NIH (USA) Initiative on Blood-Based Multi-Cancer Detection (MCD) Tests

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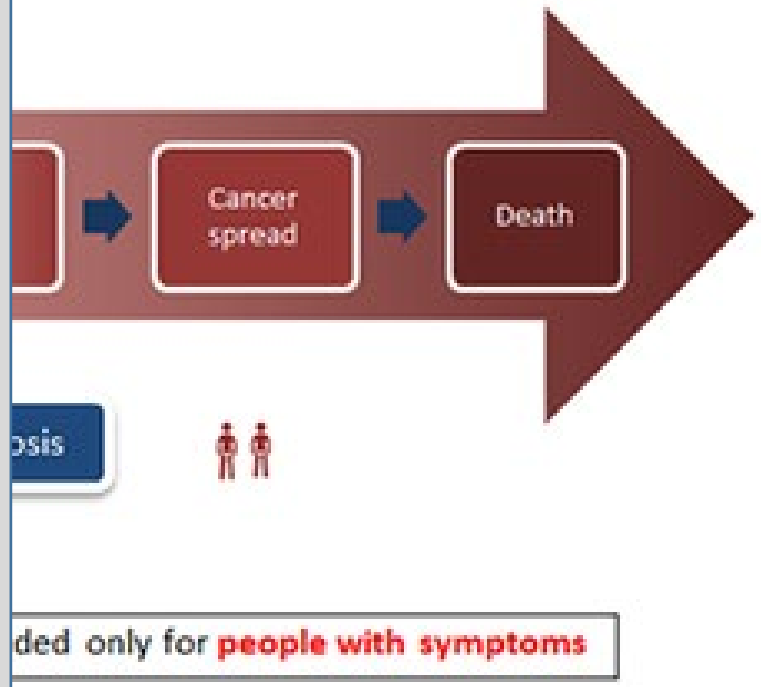
October 13, 2023

No relevant conflicts of interest to declare

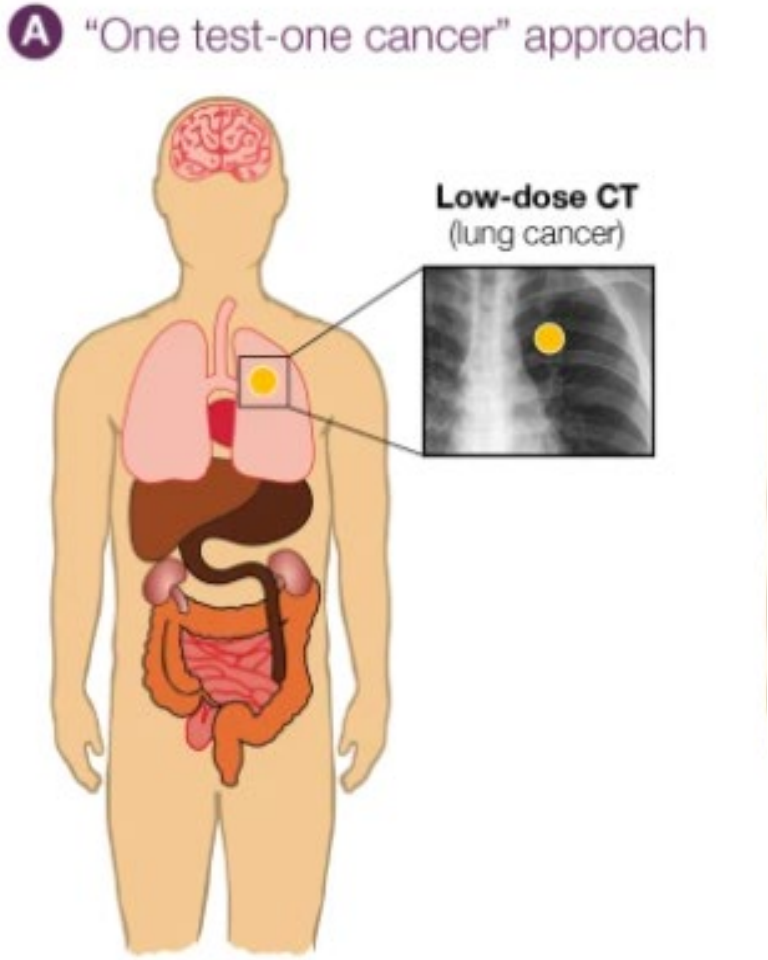
Standard Cancer Screening Paradigm

The “ideal” screening test

- Sensitive/specific
- Inexpensive
- Easy to administer
- Can detect the disease early enough to meaningfully intervene
- Few false positives



Current Recommendations for Cancer Screening in the US



1. USPSTF recommends average risk screening for colorectal, cervix, breast and lung (some smokers) cancers

   (+) screen ⟶ organ specific w/u

2. Test characteristics are variable

3. Uptake is suboptimal

4. Huge disparities in utilization

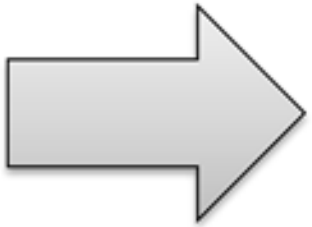
The Problem(s) with “One Test-One Cancer”

- Unscreened cancers: 60% of all cancer diagnoses; >70% of cancer deaths
- Aggregate false positive rate of single site screening: 31% (men), 43% (women)
- Annual incidence of OTHER cancers is 2-24x higher than single target sites

A Better Paradigm?

CURRENT

- "One organ at a time" detection
- Excludes most cancer types
- Multiple modalities
- Inefficient
- Costly



UNIVERSAL

- Simultaneous multi-organ detection
- Potentially includes all cancers
- Single medium/modality
- Efficient, highly integrated
- Potentially cost-saving

Ahlquist, Nature Precision Oncology, 2018

Liquid Biopsy

Tumor components released into various fluids

Proteins: CEA, survivin, APC, TIMP, osteopontin

Tumor Associated Antigens: CCSA-2,-3,-4, cyclin B, CA 19-9

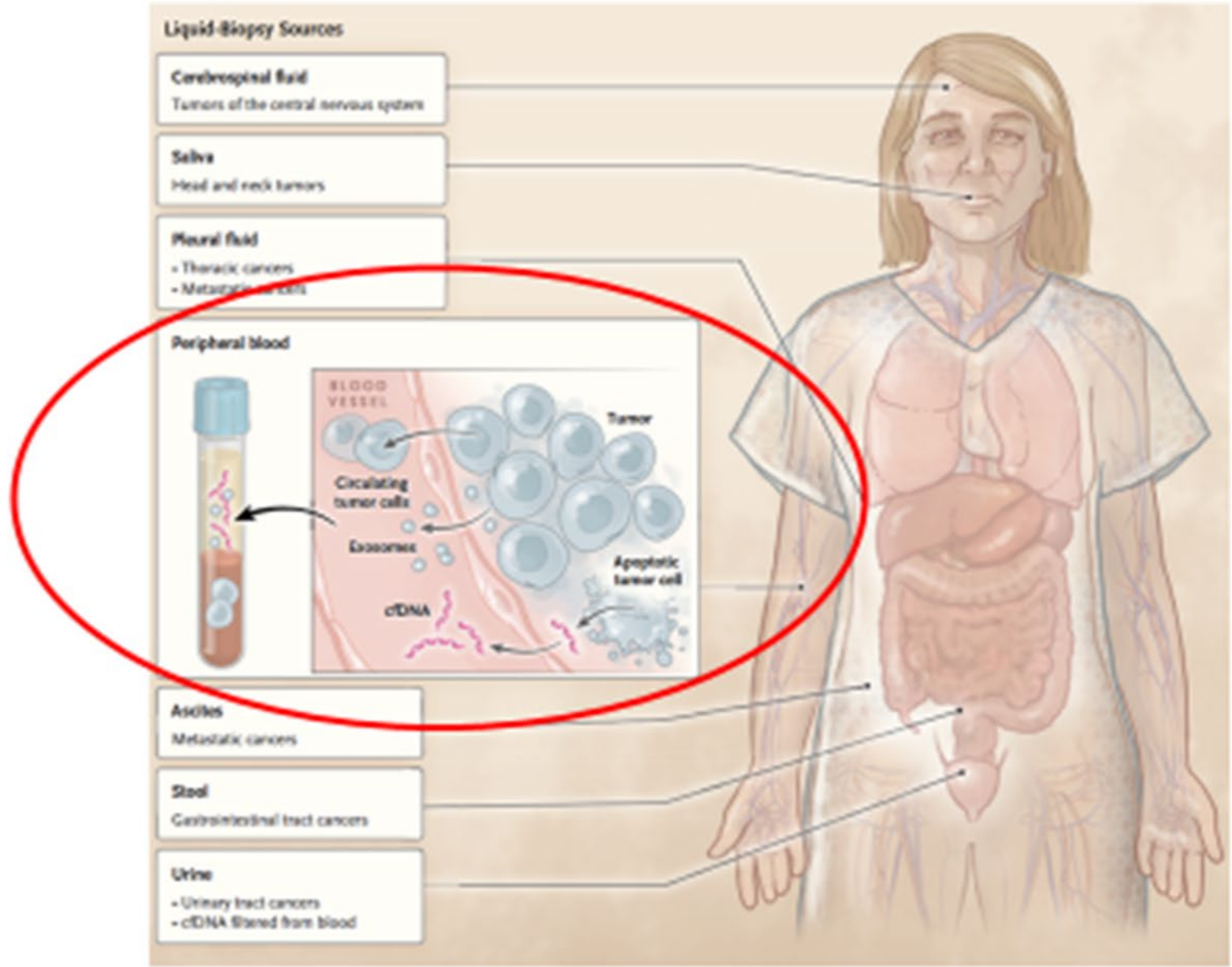
Cytokines: G-CSF, IL-6, IL-3

Circulating Tumor cells

Hypermethylated genes: Sept 9, FOXE1

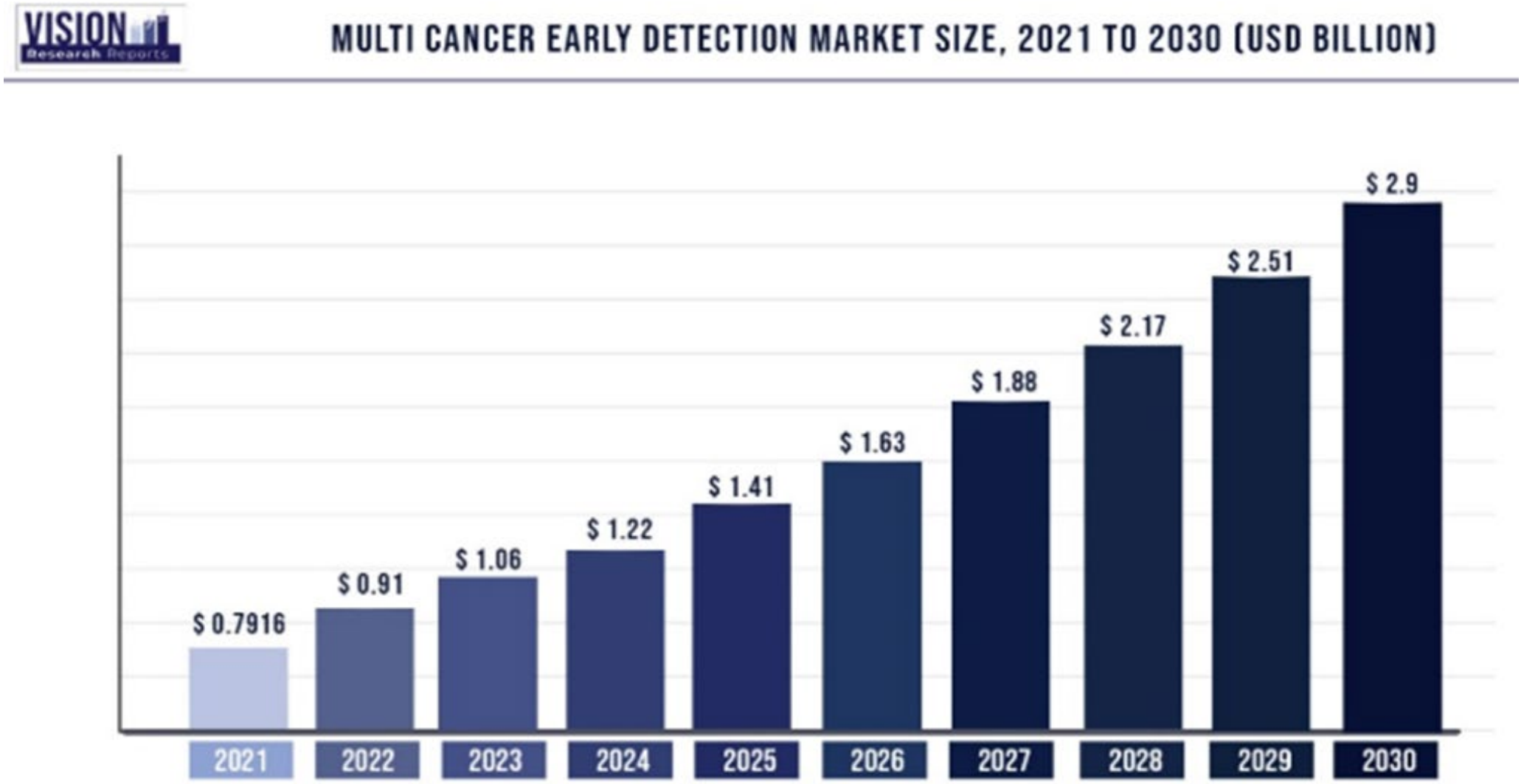
mRNA transcripts

microRNA

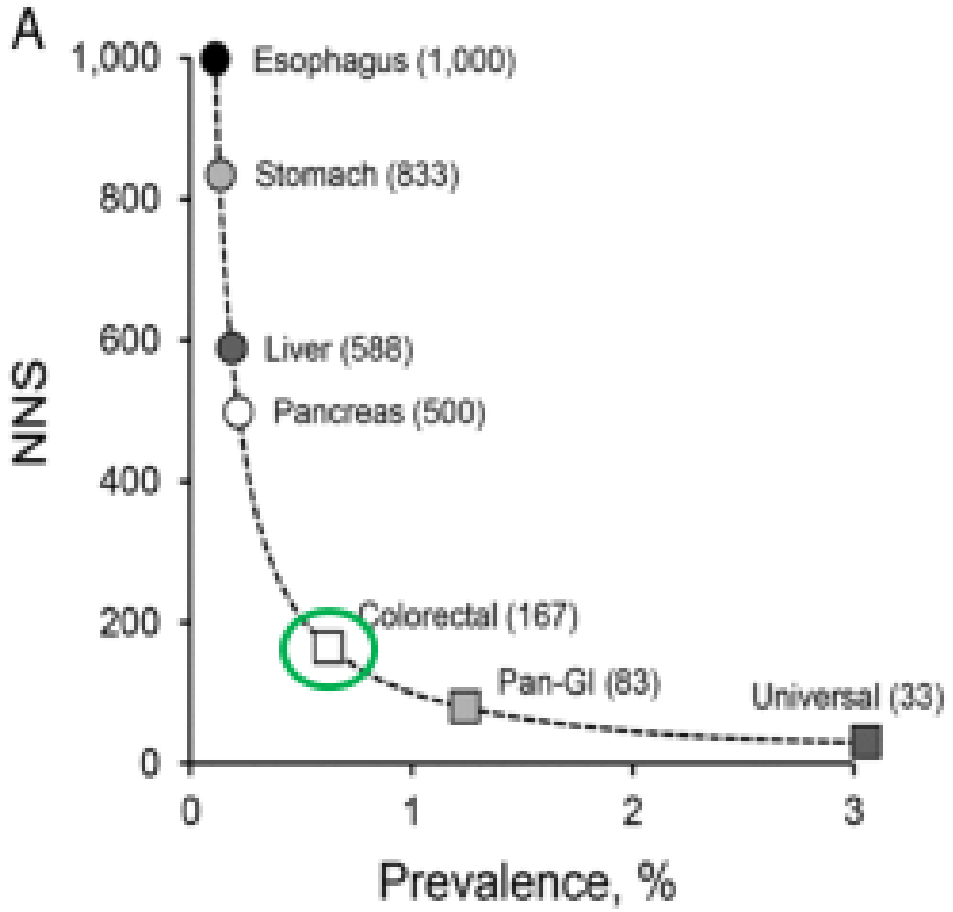


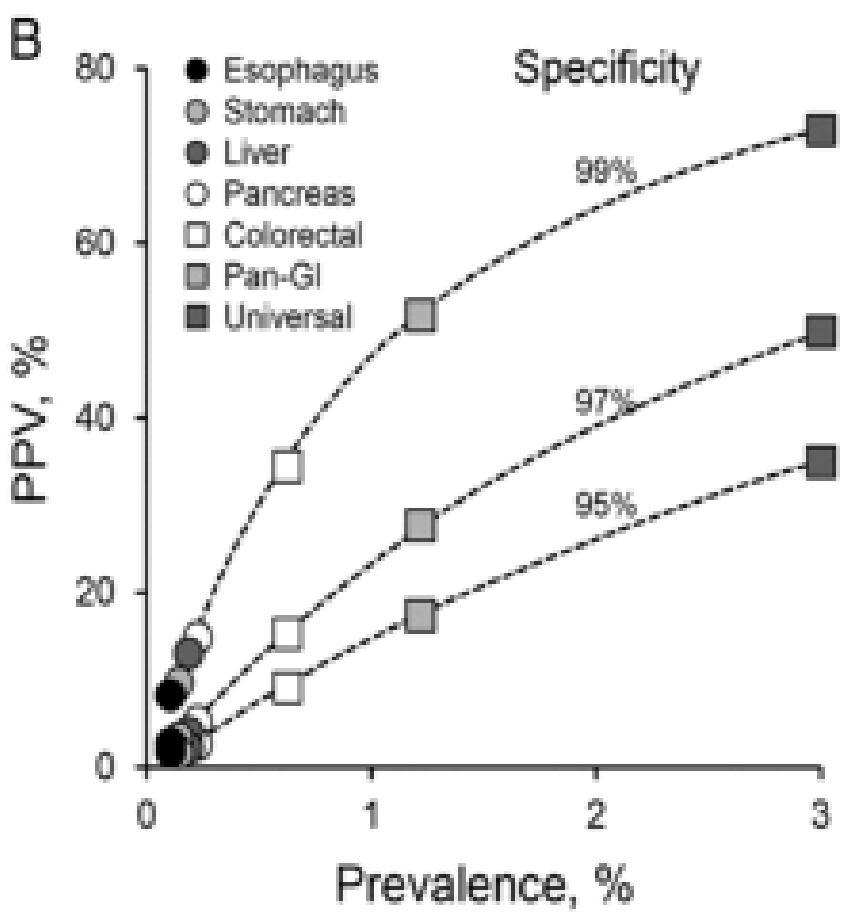
Corcoran RB et al. New Engl J Med 2018

Multi-Cancer Early Detection



One Argument for Multi- Organ Site Screening





ASSUMES 100% SENSITIVITY

Ahlquist, Nature Precision Oncology (2018)

Theoretical Arguments: **For** and Against

- There is a 1.3% annual incidence of any cancer in US adults (n=1.2 million).
- Cumulative detection rate using USPSTF tests is about 16% with 10% adherence.
- MCD with 55% sens/99% spec would detect 715 cancers/100,000 screened with a FP rate of 691/100,000. Cumulative PPV = 51% [1]
- MCD + SOC screening adds 0.34 QALYs/person and is cost effective[2]

[1] Liu et al Annals of Oncology 2020
[2] Ortendahk et al Value in Health 2020

Theoretical Arguments: For and **Against**

- Cancer screening built on the premise that earlier detection is ALWAYS better than late.
- Increasing awareness of the harms of over diagnosis and over treatment
- 3 “kinds” of cancer:

    1. slowly progressive -- early detection benefit (+)
    2. rapidly progressive -- early detection benefit (?)
    3. indolent -- early detection benefit (-)

At present no way to consistently distinguish among the 3

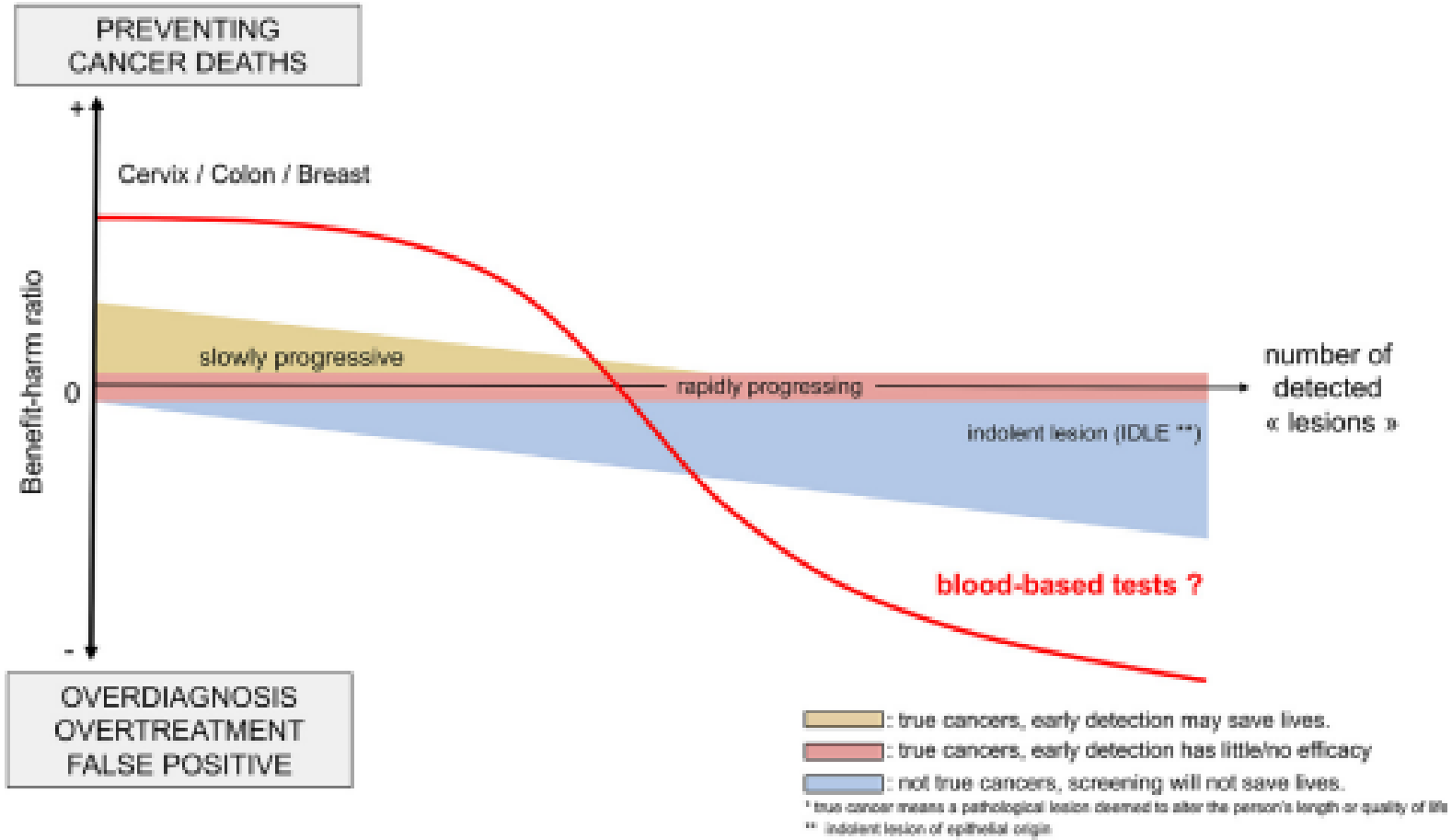


Figure Model of screening outcomes based on 3 different types of detected lesions. The more detected lesions (increase sensitivity), the more detected indolent lesions (decrease specificity for "true cancers"). IDLE = indolent lesion of epithelial origin.

Olivier et al, Am J Medicine, 2022

Theoretical Arguments: For and **Against (2)**

Model using SEER data for 40-79y population: Down stage 33% of Stage IV to Stage III (+ similar reductions for Stage III and Stage II…), leads to a **15% reduction** in cancer deaths[1]

Adjusted population, the observed # cancer deaths after 5 years follow up is 285/100,000. The 15% reduction saves 71 lives/100,000.

- Application of a novel MCD with a FP rate of 0.5%, would lead to 500 FP cancer diagnoses for every 71 cancer deaths prevented

[1]Clarke CA et al, CEBP, 2020

Many Unknowns for MCDs

- Appropriate diagnostic work up(s)
- Follow up of (+) tests without a cancer identified immediately
- Potential harms of FPs, over diagnosis of indolent disease
- Real world use strategies (how often etc.)
- Equitable dissemination strategies across populations

Vanguard Pilot (NCI): Objectives

- Assess willingness to be randomized to MCED cancer screening versus control.
- Determine adherence to MCED testing and diagnostic follow-up.
- Evaluate the feasibility of defined diagnostic workflows to detect various cancers.
- Determine performance of participating MCED companies to process specimens and return results.
- Identify facilitators and barriers to diverse enrollment in an RCT, especially underserved populations.

Vanguard Pilot (NCI), n=24,000

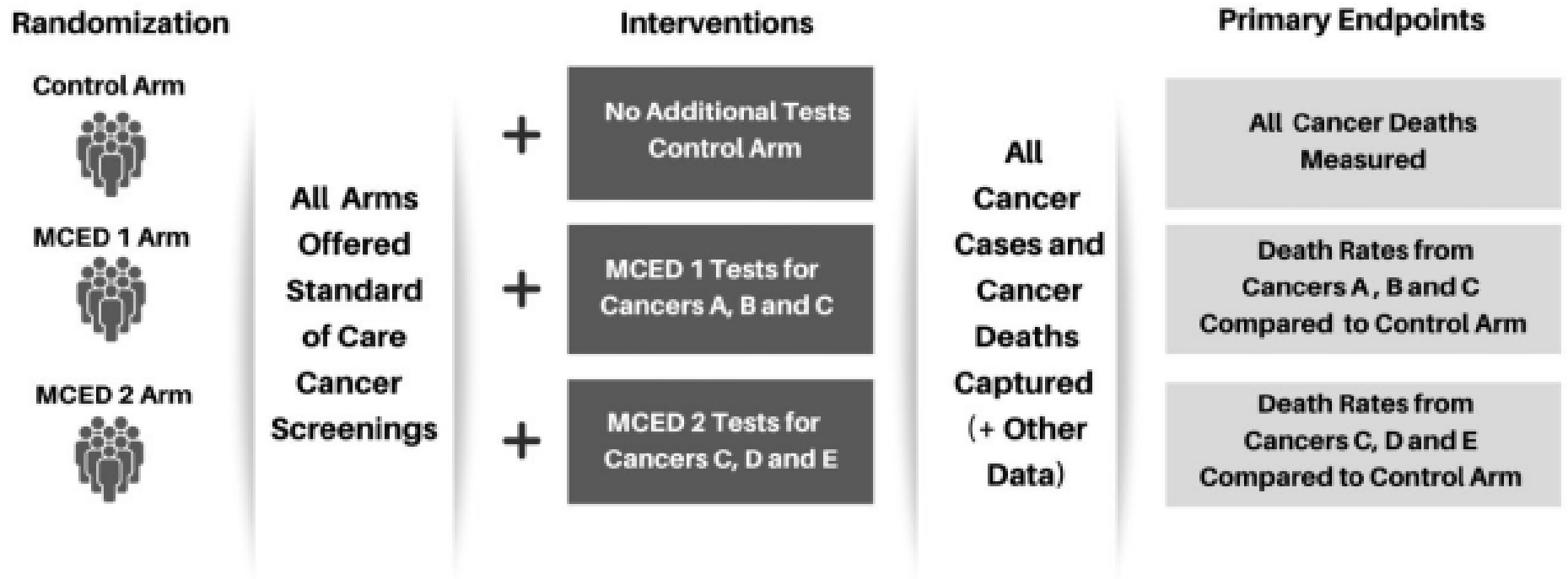


Figure 1. Platform study design schema. MCED = multicancer early detection

Minasian LM et al , JNCI 2023

Summary

- MCD testing offers a “brave new world”
- In the US, many will want the test
- Demand by patients and industry to move faster than the science
- Vanguard Study will provide key preliminary information