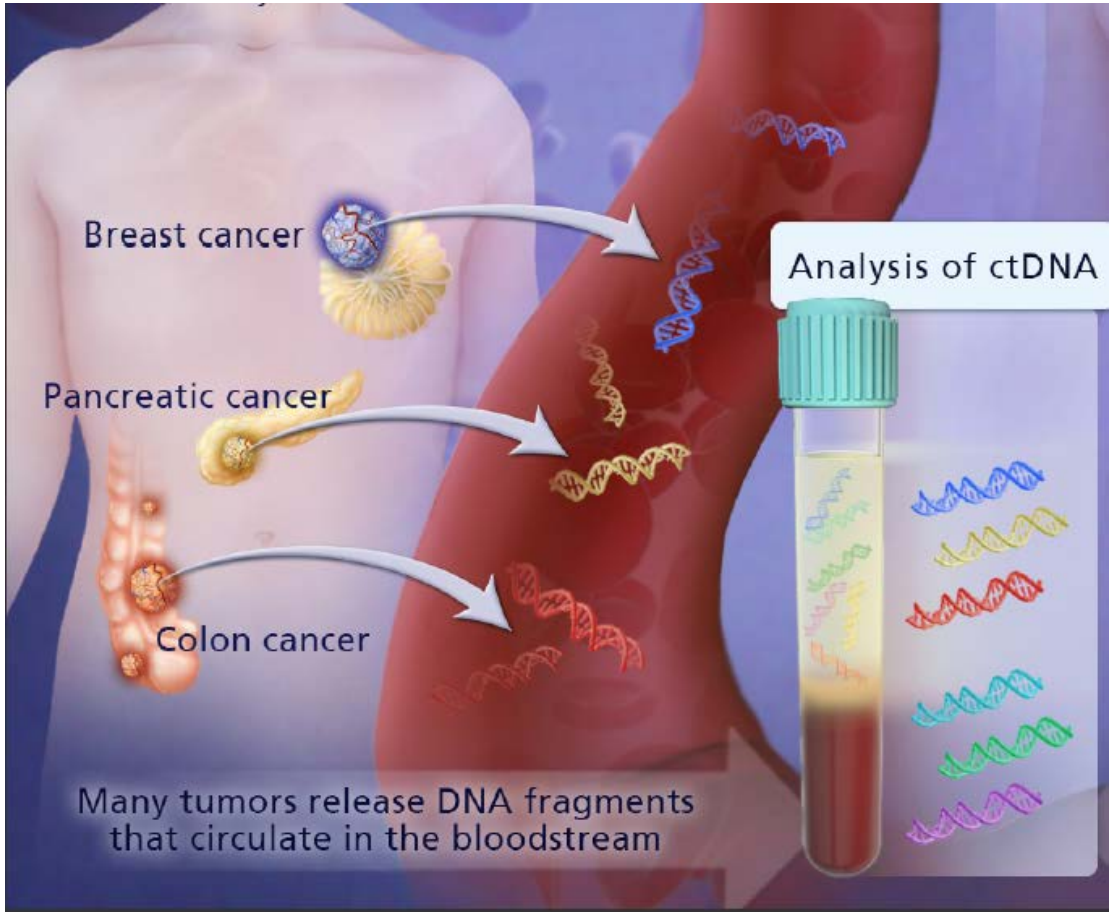
Excludes most cancers
Combined compliance less than 10%
Multiple modalities



Multi-Cancer

Inclusive
Better compliance - Efficient
Single modality

Liquid Biopsy –
Opportunity to Develop a Screening Test that:



- Is minimally-invasive
- Should have high compliance
- Should be able to reach many demographics – access
- Can utilize Aggregate Prevalence

Challenges to Early Detection

- Social – Society and individuals tend to give priority to reactive rather than proactive solutions.

- Psychological – Communication of a result is important:
  - Positive - Anxiety or even depression upon delivering test results.
  - Negative result - Individuals should not made believe that they are at zero risk.

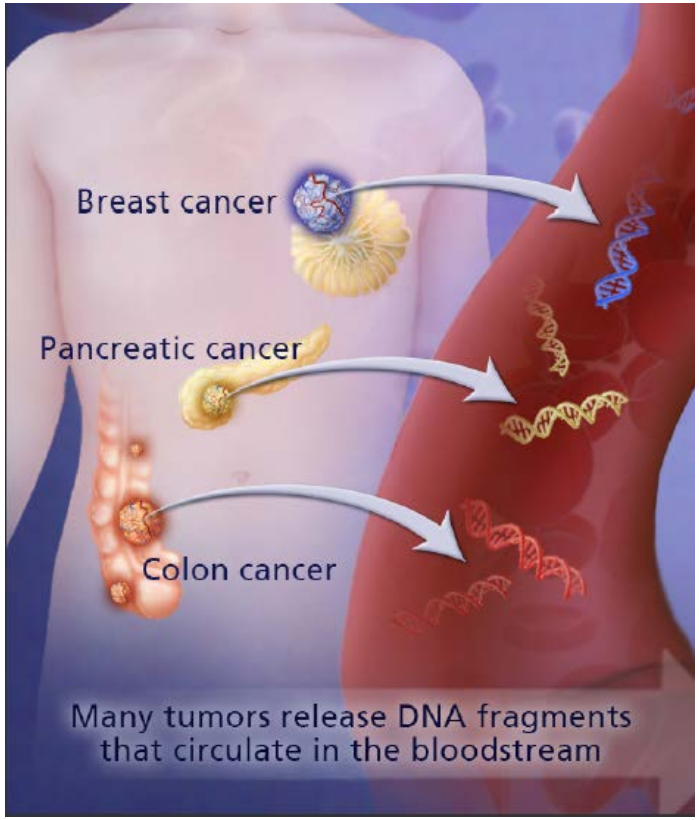
- Technical – Characteristics of the test; Location of the cancer

- Overdiagnosis – leading to Overtreatment and unnecessary follow ups – risk/benefit
- Cancers are missed – individuals that present with advanced disease - risk due to underdiagnosis

- Economical – Needs to be cost effective to administer across the population.

- Practical – Needs to be readily deliverable across the population.

What can be detected



Bettegowda et al.
Sci Transl Med. 2014 Feb 19;6(224):224ra24.

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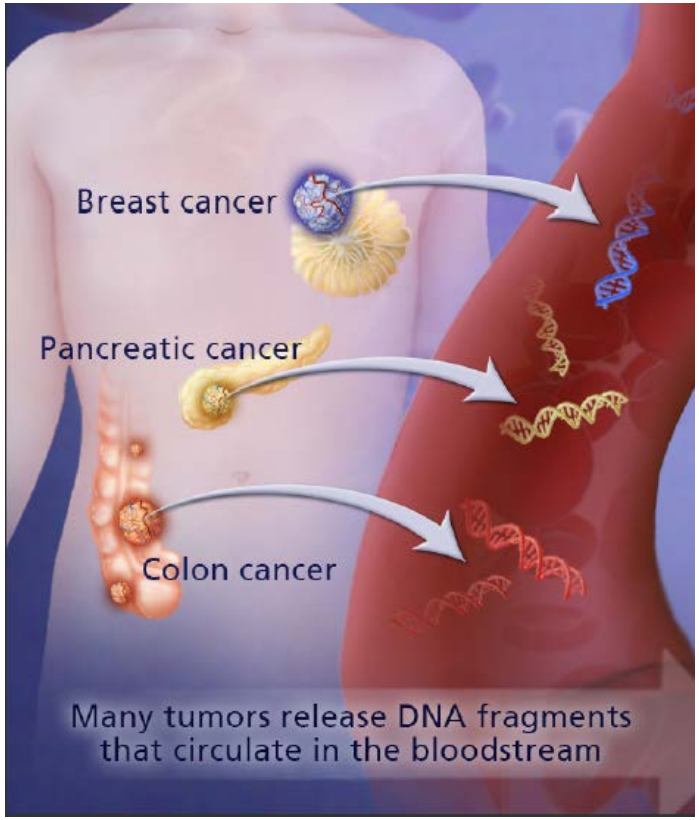

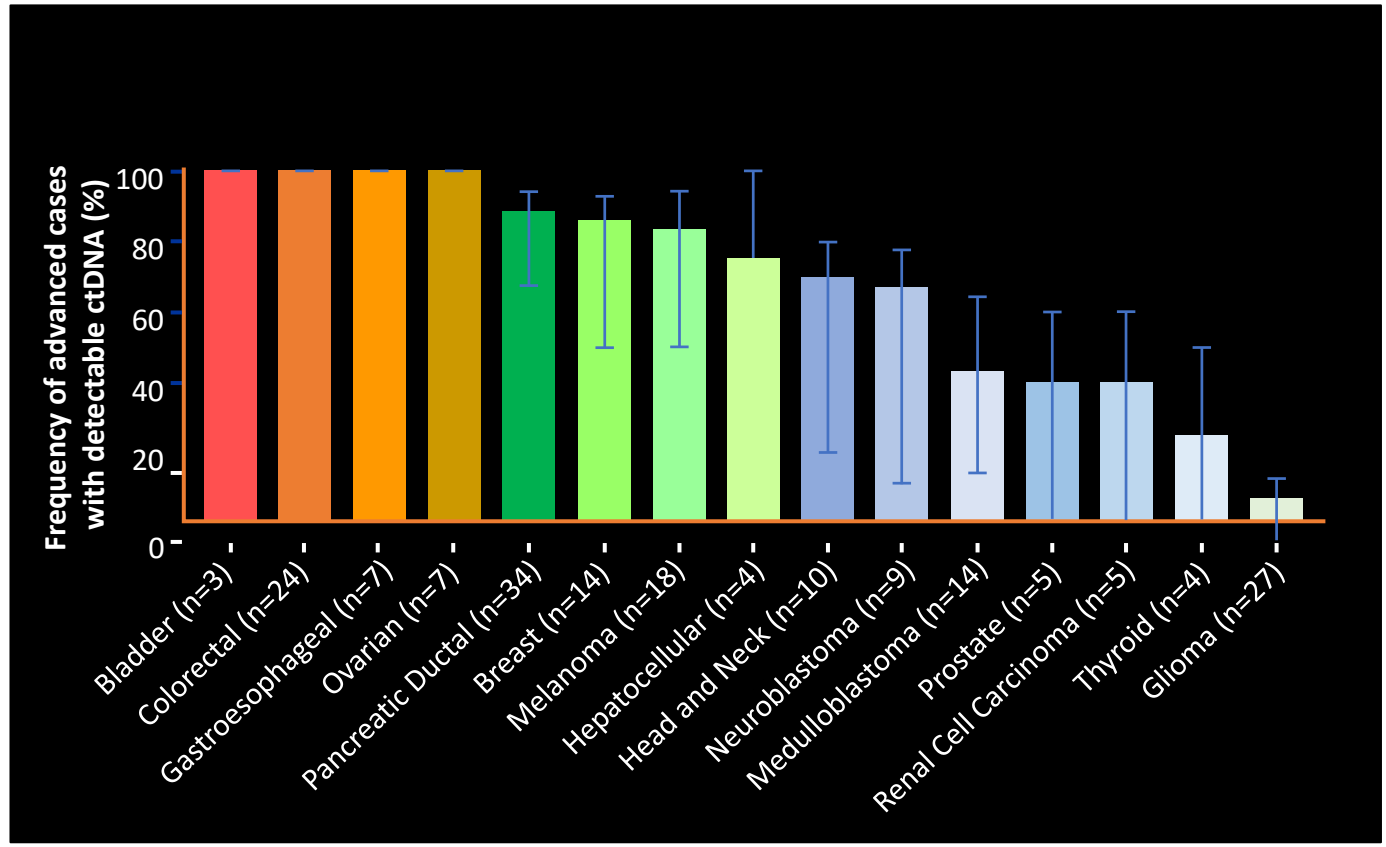

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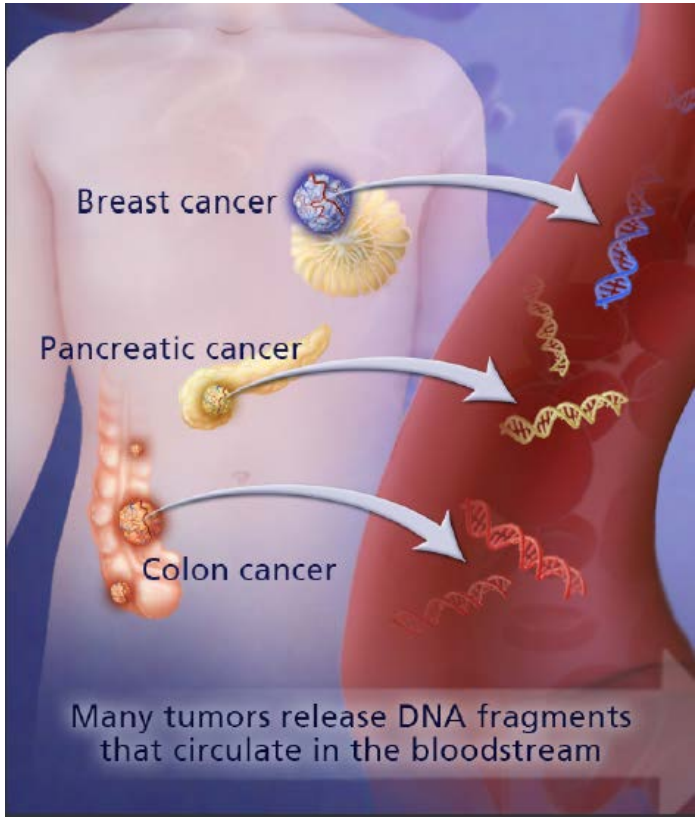

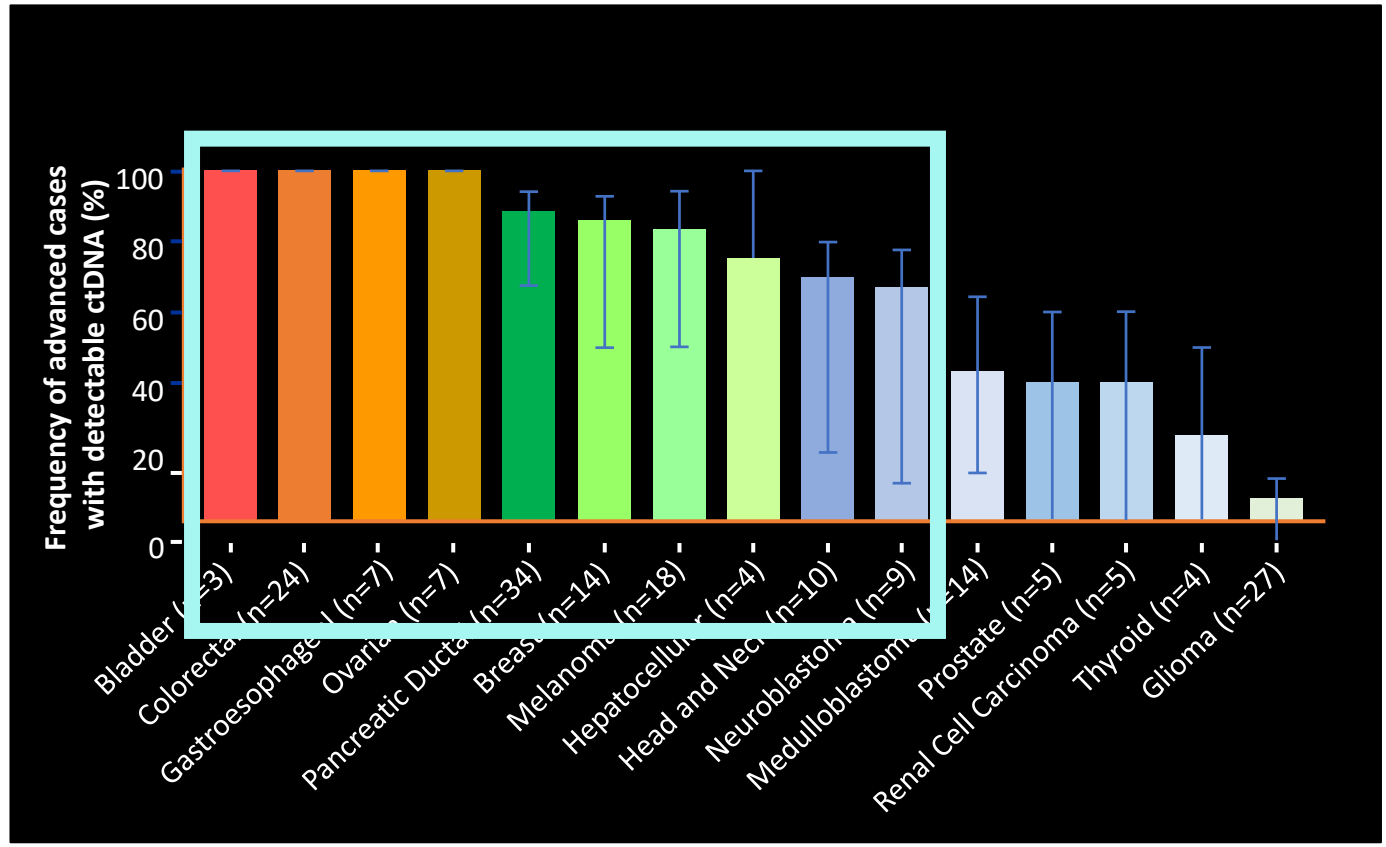

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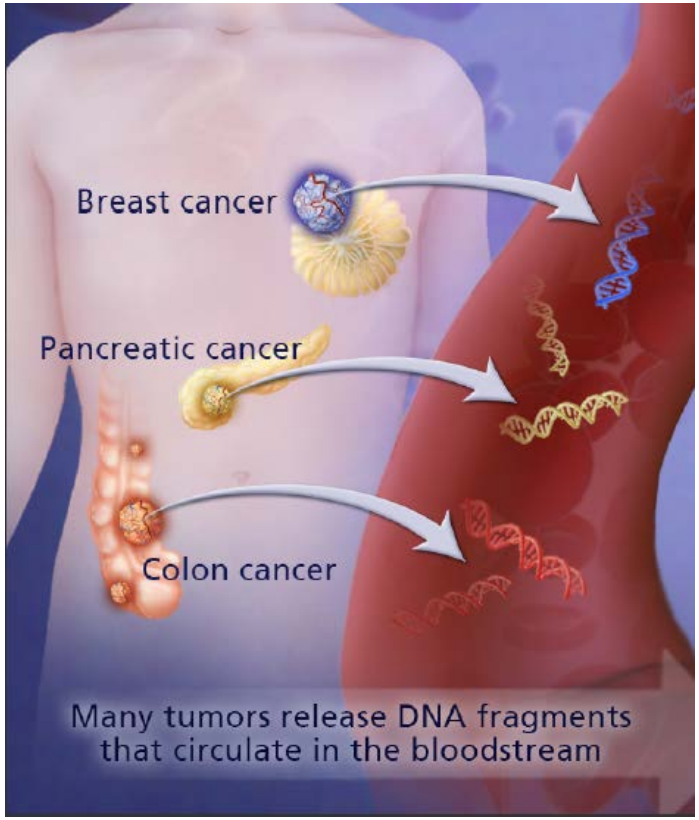

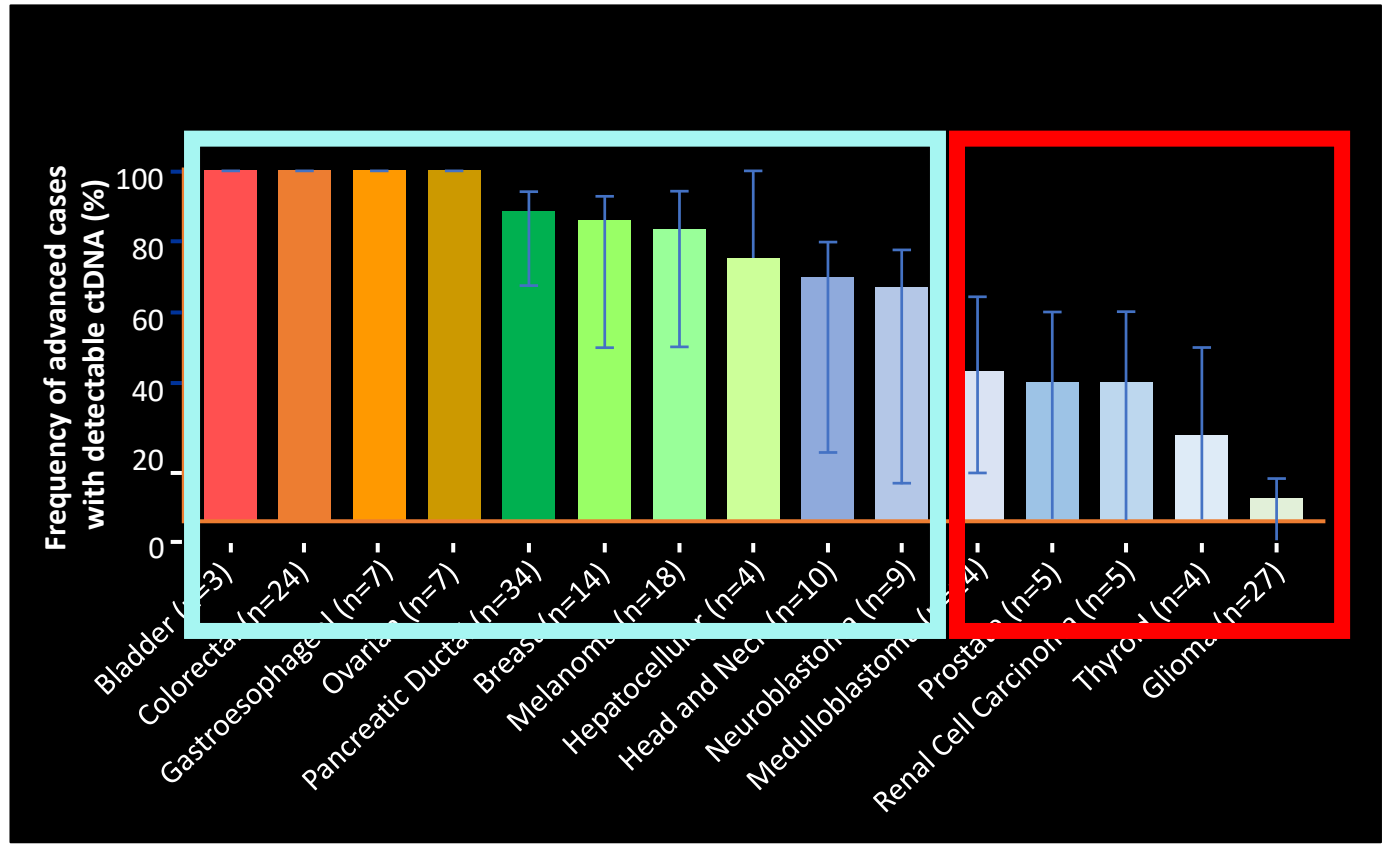

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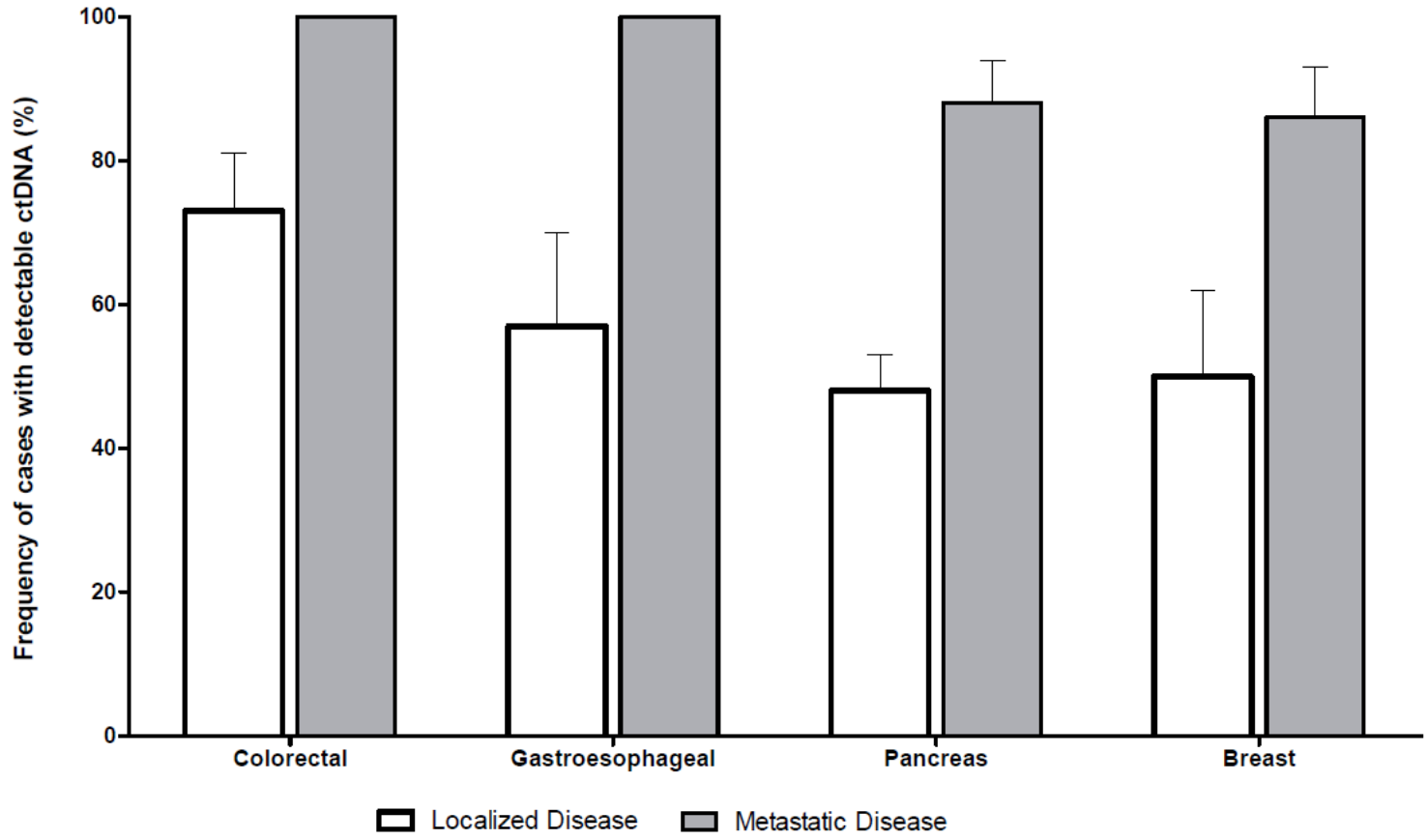
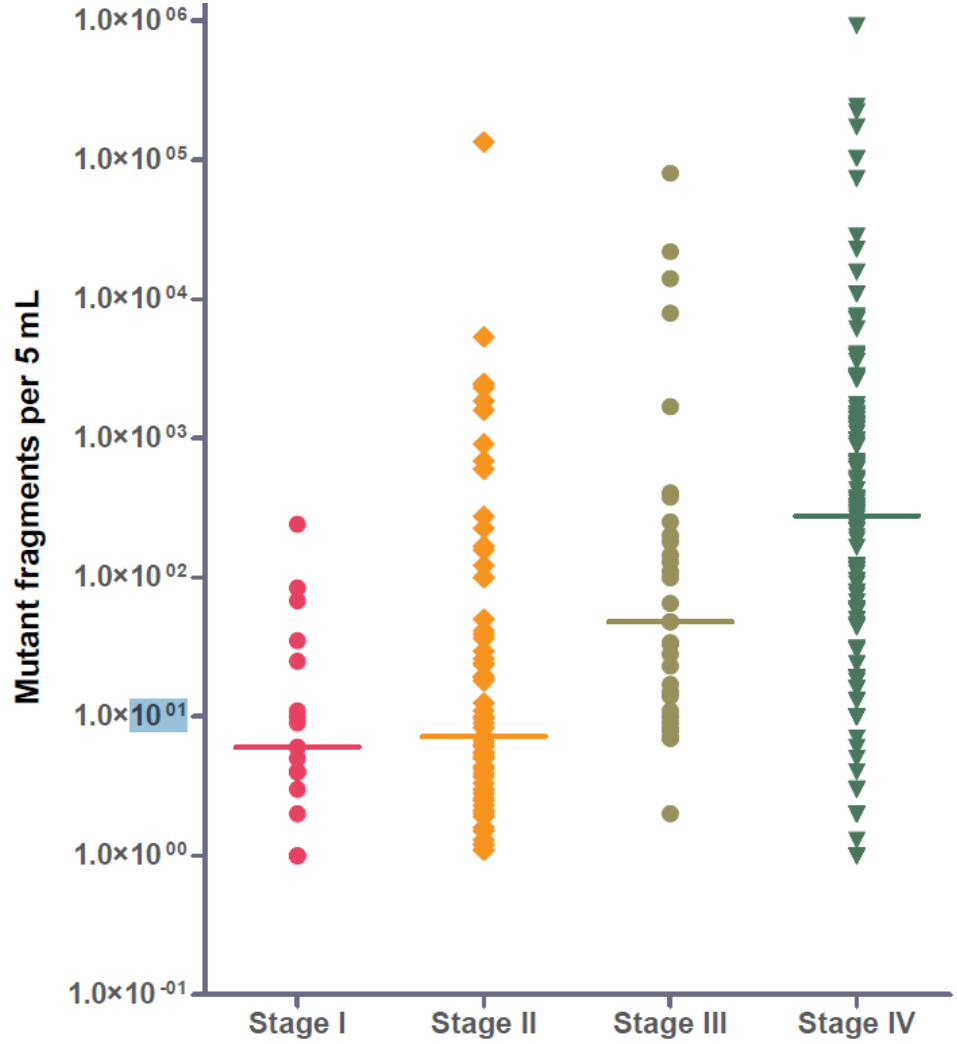
Detection of cancers in Plasma



Limited Molecules

ctDNA versus Stage



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Sci Transl Med. 2014

What can NOT be detected

- The detection of early stage disease is not as sensitive as detection of late stage disease
  - Biology plays a role
    - Needle in the haystack
    - No shedding from the tumor
  - Should we detecting these tumors?

- Detection of precancerous lesions is very low
  - Unintendedly reduction of overdiagnosis?

Distinguishing Cancer from Non-cancer

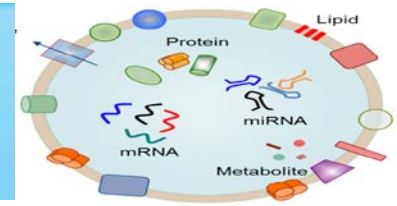
DNA Mutations

Transcripts

DNA Copy Number

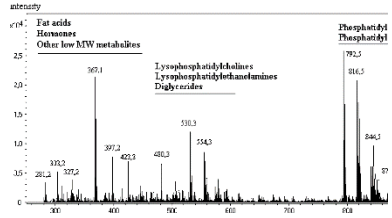
Proteins

Exosomes

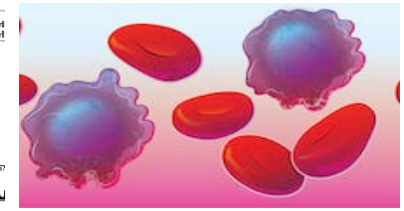


DNA Methylation

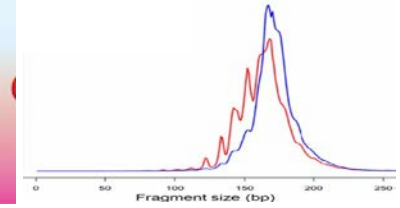
Metabolites



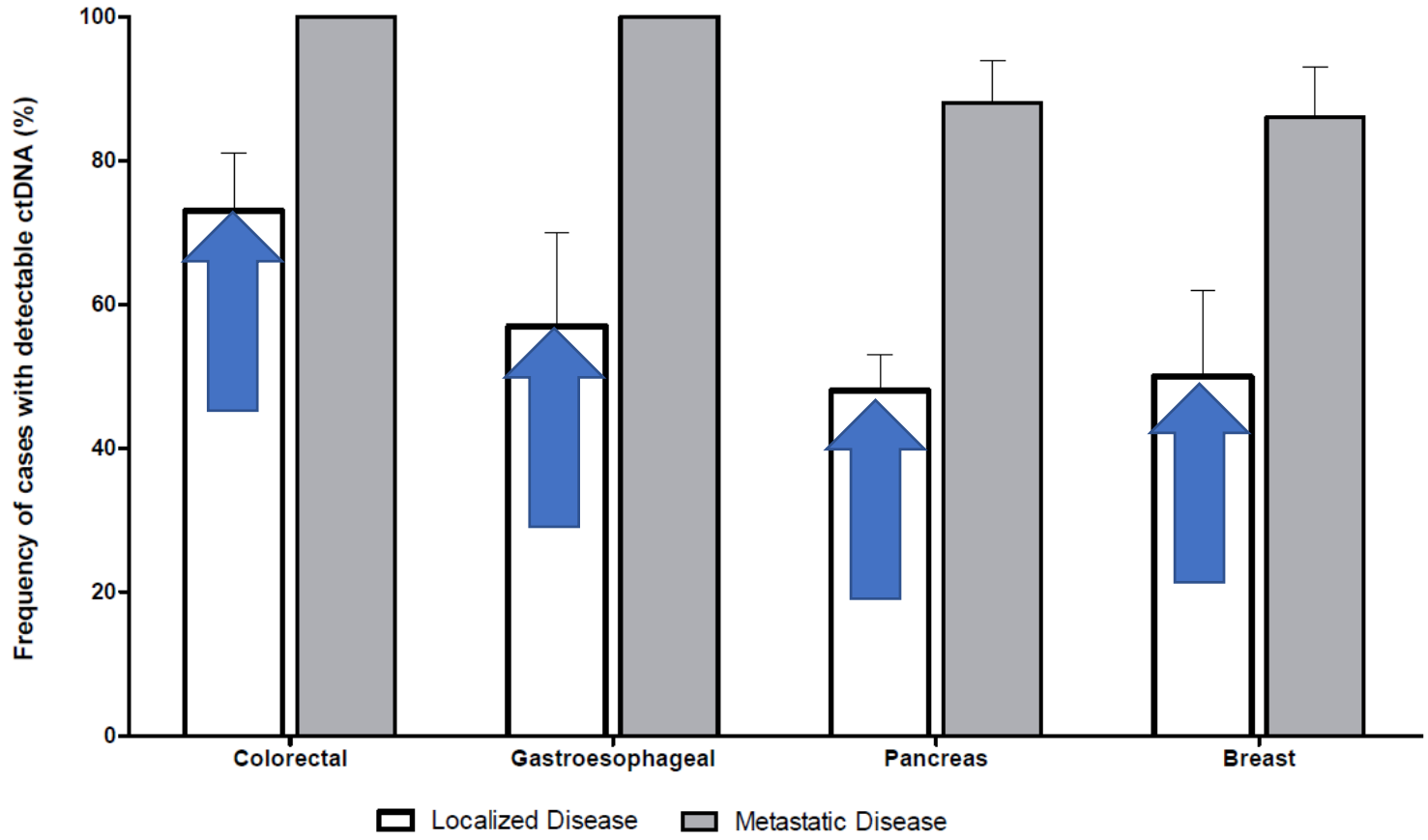
Cells



DNA Size



Increase Sensitivity



Combination of Markers

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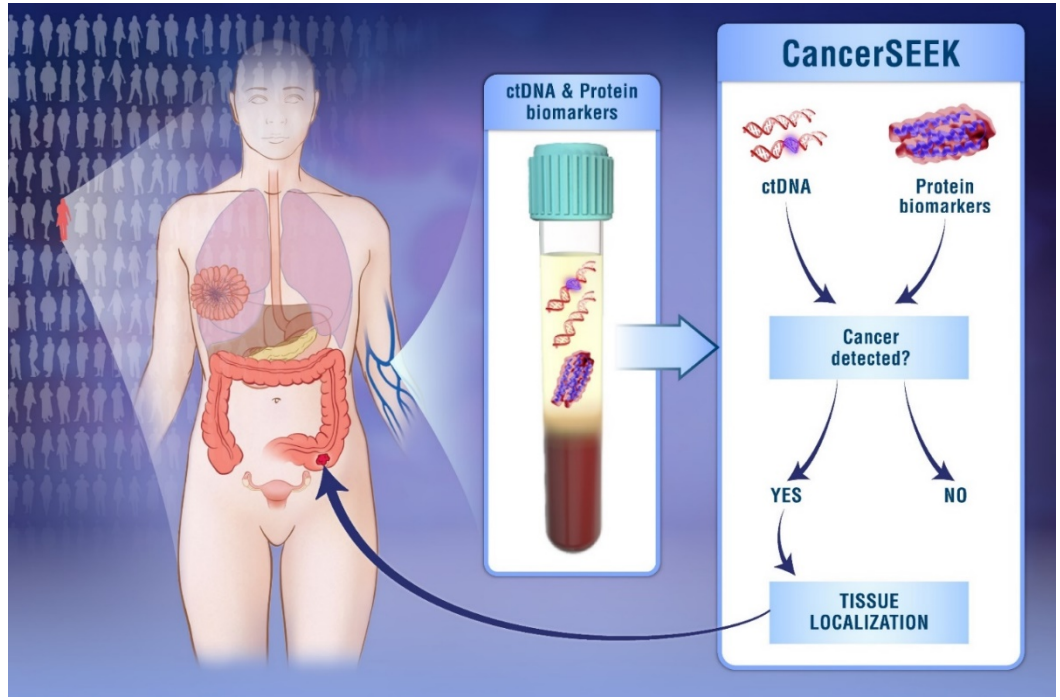


Cohen et al., *Science* , 2018

Cancer BioMarkers

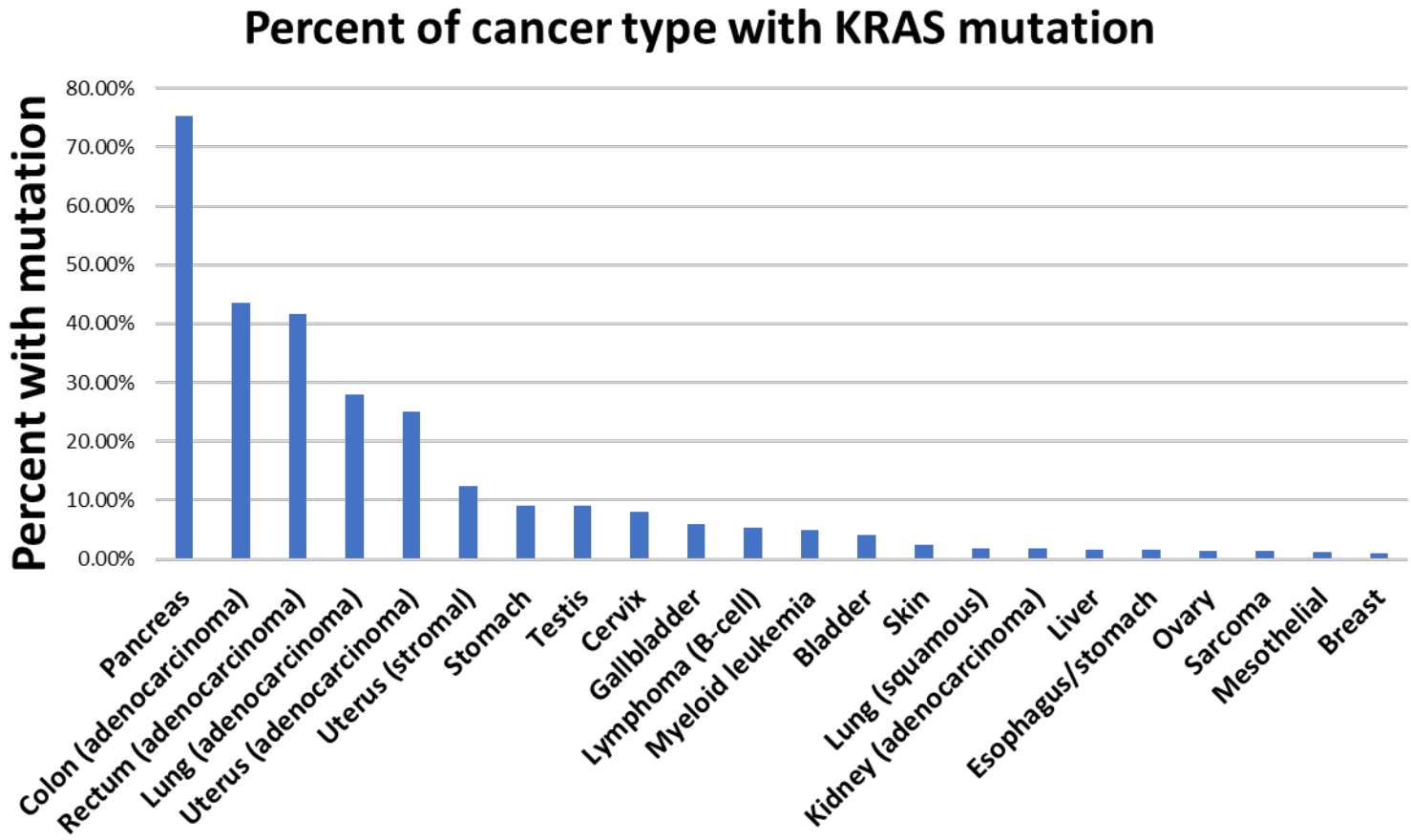
Cancer BioMarkers

- Not Cancer type specific

- Can design small panels that detect many tumor types
- Favors Universal Screening

- Need for markers to distinguish non-life threatening from life threatening lesions

Blood-based detection of mutant DNA is fundamentally cancer agnostic



Cancer BioMarkers

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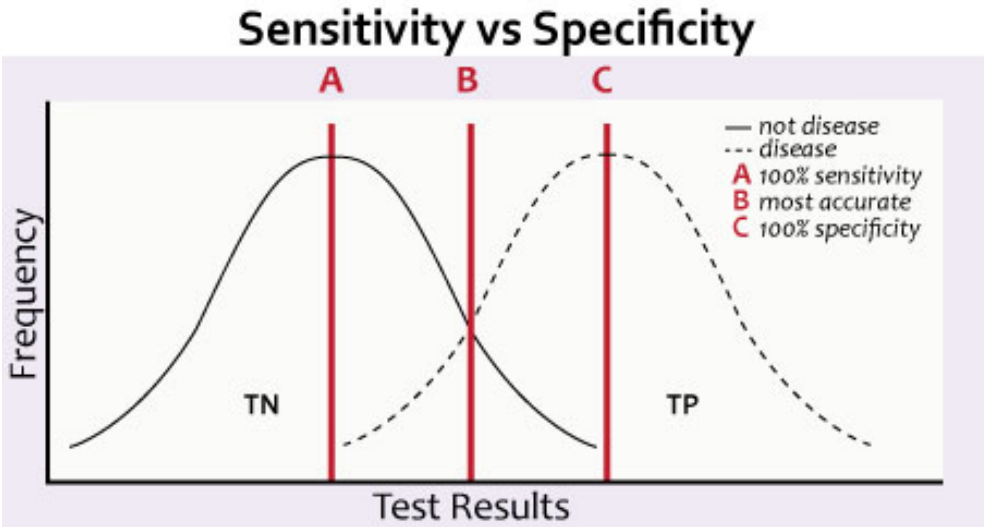
- Biological Background

- Clonal proliferation
- Other non-cancer conditions
- Age related presence of DNA alterations due to stochastic error

Test - Design

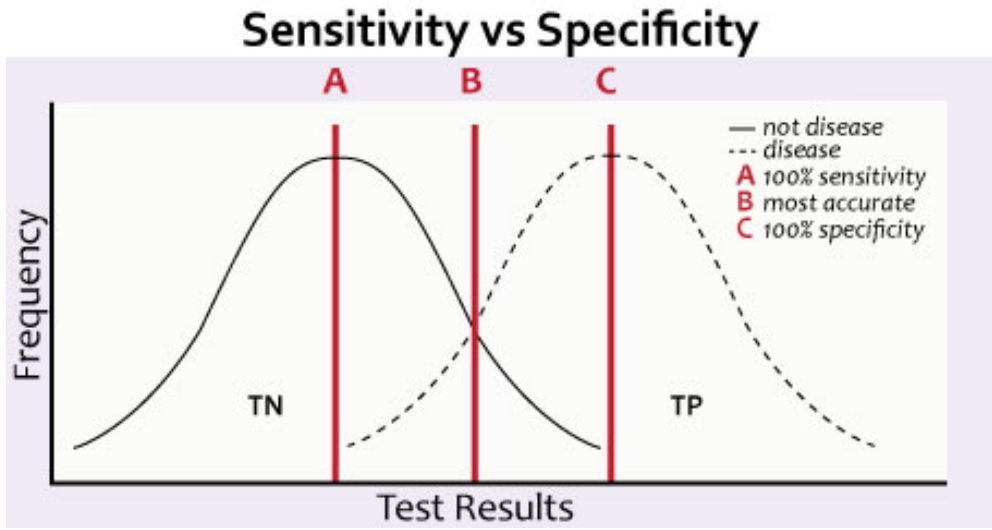
- Error-reducing technology
- Algorithms to discriminate technical background
- Pre-selected markers based on biology
- Algorithms to discriminate biological background
- Efficient Design
- Cost Effective
- Easy to implement

Test Performance



Prevalence will determine Predictive Values

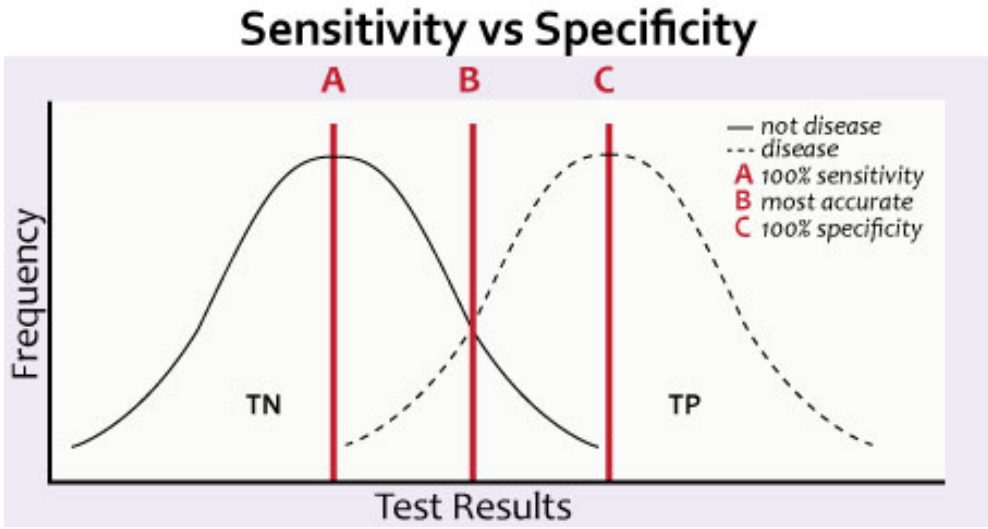
Test Performance



SPECIFICITY → SCREENING

Prevalence will determine Predictive Values

Test Performance



SPECIFICITY → SCREENING

SENSITIVITY → DIAGNOSTIC

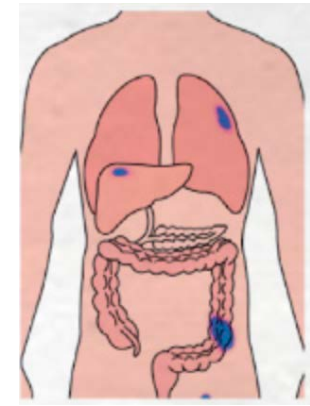
Prevalence will determine Predictive Values

Concepts for Study Design for Multi-Cancer Tests

- Prospective studies on target population with RC arm – access clinical applicability
- Interventional studies to access risk vs benefit – focus on specificity at the expense of sensitivity…..at least initially
- Cumulative sensitivity and specificity – contribution to SOC screening
- Decrease the time frame for approval – fewer late stage cancers
- Real world evidence post approval to access clinical utility – reduction in mortality

Earlier Detection

Earlier Detection



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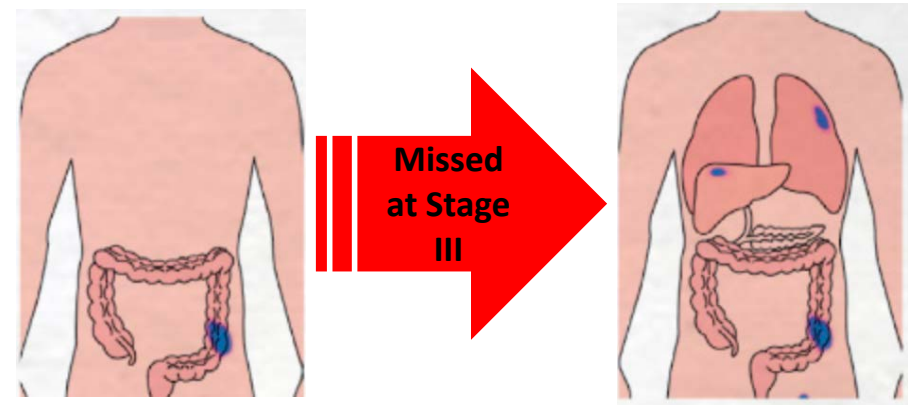

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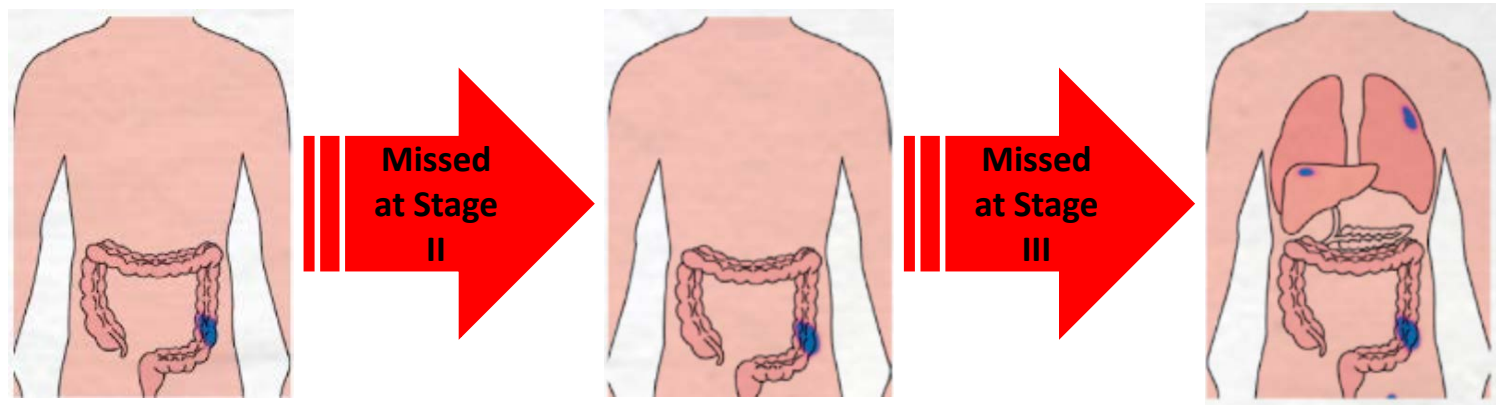

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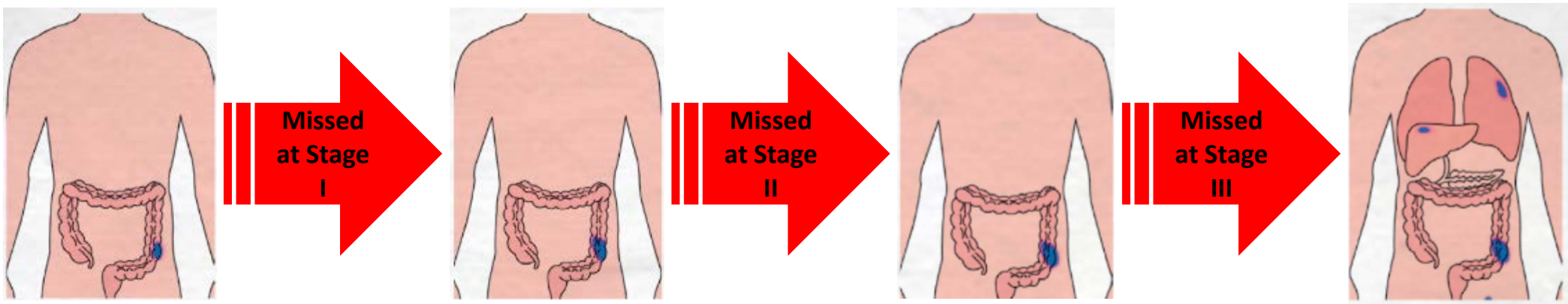

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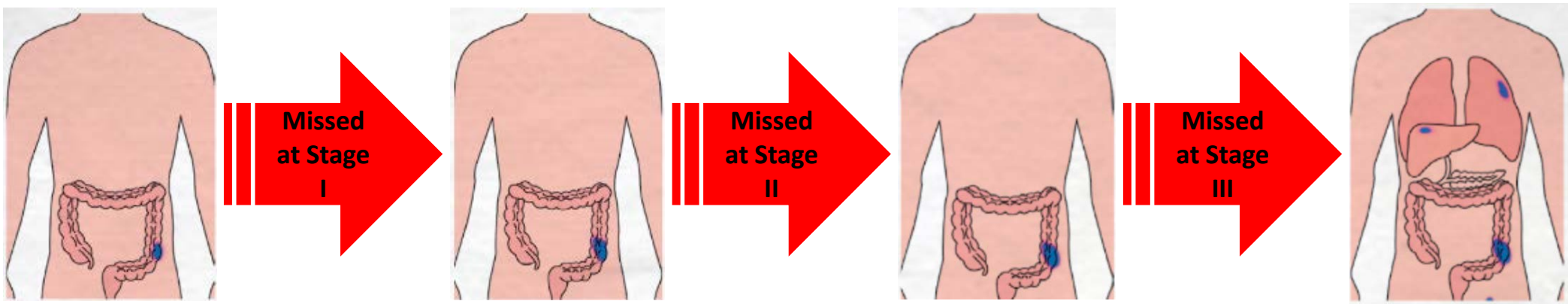
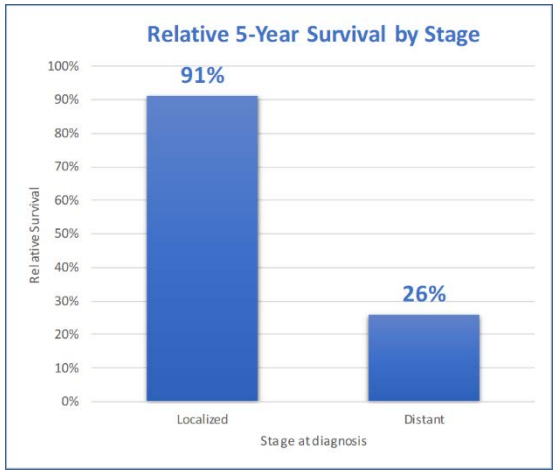
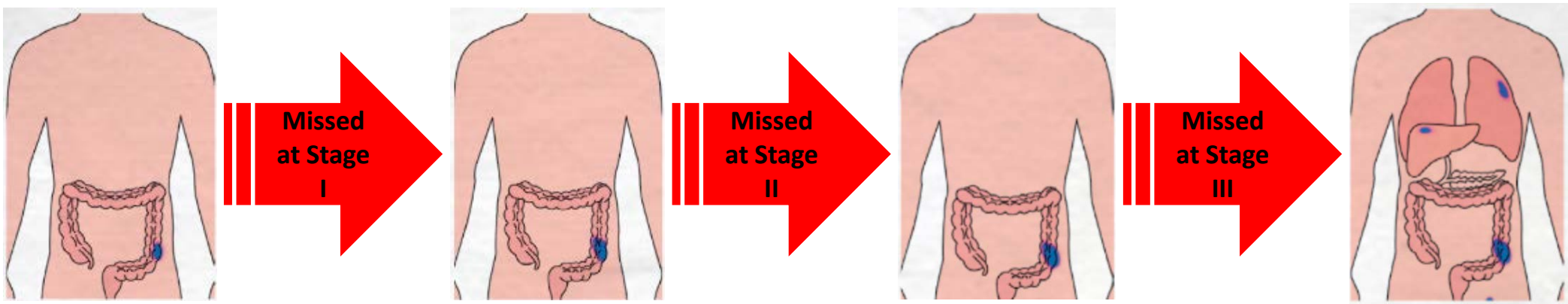
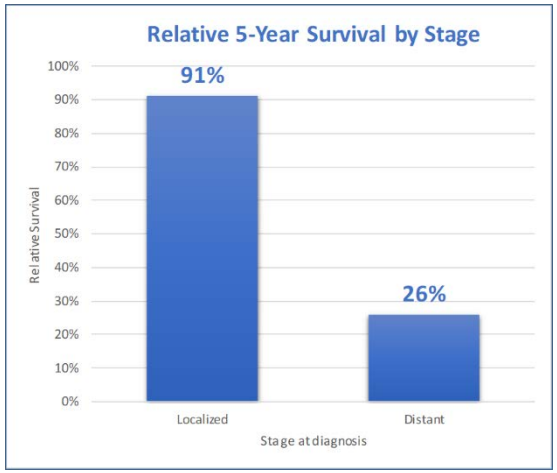




SEER

Earlier Detection





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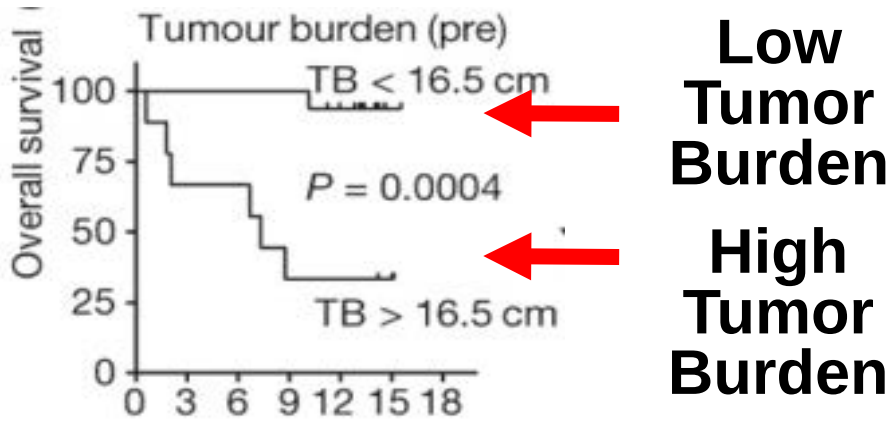

Huang et al. Nature 1–6, 2017
doi:10.1038/nature22079

Rational for Non-plasma based liquid biopsies

- Advantages:
  - Provide opportunity for early detection of tumor-types not easily detectable in plasma
  - Appropriate for special clinical applications and high risk groups
    - Example: hematuria - urine

- Disadvantages:
  - In some cases obtaining the fluid is more invasive
  - Not universal
  - Custom panel of analytes

Vision

- Prevent advanced tumors by integrating such tests as part of routine screening and management