An Oncologist's Perspective on the Status of MCD Testing in 2024

National Cancer Policy Forum Workshop on MCD Testing

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Disclosures

Deb Schrag MD MPH: October 2024 update with lookback of 3 years

I have the following relevant financial relationships to disclose:

Grant/Research support from: GRAIL manufacturer of a prototype MCD assay

PI 2017-21 funding to: Dana Farber Cancer Institute/Harvard Medical School

Currently employed by Memorial Sloan Kettering in NYC

Consultant for: No remuneration from commercial firms since 2021

Reimbursement for travel from health tech firms, EPIC, health insurers and CMS

Compensation from JAMA for editorial services through 12/2023

Stockholder in: family member holds stock in Merck

Reimbursement for travel and EAB membership from: NHS in UK, EU, several US states, health systems/cancer centers in US, Canada, Europe, Australia, Argentina, Egypt, Nigeria, Argentina in past 3 years

5 Phases to Develop a MCD Test for Cancer Screening

1. Test Discovery assays may be biomarker, panels, imaging tests or algorithms
2. Analytic validation of test-it can reliably and consistently identify cancer
3. Test can identify preclinical cancers-ones where its plausible that early detection will confer benefit
4. Clinical utility, feasibility, deployment, PPV, sensitivity, specificity quantified: prospective cohort study
5. Ability of test to improve population health by reducing deaths from cancer: needs RCT

Ready for scaling and implementation

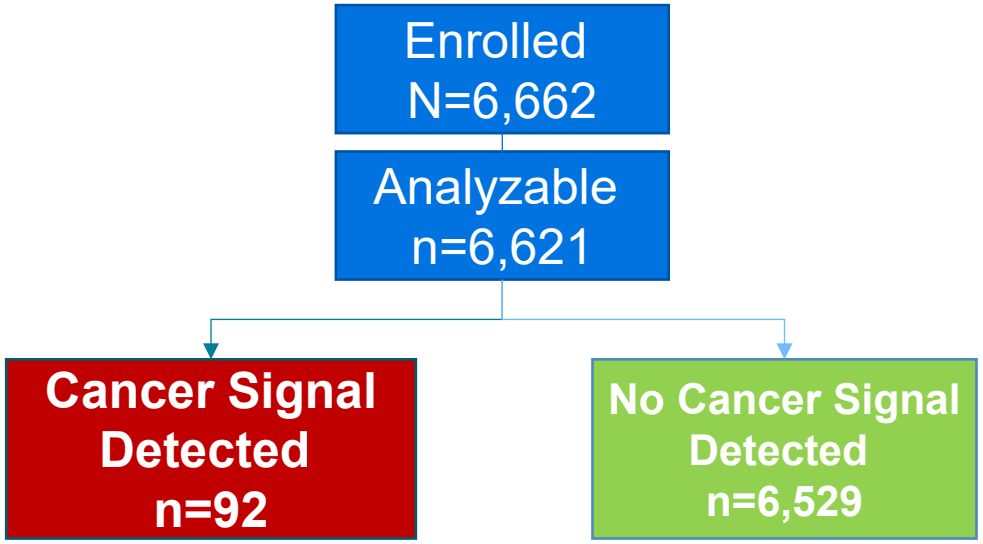
Adapted from principles set forth by the NCI Sponsored Early Detection Research Network See Commentary by Pepe in JNCI Vol 18 2001

Individuals with a history of cancer and the clinicians who care for them are strategically situated to accelerate efficient development and evaluation of the effectiveness of MCD tests for screening in the general population

Why Prioritizing Inclusion of Cancer Survivors for Studies to Develop MCD tests is Strategic

- Statistics
- Psychology
- Ethics
- Economics

PATHFINDER: Pilot Study of MCD Testing (2019)



- Recruited from ambulatory clinics of 7 health systems
- An early version of Grail's Galleri test
- Testing was straightforward and process was acceptable to participants with a high consent rate
- Participants did not pay for the test
- Participants did not pay for any attendant workup

PATHFINDER: NCT04241796

Participants were enrolled from December 2019 to December 2020 in the ambulatory care practices at 7 US health care systems and followed thru Dec 2021

Schrag Beer, McDonell et al Lancet 2023

PATHFINDER Eligibility Criteria

Inclusion:

- **Adults ≥50 years**:
- **High Risk Cohort:**
  - **Lifetime history of smoking at least 100 cigarettes**
  - **Hereditary cancer predisposition[a]**
  - **A history of cancer with no treatment for >3 years[b]**
- **Not High-Risk Cohort:**
  - **None of the above risk factors**

Exclusion:

- **Clinical suspicion of malignancy**
- **Undergoing diagnostic evaluation for possible cancer**
- **History of any cancer or cancer treatment within past 3 years**

[a]Genetic cancer predisposition, hereditary cancer syndrome, or meeting criteria for germline testing based on NCCN guidelines.
[b]Personal history of invasive or hematologic malignancy, with definitive treatment completed >3 years prior to enrollment. Adjuvant hormone therapy for breast cancer was permissible.

Results of MCD Testing in PATHFINDER

	Total Cohort N = 6,621
% of total cohort	100%
Signal Detected 92	1.4%
No Signal Detected	98.6%
PPV	35/92=38%
Diagnostic Yield 35 people with cancer	0.53%

Schrag, Beer, McDonell et al Lancet 2023

Results of MCD Testing in PATHFINDER

	Total N = 6,621	No Additional Risk n = 2,940	Any Additional Risk[a] n = 3,681
% of total cohort	100%	44%	66%
Signal Detected	1.4%	1.2%	1.5%
No Signal Detected	98.6%	98.8%	98.5%
PPV	35/92=38%	11/36=31%	24/56=43%
Yield	0.53%	0.37%	0.65%

Higher risk group has higher yield

Schrag, Beer, McDonell et al Lancet 2023

[a]Previous history of cancer, smoking, and genetic risk.

Results of MCD Testing in PATHFINDER

	Total N = 6,621	Additional Risk was history of cancer n = 1,622	No history of Cancer N=4999
% of total cohort	100%	25%	75%
Signal Detected	1.4%	2.0%	1.2%
No Signal Detected	98.6%	98.0%	98.8%
PPV	35/92=38%	14/33=42%	21/59=36%
Yield	0.53%	0.86%	0.42%

Participants with personal history of cancer had highest yield

Of 33+ tests in persons with a history of cancer, 14 people had cancers found: 7 recurrent, 6 new and 1 had both

Schrag, Beer, McDonell et al Lancet 2023

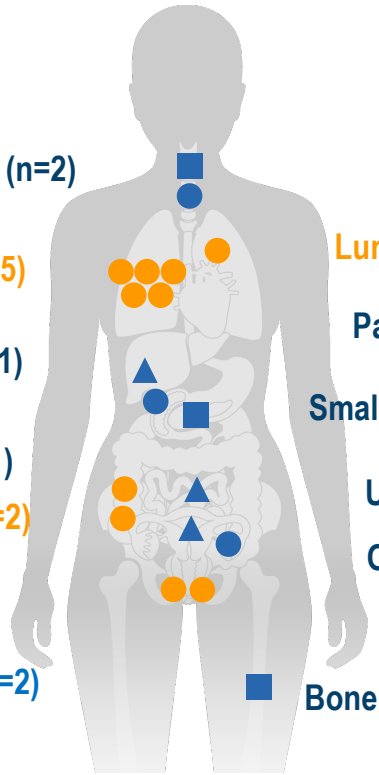
Cancers Diagnosed After a True+ MCD Signal

6621 people received a test result

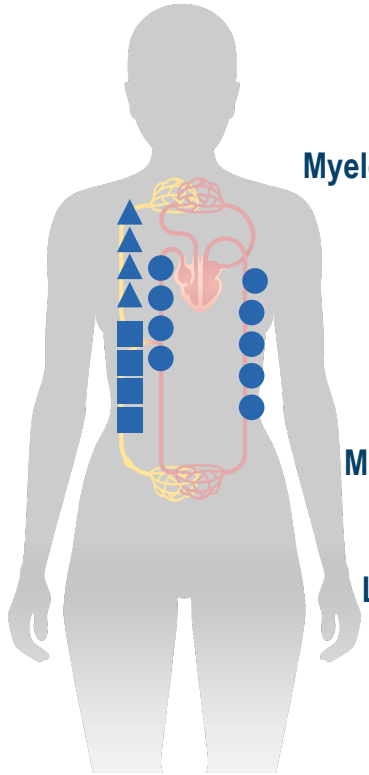
35 people were diagnosed with 36 cancers

- 24 in high-risk cohort=69%
- 11 in average-risk cohort=31%

18 people diagnosed with a Solid Tumor



17 people diagnosed with a Hematologic Malignancy



AJCC Staging: ▲ Stage I ■ Stage II ● Stage III/IV/No Stage/Recurrent

Available Screening: **USPSTF cancer screening** or **No standard screening**

Schrag, Beer, McDonell et al, Lancet 2023

What I learned from listening to the participants in PATHFINDER at my center

with and without cancer

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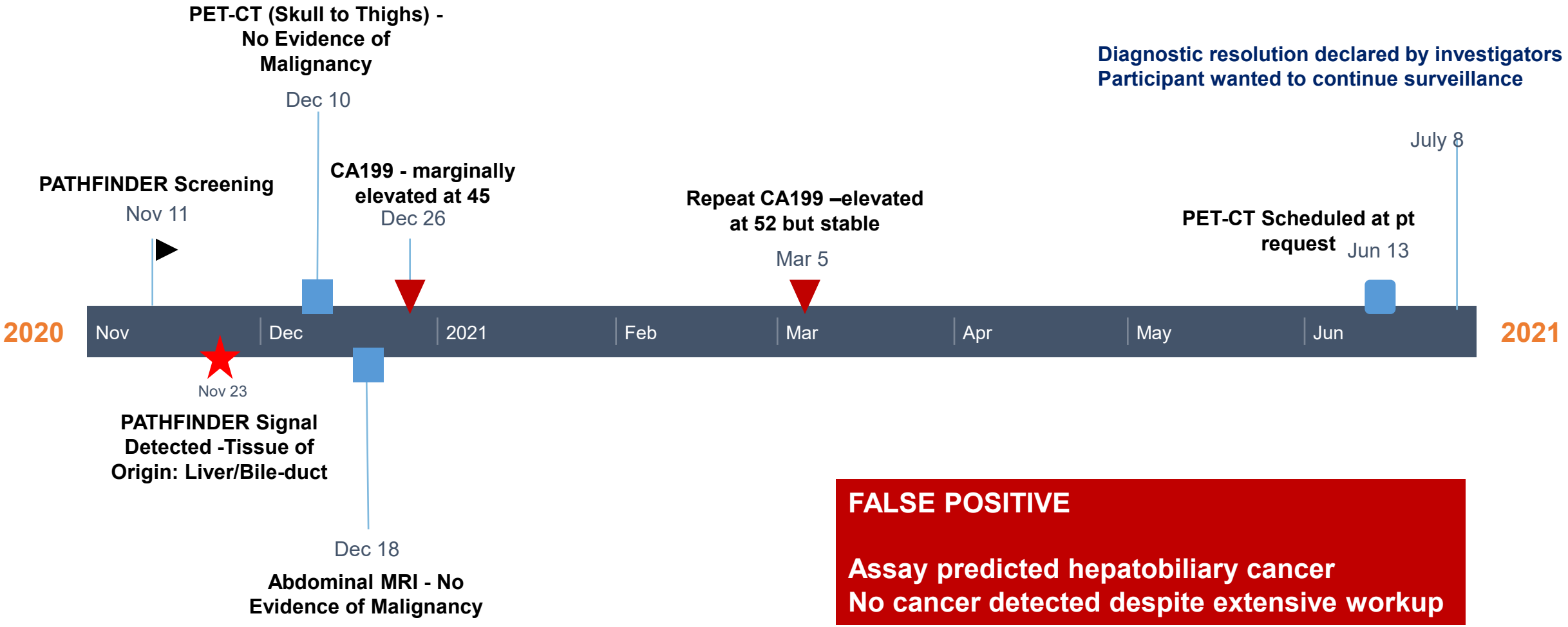
74-Year-Old Woman With no Risk Factors



FALSE POSITIVE

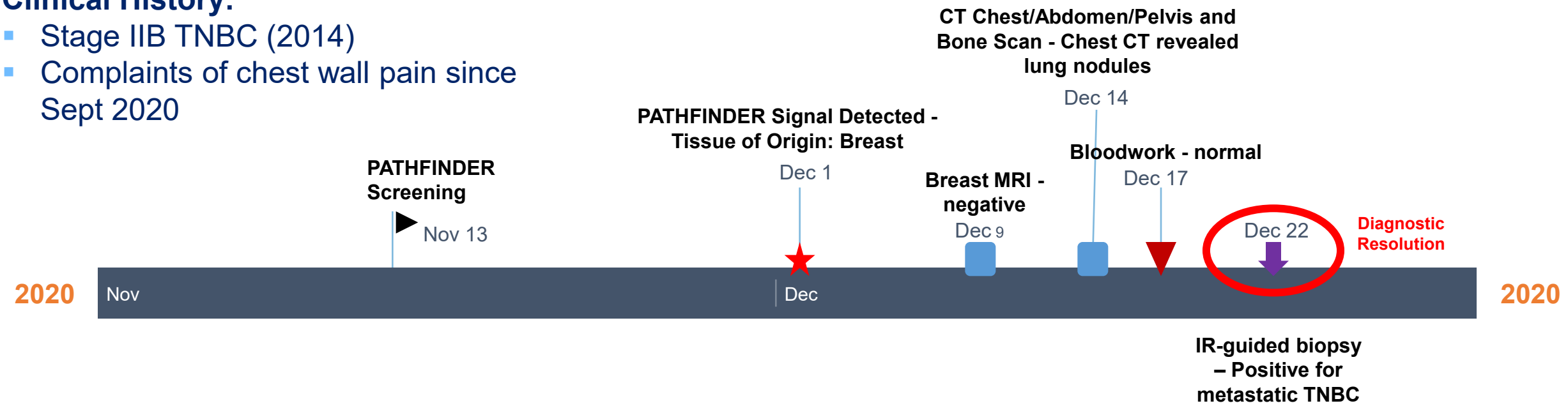
Assay predicted hepatobiliary cancer
No cancer detected despite extensive workup

Dana-Farber Cancer Institute

55-Year-Old Woman With History of Breast Cancer

Clinical History:

- Stage IIB TNBC (2014)
- Complaints of chest wall pain since Sept 2020



TRUE POSITIVE

Metastatic cancer

Screen-detection unlikely to achieve cure

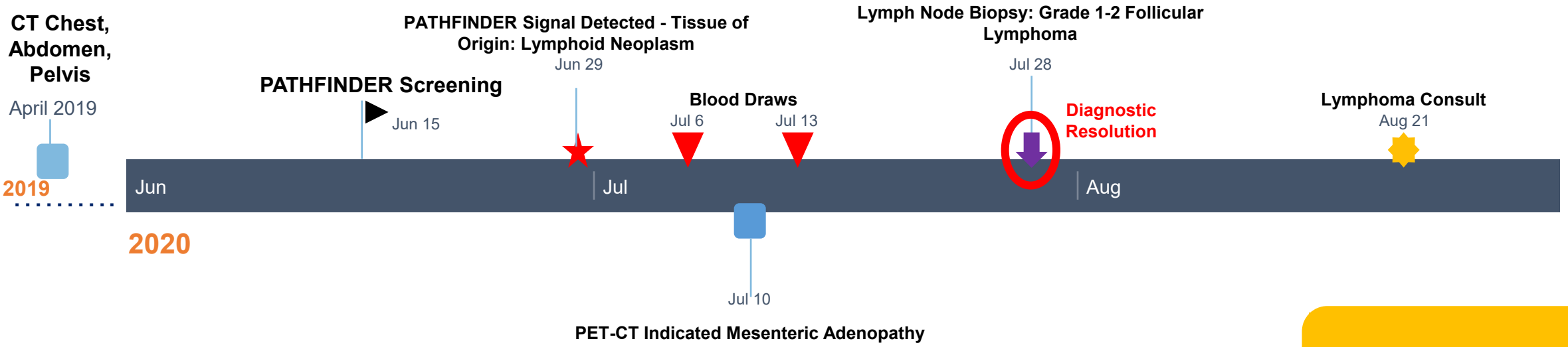
Lead time may not offer clinical benefits

Dana-Farber Cancer Institute

57-Year-Old Male with History of Stomach Cancer

Clinical History:

- pT3N3 gastric adenocarcinoma (2014)
- Enrolls in PATHFINDER at 6 year “graduation” visit to survivorship



TRUE POSITIVE

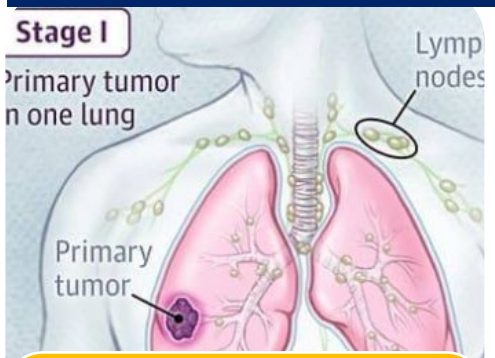
Early-Stage cancer that may never need treatment

Possible overdiagnosis

Dana-Farber Cancer Institute

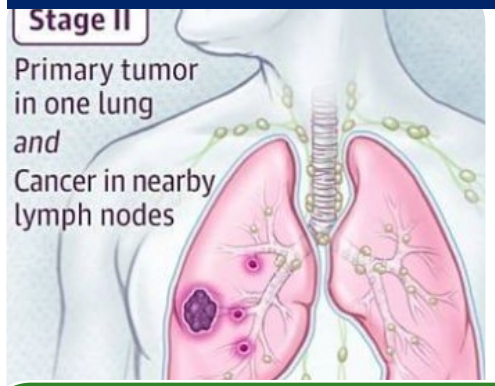
“True positive” MCD tests identify 3 categories of cancer diagnoses

Low Benefit Potential “overdiagnosis”



Early-Stage cancer that may never need treatment

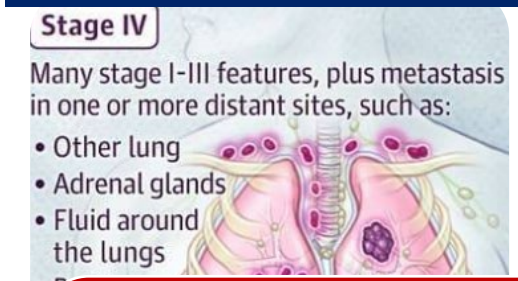
High Benefit Potential



Early-stage cancer that if undetected or treated will lead to metastasis and death

The major value proposition for MCD screening

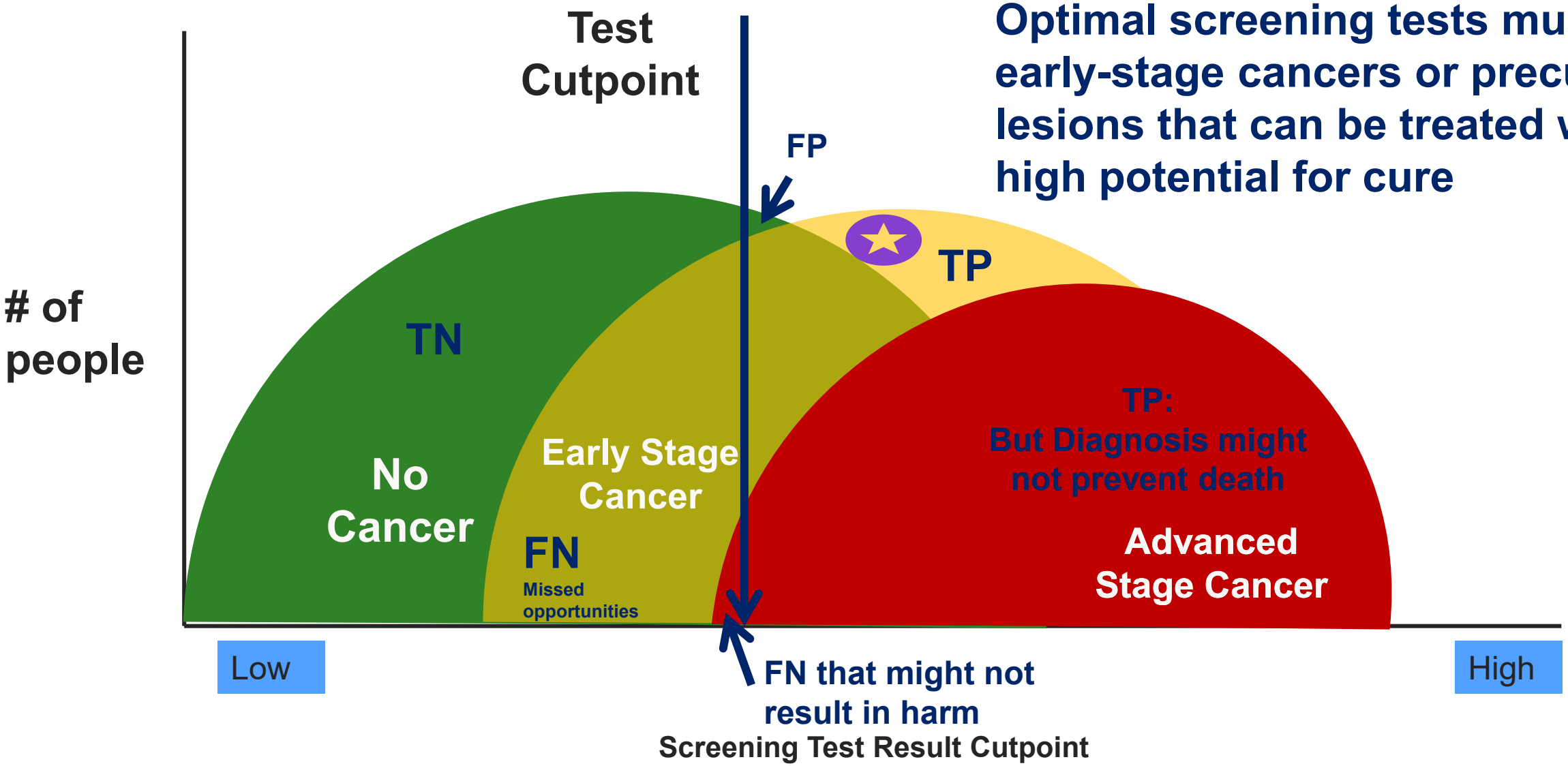
Uncertain/Low Benefit Potential “too late to cure”



Metastatic cancer

Lead time in detecting advanced disease may not offer significant clinical benefit

A Screening Test that Translates to Improved Population Health Must Find Cancers at Early Stage



Optimal screening tests must find early-stage cancers or precursor lesions that can be treated with high potential for cure

Translating Cancer Screening Tests from Research to Practice

Challenge	Opportunity
How to select the best assay for testing in RCT?	Invest in large scale referent labeled cohort of patients Leverage labeled samples from cancer patients Refine terminology for describing sensitivity (pseudosensitivty)
Lack of representation from diverse settings and people with varied risk profiles	Oversample underrepresented groups Build trust, engage communities, explain the “why”
Lack of data about natural history of screen vs. symptom detected cancers	Add the mode of cancer detection to tumor registries Invest in mathematical simulation models Learn from “real world” data cache
Effort required to recruit large diverse populations to RCTs	Engage participants from where people live and work Apply population/implementation science core knowledge Partner with patients, PCPs, payors, public health ministries

Perspective on MCD testing in late 2024

- For healthy individuals
- For cancer survivors

- Strategy for:
  - PCPs
  - Oncologists
  - Cancer research community
  - Payors/policy makers
  - Assay developers

Thank You!

Questions?

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Two Paradigms: Single Type vs. PAN Cancer Screening

Screening for a Single Type of Cancer

- All currently approved cancer screening tests in the USA
- Many individuals with a history of cancer are highly motivated to detect early recurrence based on the premise that detection at occult stage improves outcomes

Screening for Multiple types of cancer- PAN Cancer

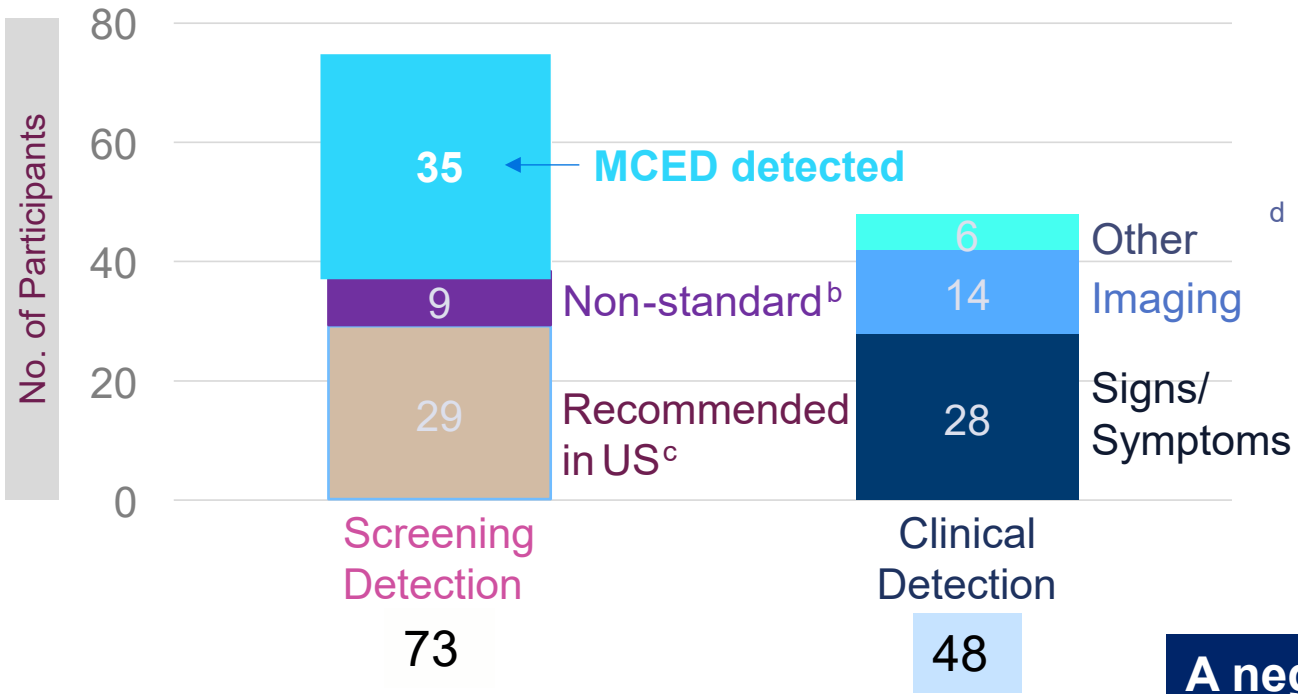
- Multi-cancer Detection Tests (MCD)
  - Aka MCED tests
- Harness technological innovations in multi-omics and the ability to distinguish tumor from normal DNA

Path Forwards

- More intensive early investment in testing assays on labeled specimens from diverse cancer patients will improve the development pathway for MCD tests
- The community of cancer survivors and the clinicians who care for them must collaborate to responsibly develop MCD and SCD technologies
- Invest in modeling studies before launching large-scale screening trials
- Prioritize enrollment in well designed clinical trials
- Ensure careful characterization of underlying risk of enrolled screening participants
- Enrolling cancer survivors and individuals with cancer predisposition (genetic or behavioral) is an efficient design strategy

Cancers Identified Within a Year of MCED Testing

121 participants had a cancer diagnosis within 1 year of MCED testing



- 35/121 (29%) had cancer diagnosed after a positive MCED
- 86/121 (71%) had cancer diagnosed within 12 months but did not have a positive MCED

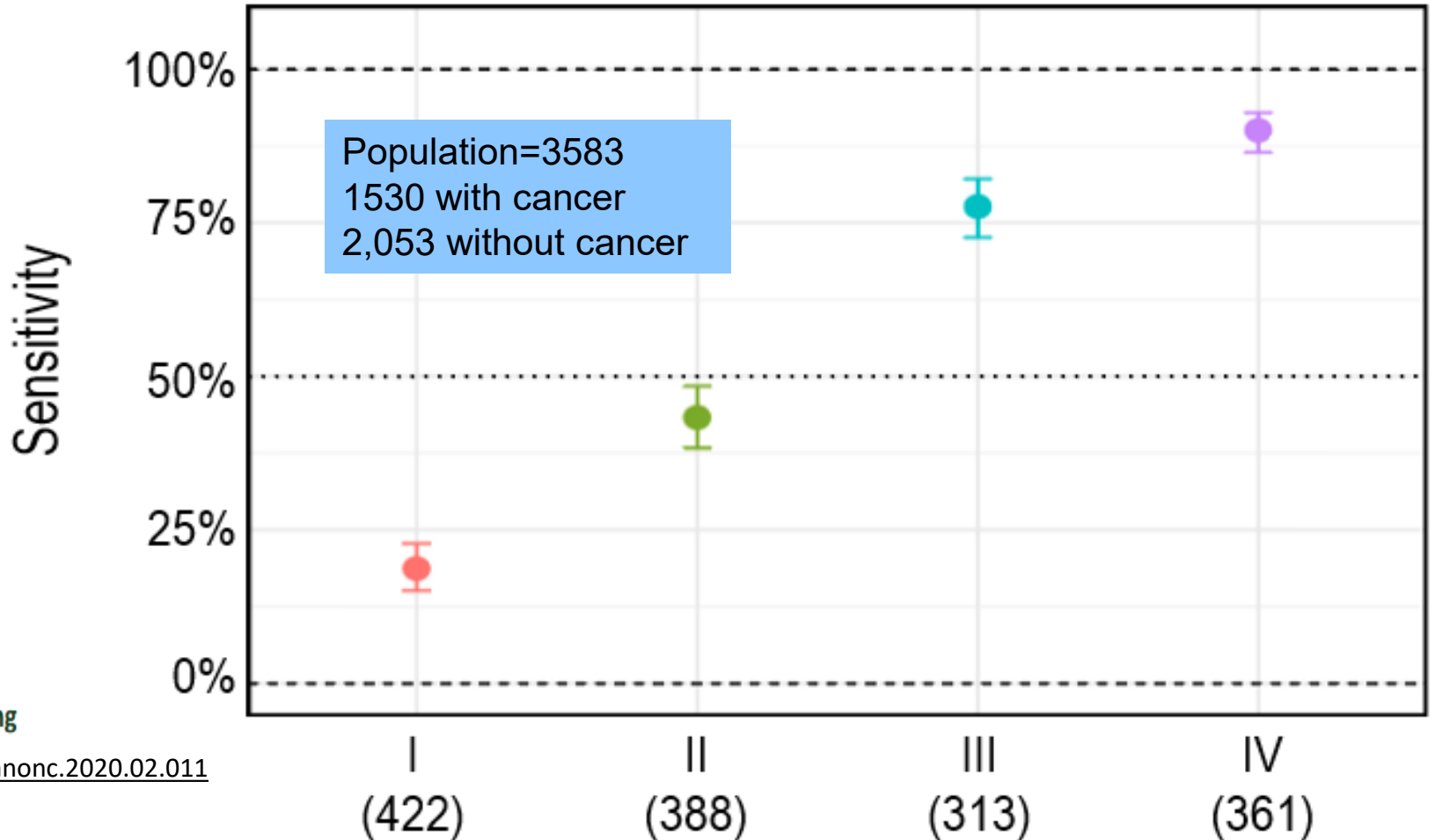
A negative MCED test result should not be used to provide reassurance that cancer will not occur Should not decrease adherence to standard screening

MCED, multi-cancer early detection.
[a]Based on participants with cancer status assessment at the end of the study.
[b]3 thyroid and 6 melanoma.
[c]Breast, cervical, colorectal, lung, and prostate cancer.
[d]1 incidental radiology finding, 1 incidental finding on routine physical exam, 2 changed lab values, 1 surveillance of prior cancer, 1 follow-up after MGUS diagnosis.

Sensitivity of MCD Assays Varies by Stage

MCD assays will generally have lower sensitivity for the detection of early-stage tumors

Overall Sensitivity of 54.7% (95% CI: 52.2-57.2%)
in Labeled Blood Samples from People with >20 types of Cancer
Specificity is fixed at 99.4%



ORIGINAL ARTICLE

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

doi.org/10.1016/j.annonc.2020.02.011

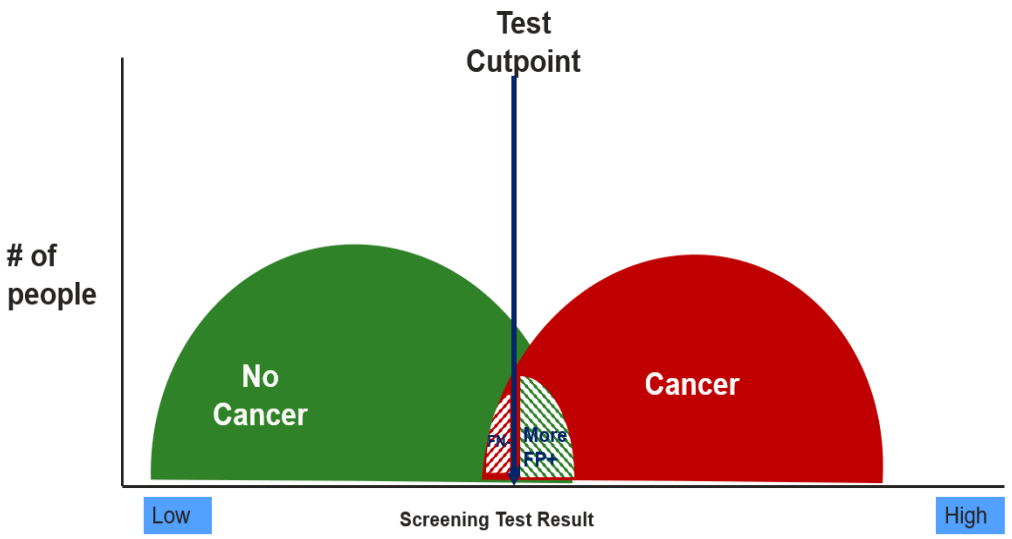
M. C. Liu[1†], G. R. Oxnard[2†], E. A. Klein[3], C. Swanton[4,5], M. V. Seiden[6*] & on behalf of the CCGA Consortium[†]

SINGLE vs. PAN Archetypes of Cancer Screening Tests:

Tests that Focus on Detecting One Type of Cancer: SINGLE

Goal is to Maximize Cancer Detection!!

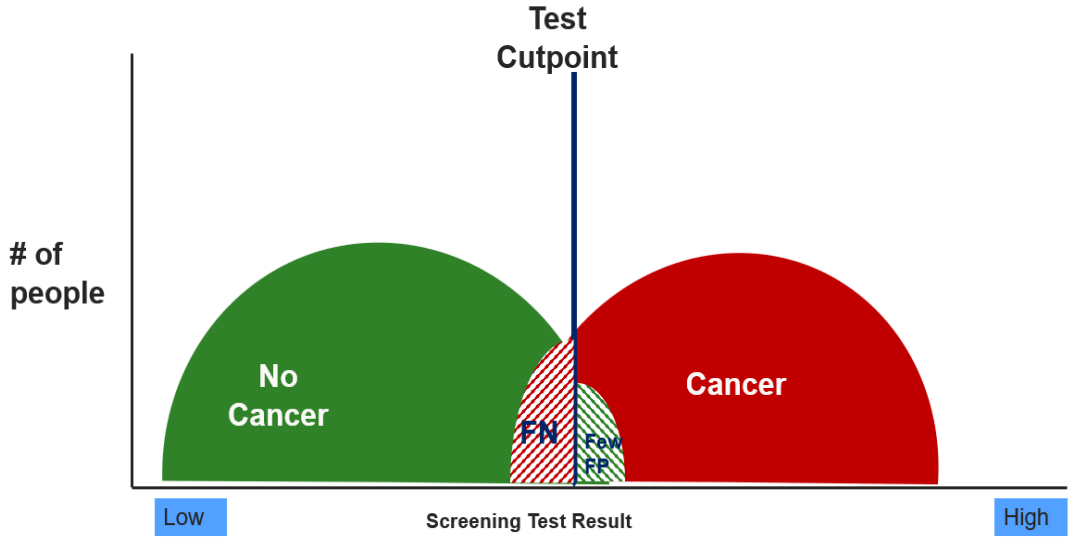
Minimize FN-, More FP+



Tests that Focus on Detecting Multiple Types of Cancer: PAN

Goal is to Minimize Need to Chase FP+s

Minimize FP+, but More FN-s

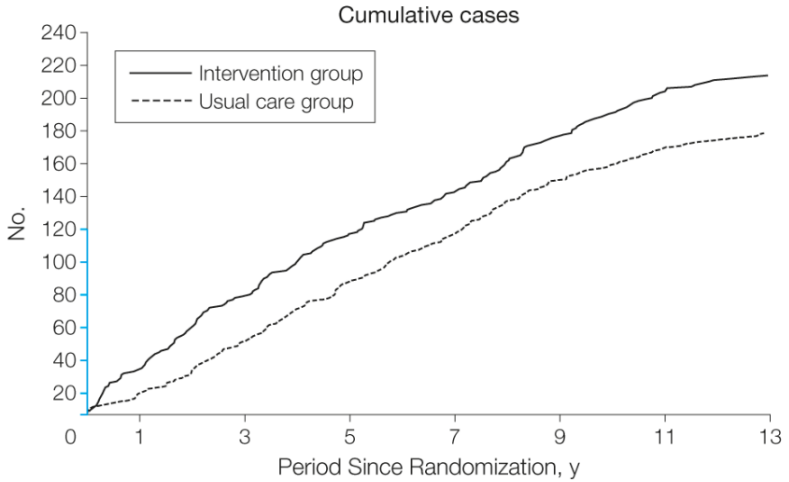


Screening Trials are Resource Intensive, Expensive and Have High Failure Rates

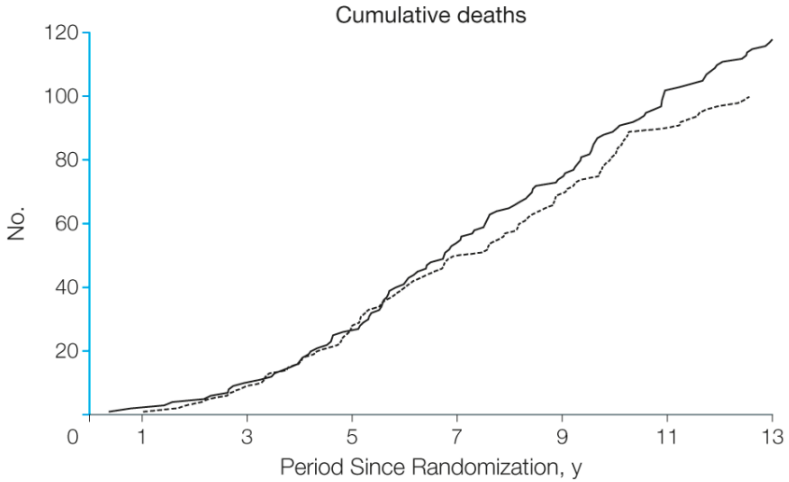
CONCLUSION: Among women in the general US population, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

78,216 women were randomized to usual care vs. CA125/Ultrasound q year for 4 years to screen for ovarian cancer

Incidence



Mortality



Intervention group													
Cumulative cancers	28	74	113	139	174	202	212	2	10	26	54	74	102	118
Cumulative person-years	33 908	100 777	166 273	230 393	292 223	341 975	371 833	34 210	102 191	169 354	235 475	299 372	350 870	381 574
Usual care group													
Cumulative cancers	13	45	83	113	146	167	176	0	9	28	50	69	90	100
Cumulative person-years	33 994	101 279	167 380	232 046	294 424	344 734	374 976	34 260	102 344	169 617	235 836	299 903	351 557	382 502

Ovarian Cohort from PLCO Trial
PMID: 21642681 Buys et al JAMA June 2011
Clinical trials.gov: NCT00002540

Minimum Criteria for Implementing a Cancer Screening Test at Population Level

1. Cancer must exist in a pre-symptomatic form

2. A potential screening test must reliably detect pre-symptomatic cancers

3. Treatment interventions for pre-symptomatic detected cancers must lead to decrease in cancer mortality

4. Screening test must be feasible to implement at population-scale with benefits outweighing the harms