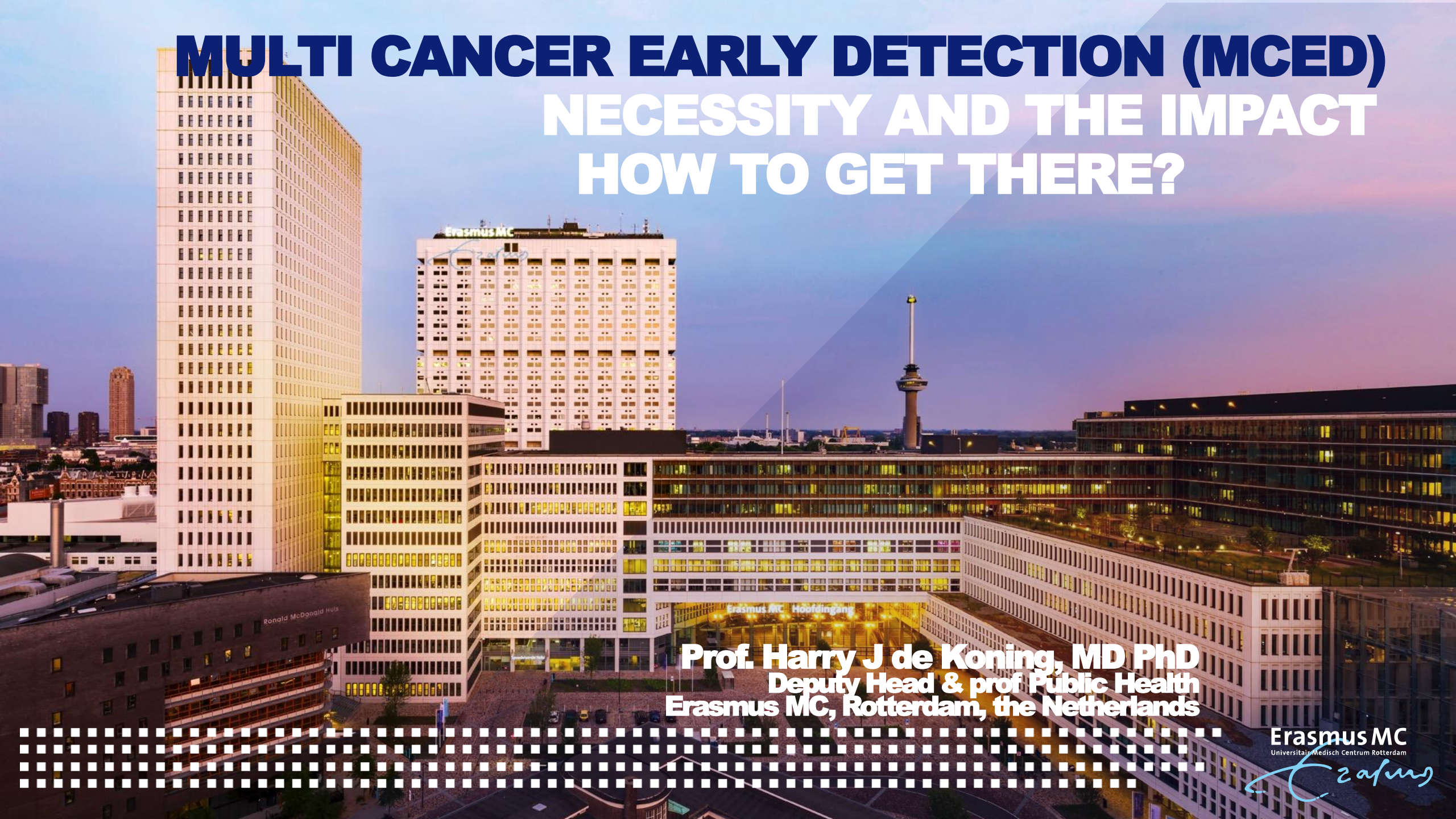
MULTI CANCER EARLY DETECTION (MCED)

NECESSITY AND THE IMPACT
HOW TO GET THERE?



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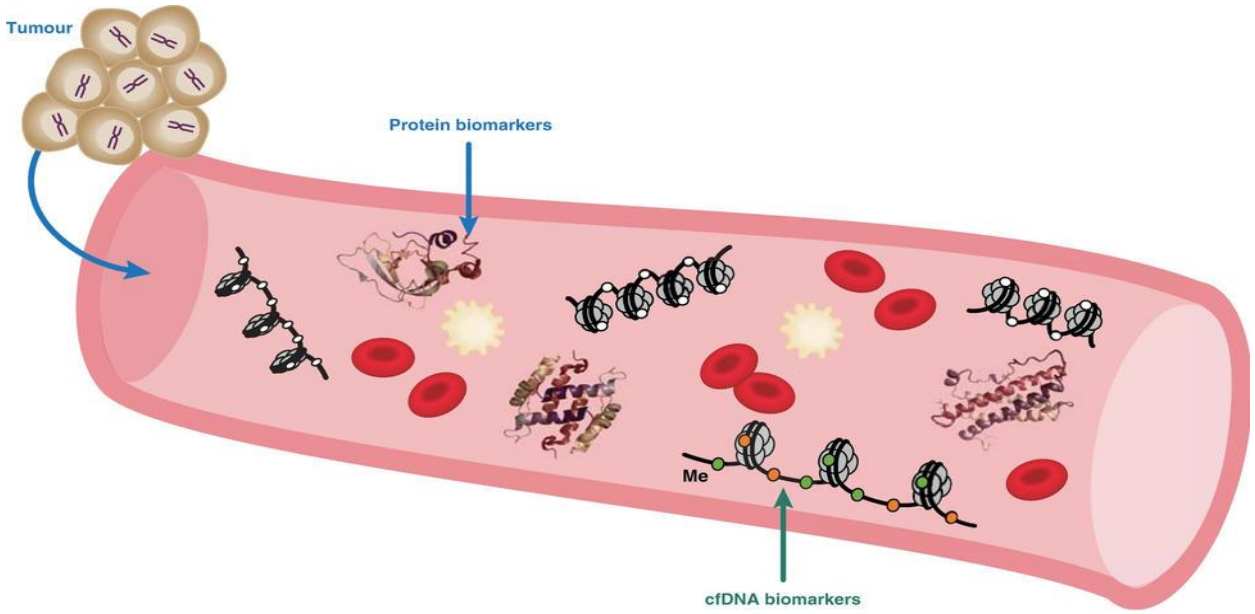
WHAT IS THE PROBLEM

1) Screening can reduce incidence and/or mortality:
   - Breast cancer
   - Cervical cancer
   - Colorectal cancer
   - Lung cancer
   - Prostate cancer
   - ..
2) But for **78% of the cancers**, there is **no** screening test available
3) Cancer screening challenges for cancers that are more rare or difficult to detect in their early stages:
   - such as pancreatic, ovarian, and liver cancers

MCED

1) MCEDs could transform cancer screening by detecting multiple cancers early in a single test
2) Simultaneously by analyzing biomarkers shed by cancer cells into the bloodstream, e.g.,:
   - Protein
   - DNA



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ascopubs.org

Comparison	Group	Cohort Number	Average Test Number	Average Sensitivity	Average Specificity	Average AUC
Single vs. Combined Factor	Single	32	1792	81.68%	80.79%	0.81
	Combined	48	970	84.58%	84.26%	0.84
MCED vs. SCED	MCED	14	2187	69.2%	96.6%	0.83
	SCED	66	1110	86.4%	80.0%	0.83
Inter-cancers (SCED)	colorectal cancer	22	1875	84.5%	83.9%	0.84
	liver cancer	11	1343	83.2%	86.9%	0.85
	lung cancer	8	299	89.8%	58.2%	0.74
	bladder cancer	6	209	83.6%	88.3%	0.86
	prostate cancer	6	562	92.1%	68.1%	0.8
	cervical cancer	4	864	92.2%	86.9%	0.89
	oral cancer	3	254	78.5%	85.3%	0.82
	breast cancer	2	520	96.5%	71.9%	0.84
	glial malignancies	1	68	100.0%	100.0%	1
	pancreatic cancer	1	139	83.8%	89.2%	0.87
	stomach cancer	1	4566	87.0%	68.4%	0.78

EARLY DIAGNOSIS?

1) Sensitivity for stage I (around 40%)
2) Sensitivity for stage III (around 80%)

Etzioni R, J Natl Cancer Inst. 2022

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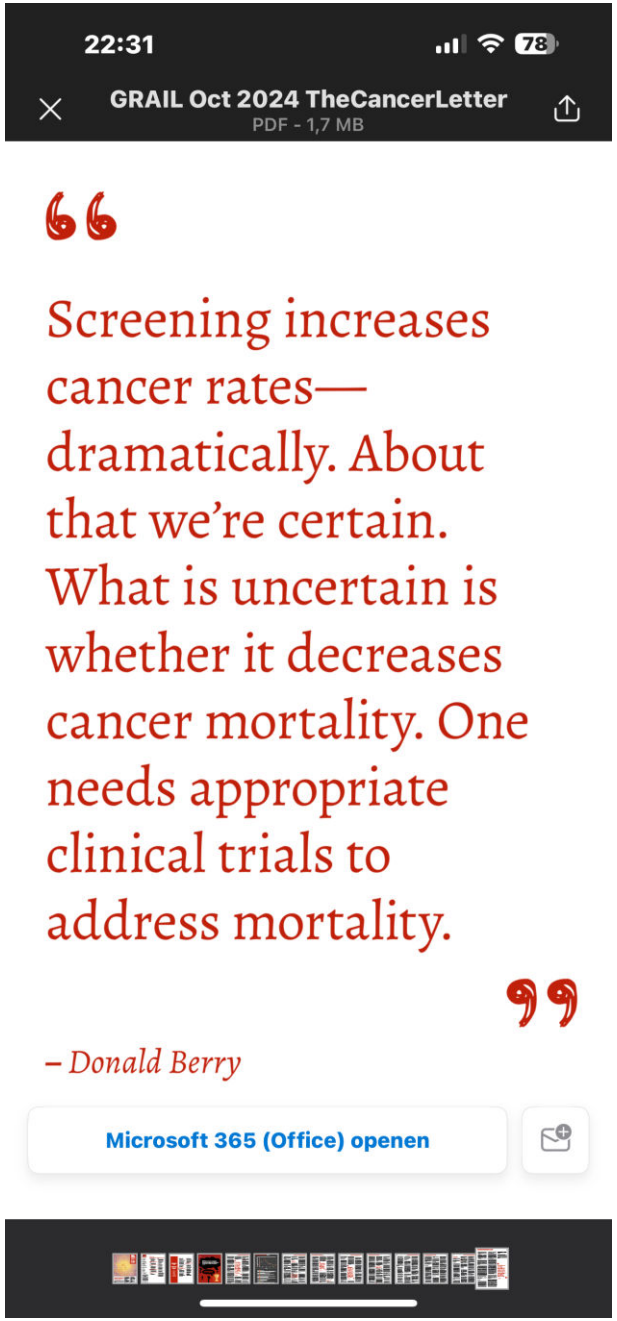
MANY QUESTIONS

1) Do these tests reduce cancer-related deaths?
2) Do these tests reduce the incidence of advanced disease?
3) How earlier is cancer being found in the ‘difficult cancers’?
4) Who should consider undergoing a MCED test?
5) What if follow-up testing doesn’t detect cancer, what does that mean for their future cancer risk?

1) Would people who receive a MCED test skip traditional, proven cancer screenings?
2) Do these tests work equally well for everyone?
3) Could it worsen racial, ethnic, or socioeconomic disparities in cancer outcomes?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GRAIL Oct 2024 TheCancerLetter
PDF - 1,7 MB
Screening increases cancer rates—dramatically. About that we're certain. What is uncertain is whether it decreases cancer mortality. One needs appropriate clinical trials to address mortality.
– Donald Berry
Microsoft 365 (Office) openen

ONGOING PROSPECTIVE TRIALS

1) PathFinder study US amongst 6,621 participants – >50 cancers (solid and non-solid)
2) DETECT-A study in the US amongst 3,870 – 8 cancers (ovary, liver, stomach, pancreas, esophagus, colorectum, lung and breast)
3) ASCEND-2 study amongst 6,354 – 56% sensitivity

4) NHS-GRAILS Galleri trial – UK – 140,000
5) Medicare-GRAILS Galleri (REACH) – US – 40,000

6) 20/20 GeneSystem'sOneTest
7) Precision Epigenomics's EPISEEK

SAN FRANCISCO FIRE FIGHTERS

- 1,786 active and retired firefighters
- Dec 6th 2022; 1 million dollars fund

- 5 detected cancers (expected 29)
- 6 false positives

- 2 cases already known
- 2 advanced cases (lung with now brainmetastases; pancreatic now in hospice)

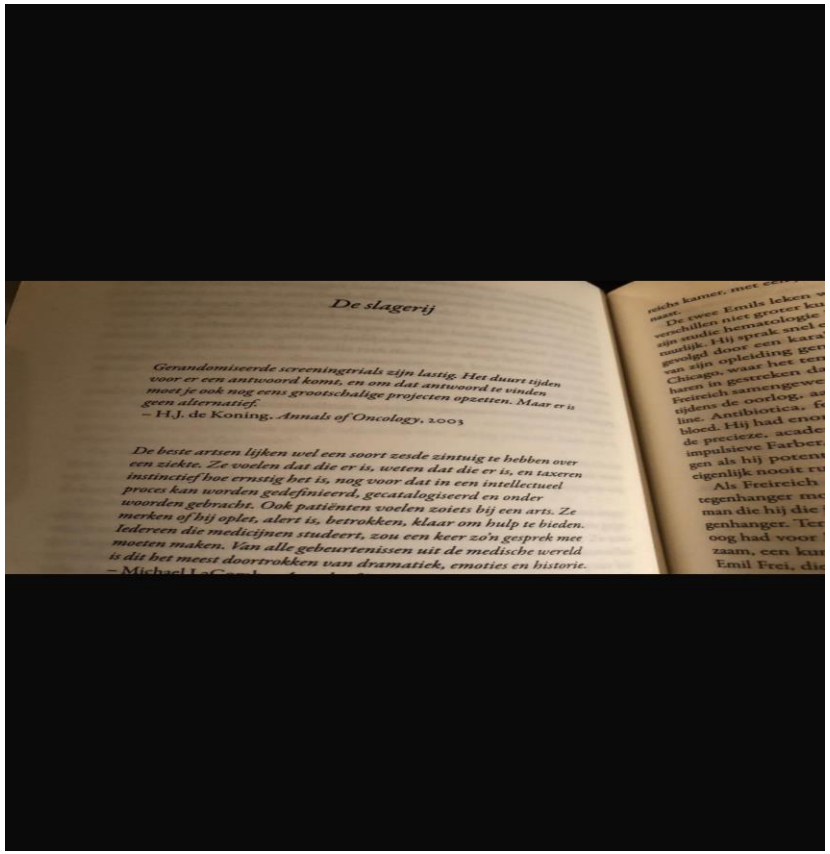
- 6 missed cancers (melanoma, prostate, lymphoma)

THE EMPEROR OF ALL MALADIES

Randomised controlled trials are bothersome.

It takes ages to come to an answer, and they need to be large-scale.

But there is no alternative.



HJ de Koning Annals of Oncology 2003

Quoted in The Emperor of all Maladies

by Siddharta Mukherjee

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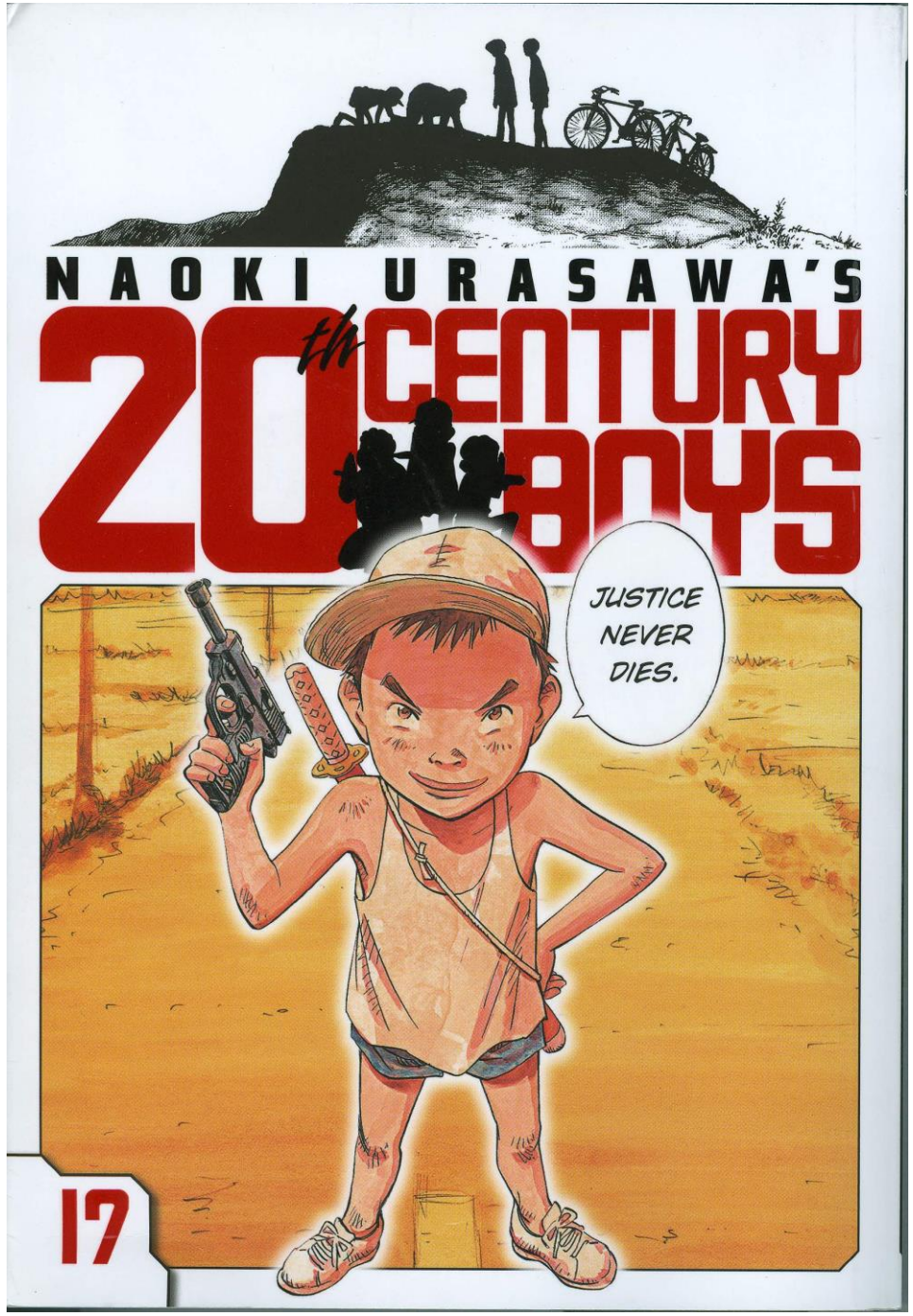

HOW TO GET THERE?

Biomarker studies specific cancer sites

- Biobanking studies
- Cancer specific grants
- More lobby

Almost impossible in NL (Health Council)

- European prospective study needed, but when is timely?
- Side study in running cohorts
- Focus on personalised care
- Pre-modelling natural histories

TEST CHARACTERISTICS – IDEAL TEST

1) Sensitive and specific
2) Inexpensive
3) Easy to administer
4) Earlier diagnosis
5) Limited harms (e.g., false positives)

PATHFINDER-PERFORMANCE

	Age ≥50 years with additional cancer risk (n=3681)	Age ≥50 years without additional cancer risk (n=2940)	Total (n=6621)
Resolution			
All	56 (1·5%)	36 (1·2%)	92 (1.4%)
True positive	24 (0·7%)	11 (0·4%)	35 (0·5%)
False positive	32 (0·9%)	25 (0·9%)	57 (0·9%)
Positive predictive value	24/56; 43% (30·8–55·9)	11/36; 31% (18·0–46·9)	35/92; 38% (28·8–48·3)
Negative predictive value	3449/3502; 98·5% (98·0–98·8)	2786/2819; 98·8% (98·4–99·2)	6235/6321; 98·6% (98·3–98·9)
Specificity	3449/3480; 99·1% (98·7–99·4)	2786/2810; 99·1% (98·7–99·4)	6235/6290; 99·1% (98·9–99·3)
Yield rate	24/3681; 0·65% (0·41–0·92)	11/2940; 0·37% (0·17–0·61)	35/6621; 0·53% (0·36–0·71)
Number needed to screen	3681/24; 153 (108–245)	2940/11; 267 (163–588)	6621/35; 189 (141–276)
Predicted origin accuracy*			
First CSO correct	20/23; 87% (67·9–95·5)	9/11; 82% (52·3–94·9)	29/34; 85% (69·9–93·6)
First or second CSO correct	23/23; 100% (85·7–100)	10/11; 91% (62·3–99·5)	33/34; 97% (85·1–99·8)

Data are n (%), n/N, or % (95% CI). CSO=cancer signal origin. *Excludes one participant with indeterminate CSO from the true-positive set.

Table 2: **Multicancer early detection test performance**

Schrag, Lancet 2023

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FALSE-POSITIVES

1) Between 62-75% has a false-positive result
2) Tissue of origin identified in 75% and 93% of cancer cases (retrospective study!)

Etzioni R, J Natl Cancer Inst. 2022

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