Circulating Tumor DNA (ctDNA): A Potentially Transformative Tumor Marker?

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Serum Tumor Markers Currently Available

Marker	Malignancy
• AFP, HCG	Germ cell
• HCG	Trophoblastic
• CEA	CRC
• CA 125	Ovarian
• CA 15-3	Breast
• PSA	Prostate
• CA 19.9	Pancreatic
• AFP	HCC, NSGCT
• Thyroglobulin	Thyroid (differentiated)
• hCG	Trophoblastic, germ cell

General Points About Existing Serum Biomarkers

- All are proteins/glycoproteins
- None are specific for malignancy
- Few elevated in early malignancy
- Elevated mostly in advanced malignancy
- No causative role in cancer formation or progression
- None predict response to therapy

- Main use: monitoring

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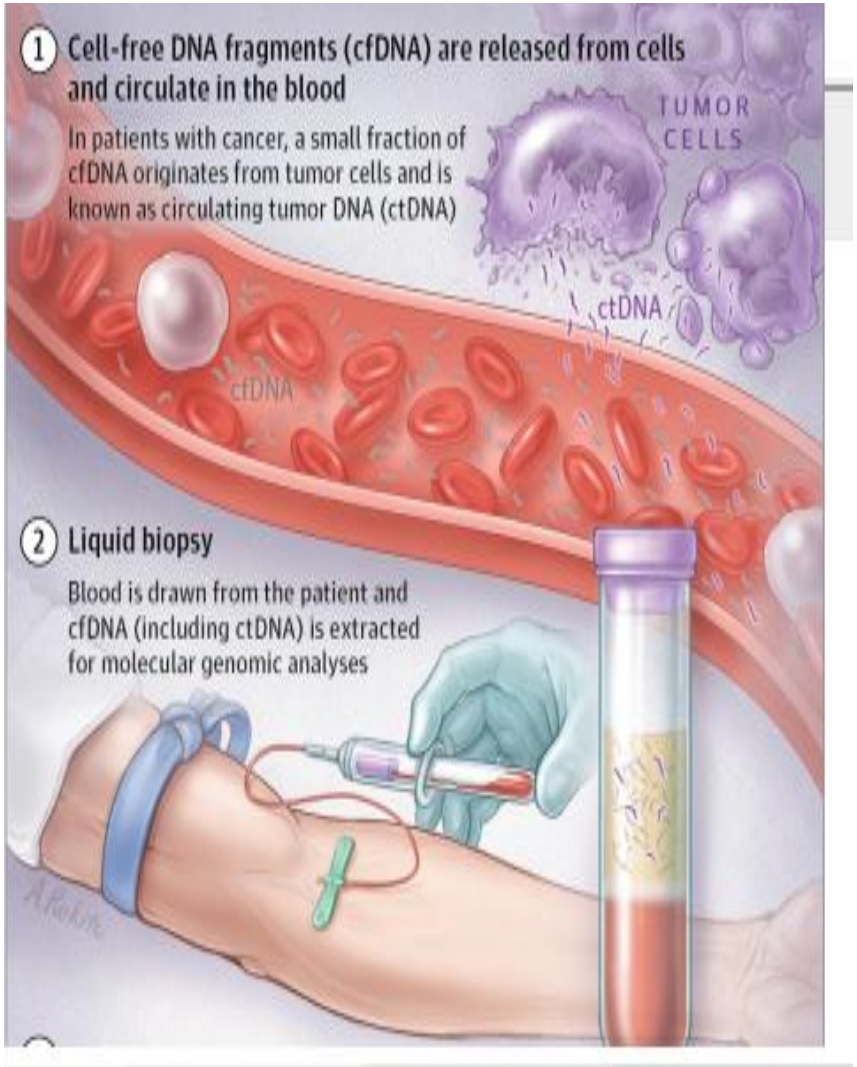
• hGG	Trophoblastic

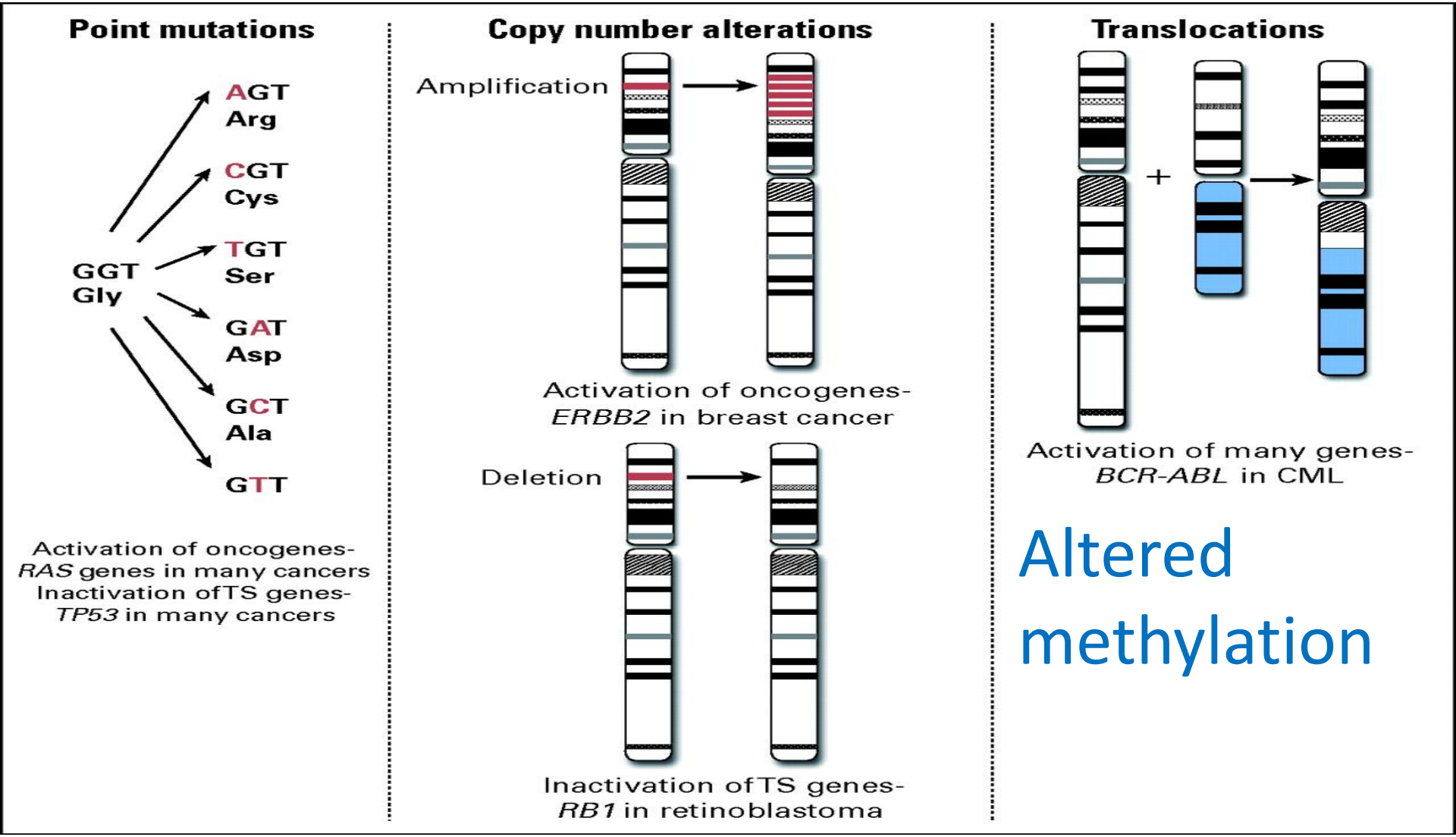
Enter a New Biomarker: Circulating Tumor DNA (ctDNA) (Liquid biopsy)

- ctDNA is the DNA released from tumors into the circulation
- ctDNA only a small fraction of DNA in blood (< 1%)
- Challenge to differentiate tumor from normal cell DNA



Husain et al, JAMA 2017;318:1272

Main classes of genomic alterations in cancer

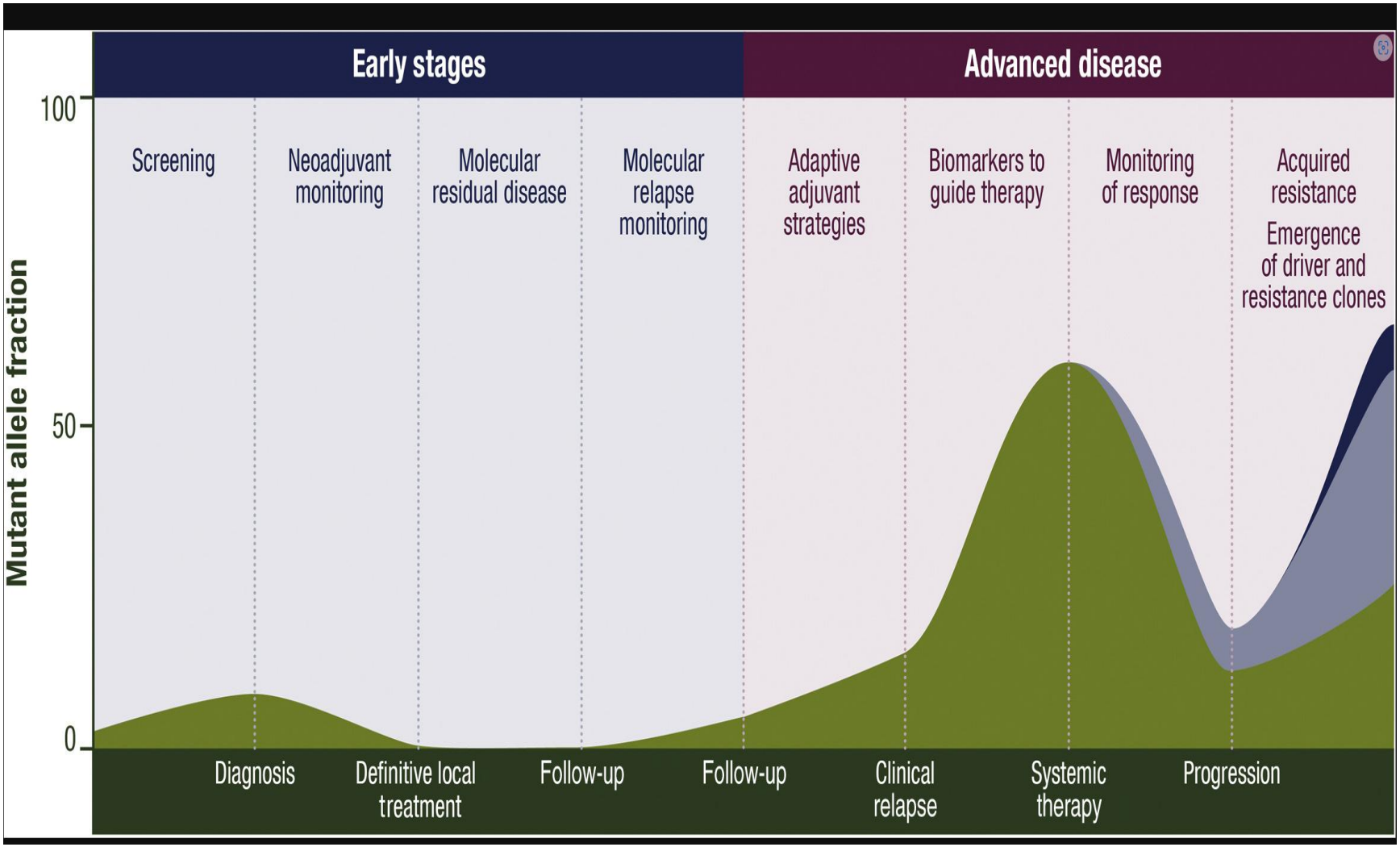


MacConaill L E , Garraway L A JCO 2010;28:5219-5228

Advantages of ctDNA vs Traditional Serum Biomarkers

- More specific for malignancy
- More sensitive for malignancy
- Shorter half-life
- Provide information on tumor biology
- **Can be used as therapy predictive biomarkers**
- **Can be used to identify mechanisms of therapy resistance**

ctDNA: Potentially Useful Across the Continuum of Cancer Care



Pascual et al, Ann Oncol 2022;33:750

- Use of ctDNA in Screening/Detecting Cancer

Current Screening Tests for Cancer

- Detect only one type of malignancy

  Lack specificity for malignancy

  Some are inconvenient/unpleasant for individuals

- Cancer screening tests only available for ~6% of cancers in the UK*

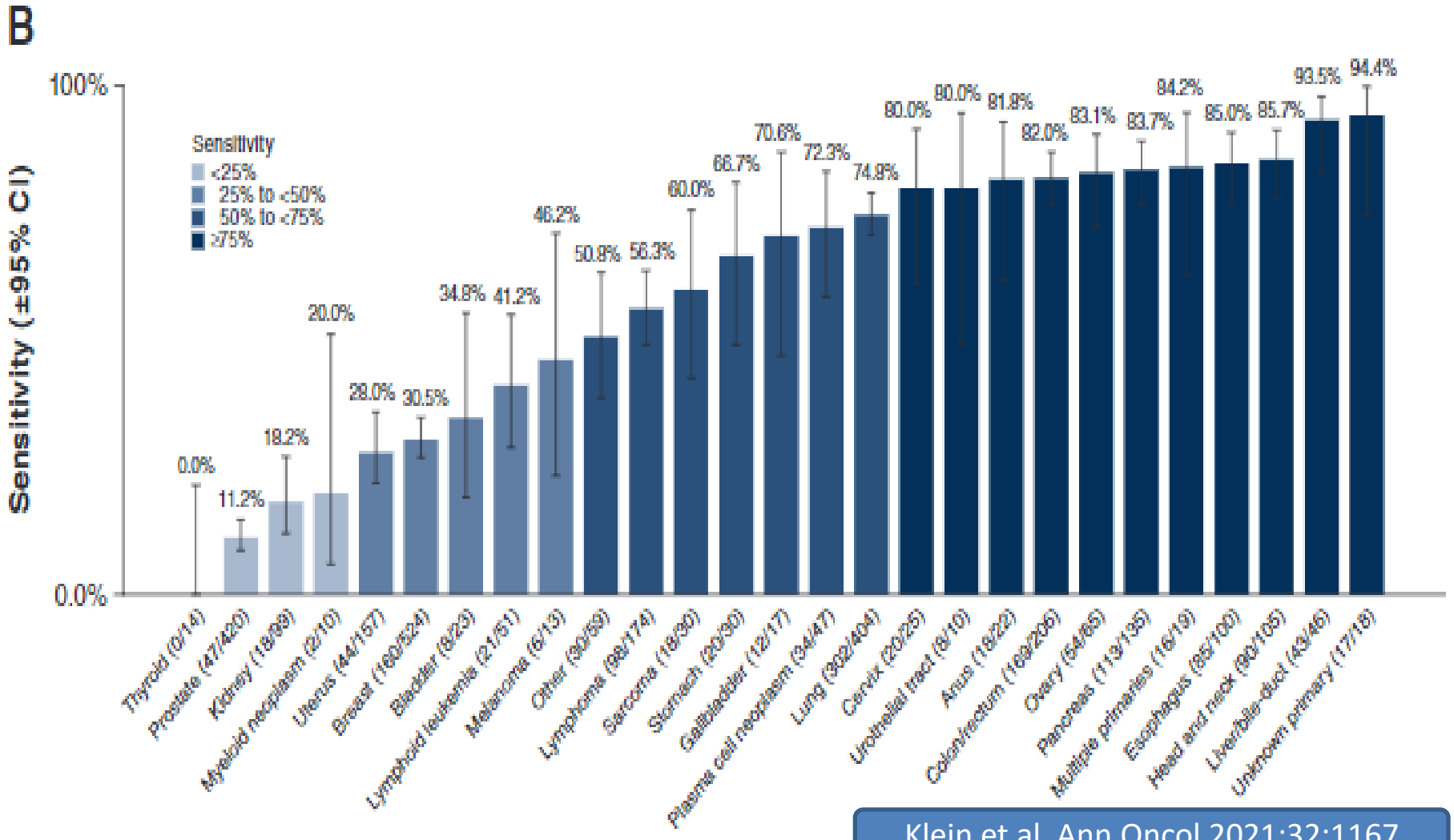
*Sasieni et al, BJC 2023

Desirable Properties of a Cancer Screening Test

- Non/minimally invasive
- Sensitive for early malignancy/premalignancy
- Specificity for cancer
- An ability to screen for multiple cancer types with a single test
- An ability to differentiate indolent from aggressive tumors
- An ability to identify location of tumor

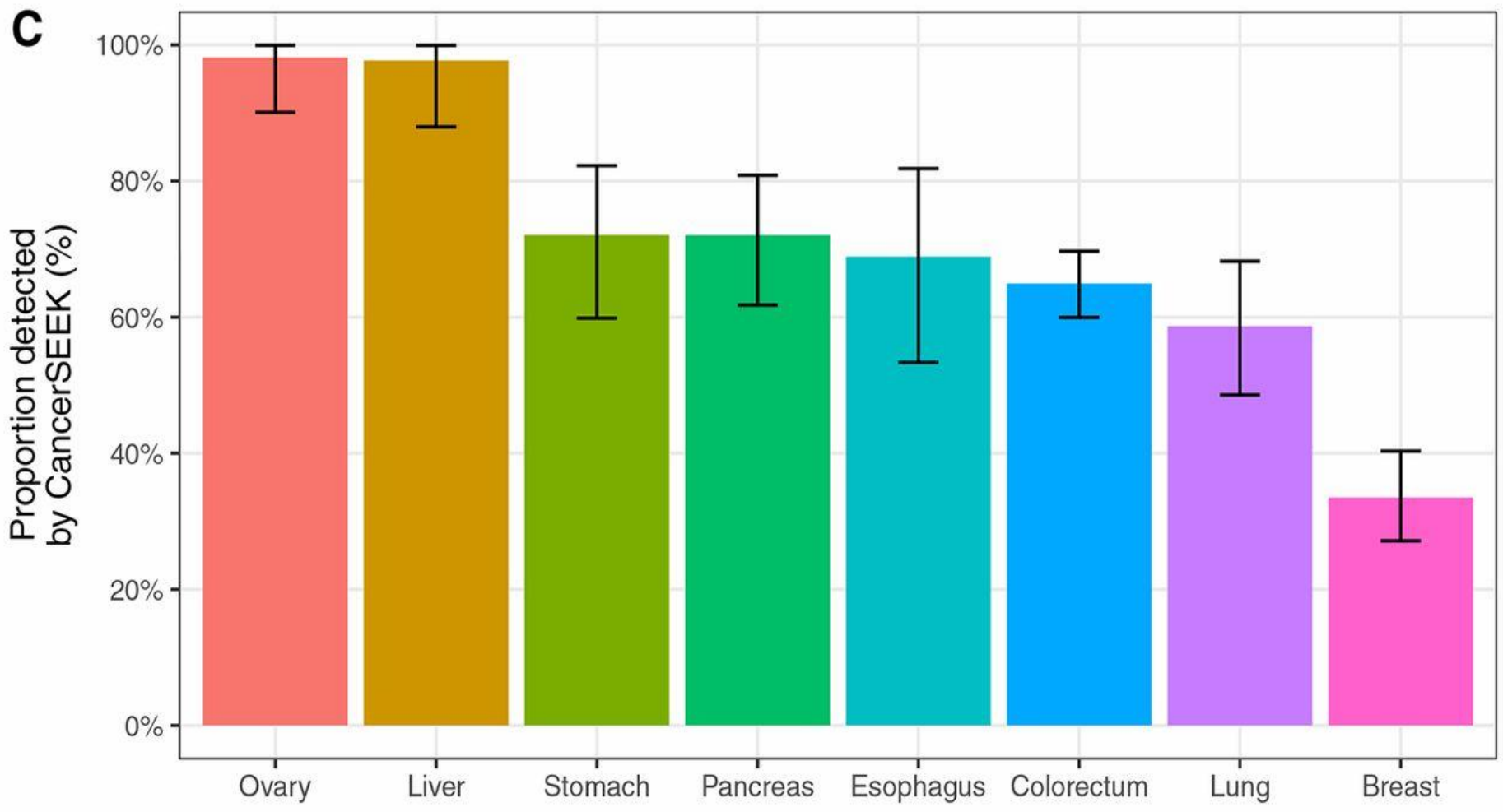
How does ctDNA meet these requirements?

Sensitivity of GRAIL Test for Symptomatic Patients (**Specificity 99.5%**)



Klein et al, Ann Oncol 2021;32:1167

Sensitivity of CancerSEEK for Symptomatic Patients (Specificity > 99%)



Joshua D. Cohen et al. Science 2018;science.aar3247

ctDNA in Screening Asymptomatic Subjects for Cancer (Grail)

- N = 23,161
- Cancer signal: 0.93%
- Specificity: 99.6%
- Sensitivity: 40%*
- PPV: 61.6%
- NPV: 99.1%

- *73.7% in 12 common cancers

Nabavizadel et al, ESMO Conf. Oct 2025

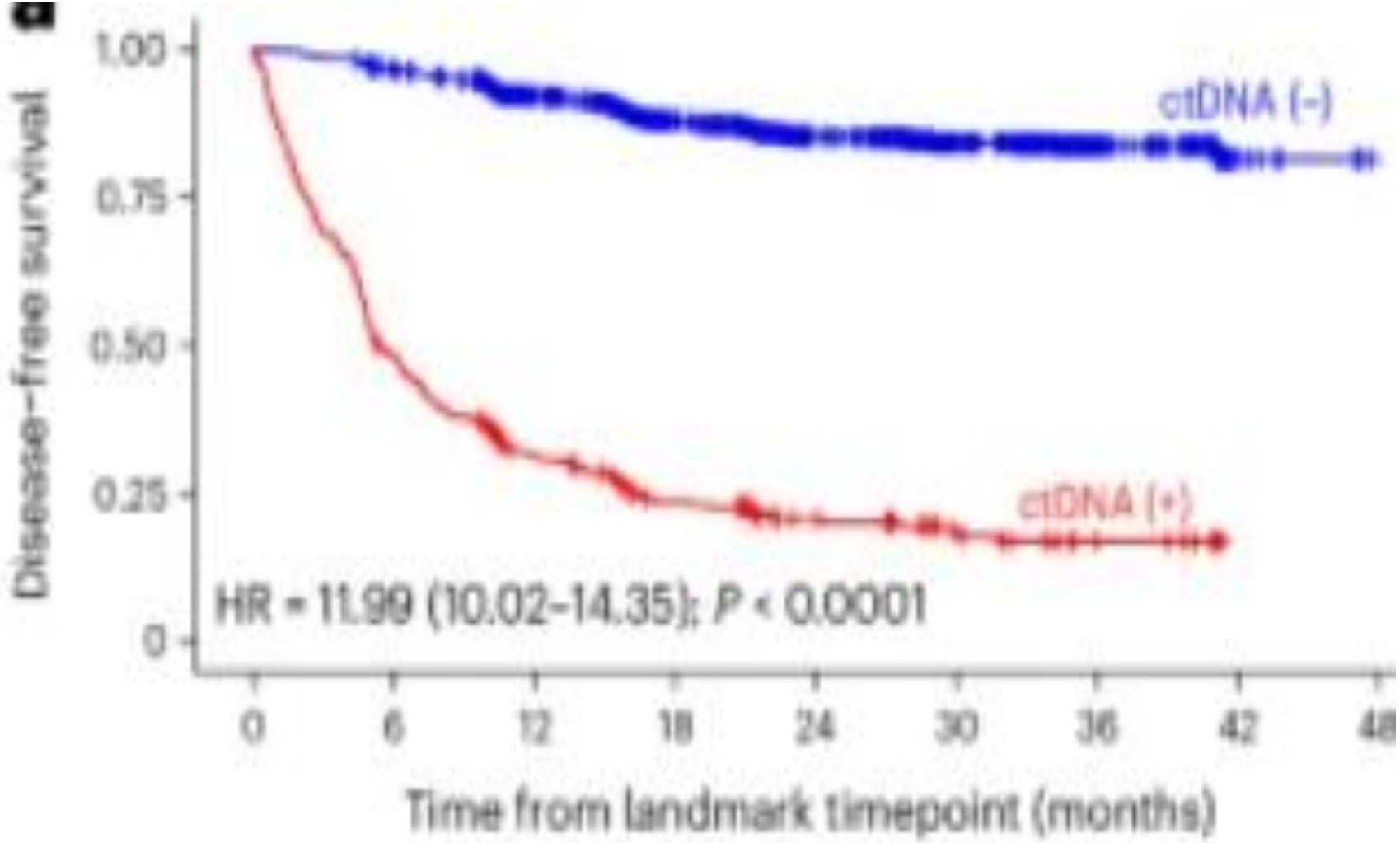
NHS Randomized Prospective Trial Using the GRAIL test (Galleri)

- 140,000 subjects 50-77 years randomized
- Primary end-point: reduction in disease stage
- Secondary end-point: reduction in cancer-specific mortality

Neal et al, Cancers 2022;14:4818

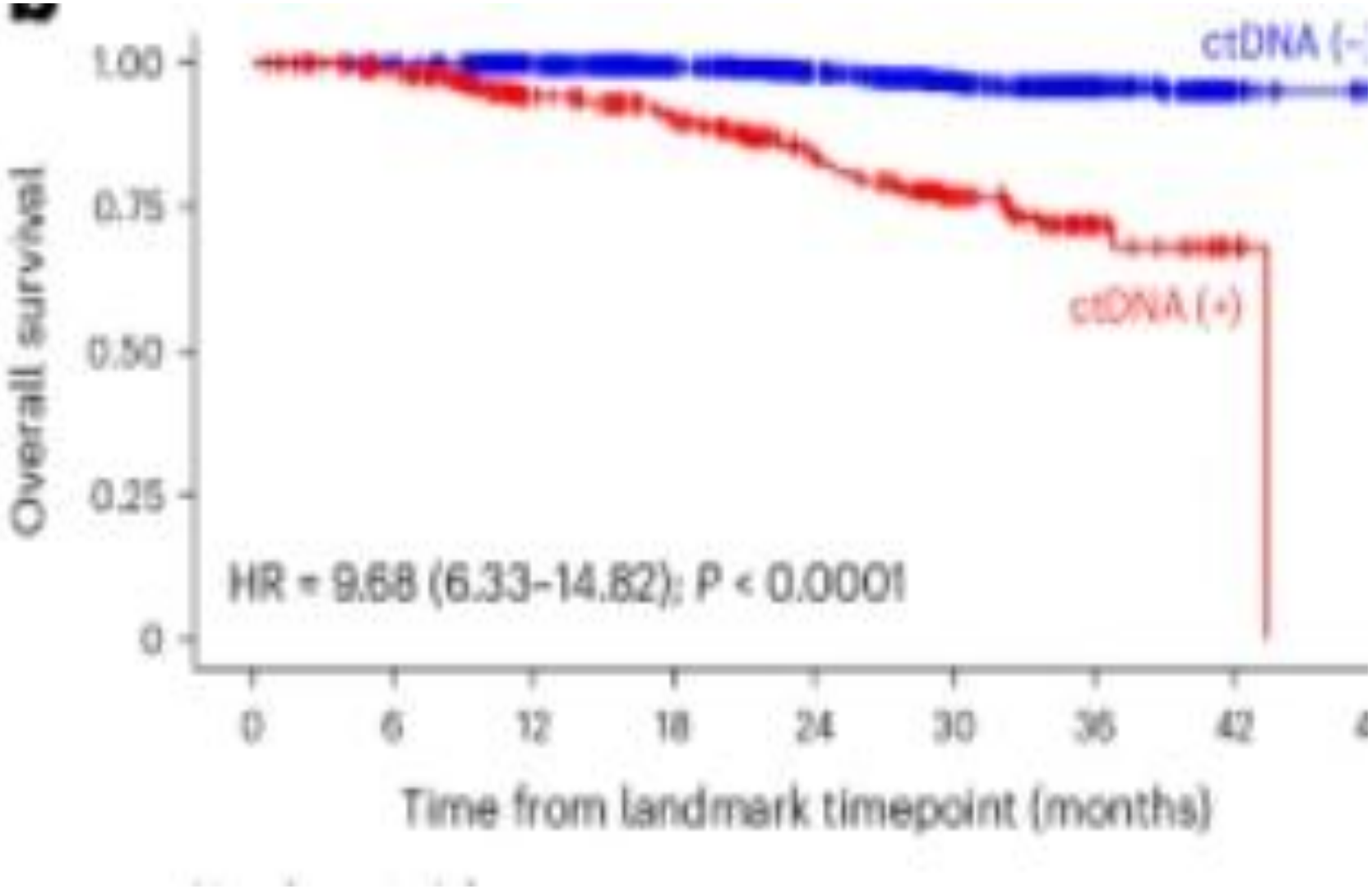
- Use of ctDNA in postoperative surveillance

ctDNA Prognostic Biomarker in Stages II & III CRC: DFI



Nakamura et al, Nature Med 2024; 30:3272

ctDNA Prognostic Biomarker in Stages II & III CRC: OS



Comparison of ctDNA With Established Prognostic Biomarkers in CRC

Factor	Hazard rate	P value
Patient age	0.98	NS
Performance status	1.27	NS
Tumor stage	1.56	NS
ctDNA	10.8	< 0.001

Kotani et al, Nature Med, 2023;29:127

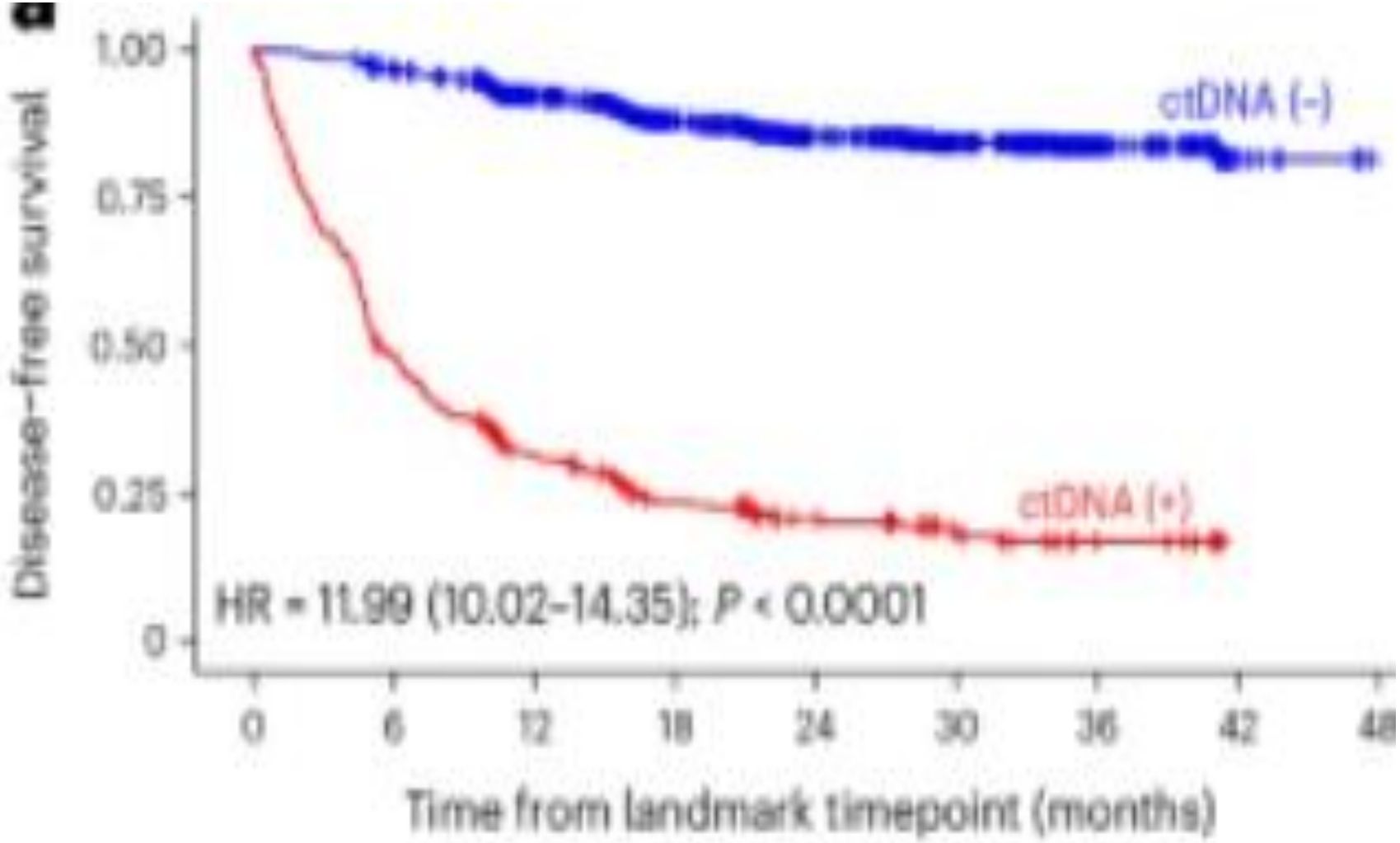
ctDNA vs CEA in Post-operative Surveillance Following Curative Surgery for CRC (Prospective study, n=125)

Characteristic	ctDNA*	CEA
Sensitivity	88%	69%
Specificity	98%	64%
Lead-time (median)	8.7 mo	0
Actionable mutations detected	81%	0

*16 patient specific mutations

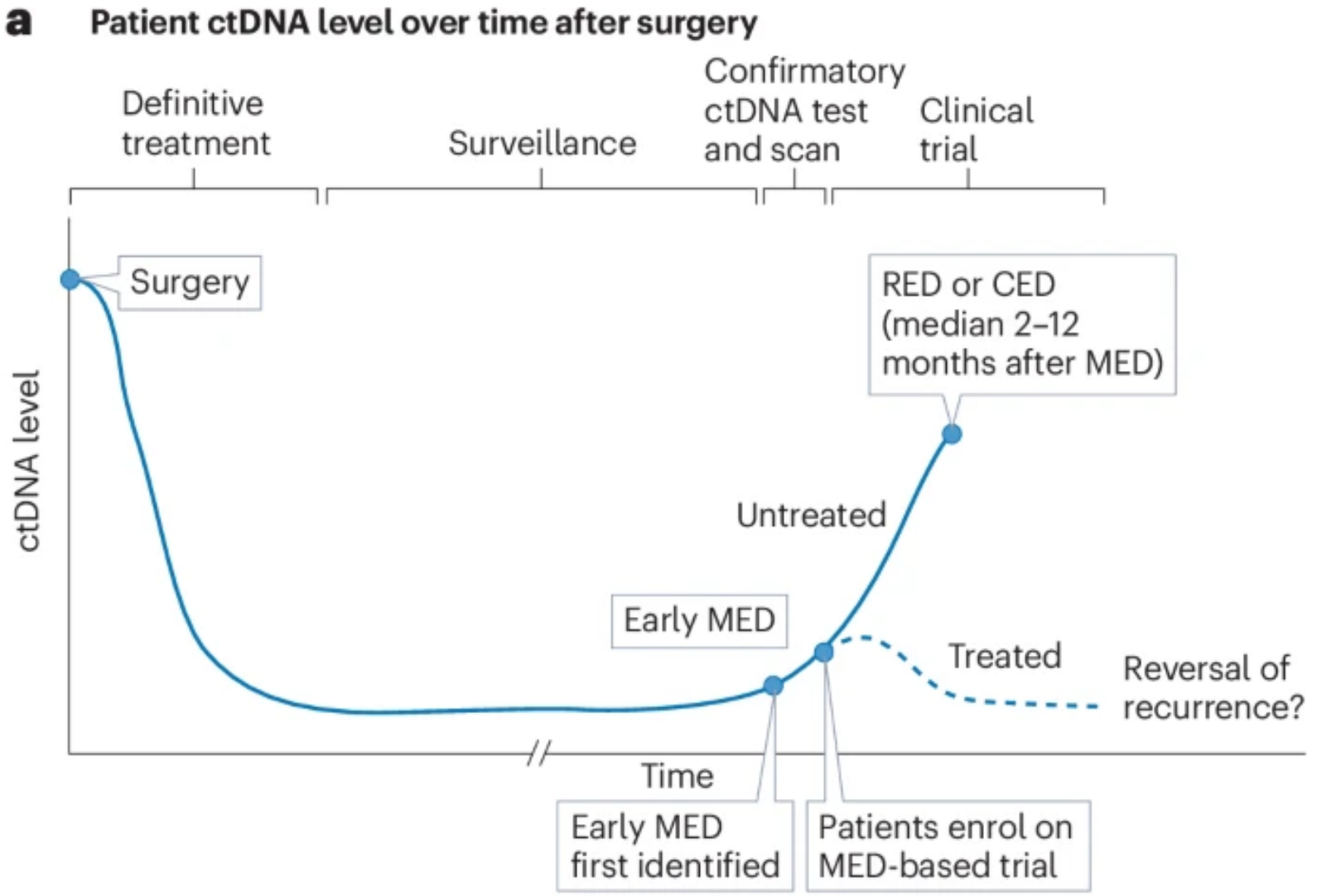
Reinert et al, JAMA Oncol 2019;5:1124

ctDNA Prognostic Biomarker in Stages II & III CRC: DFI



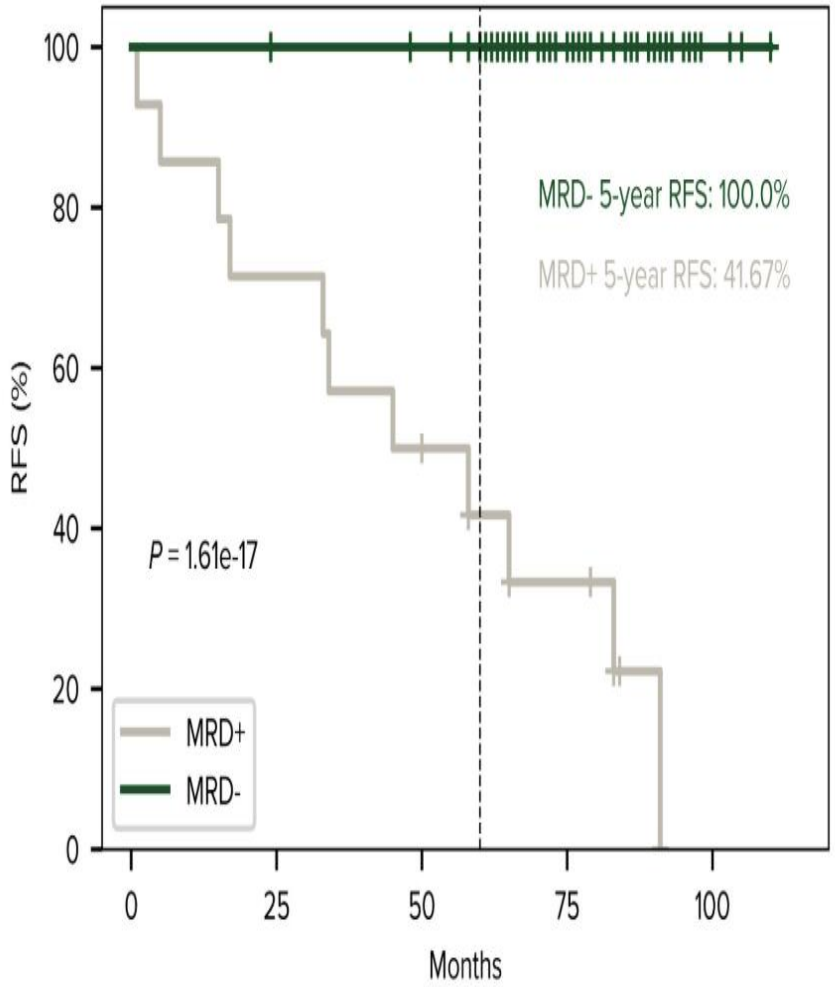
Nakamura et al, Nature Med 2024; 30:3272

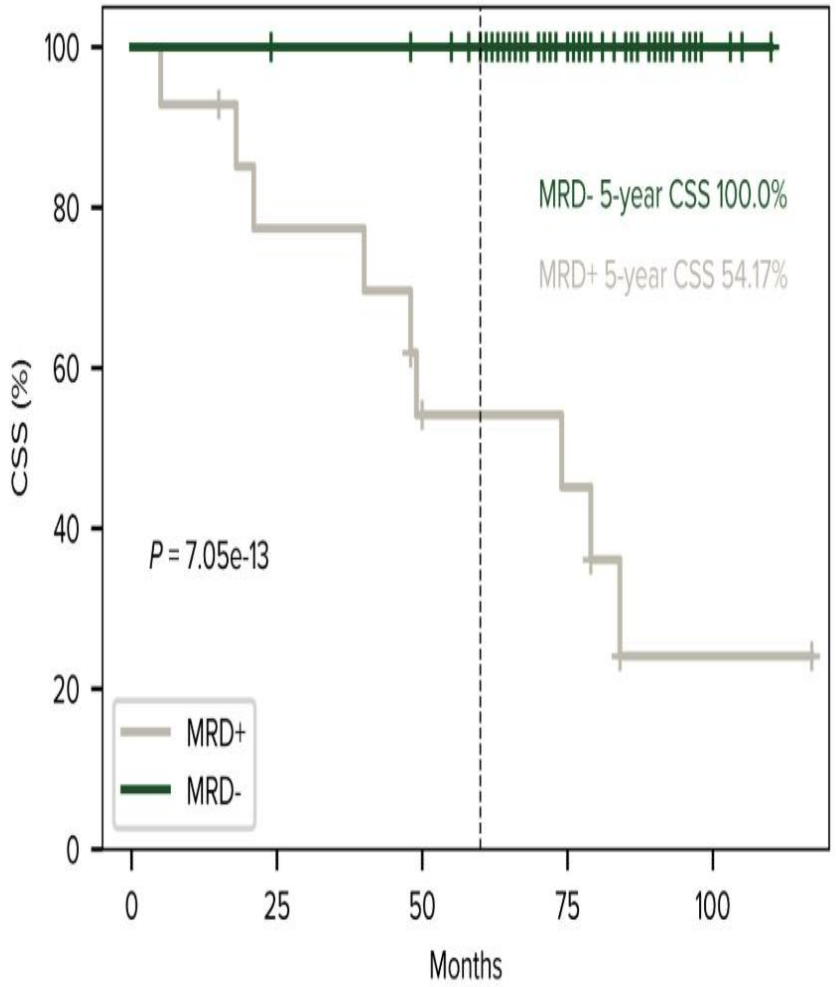
Fig. 2: Concept of early-molecular evidence of disease-based trials.



Medford et al. Nature Rev Cancer 2024:24:810

Prognostic Impact of Post-operative ctDNA in Breast Cancer (WGS)





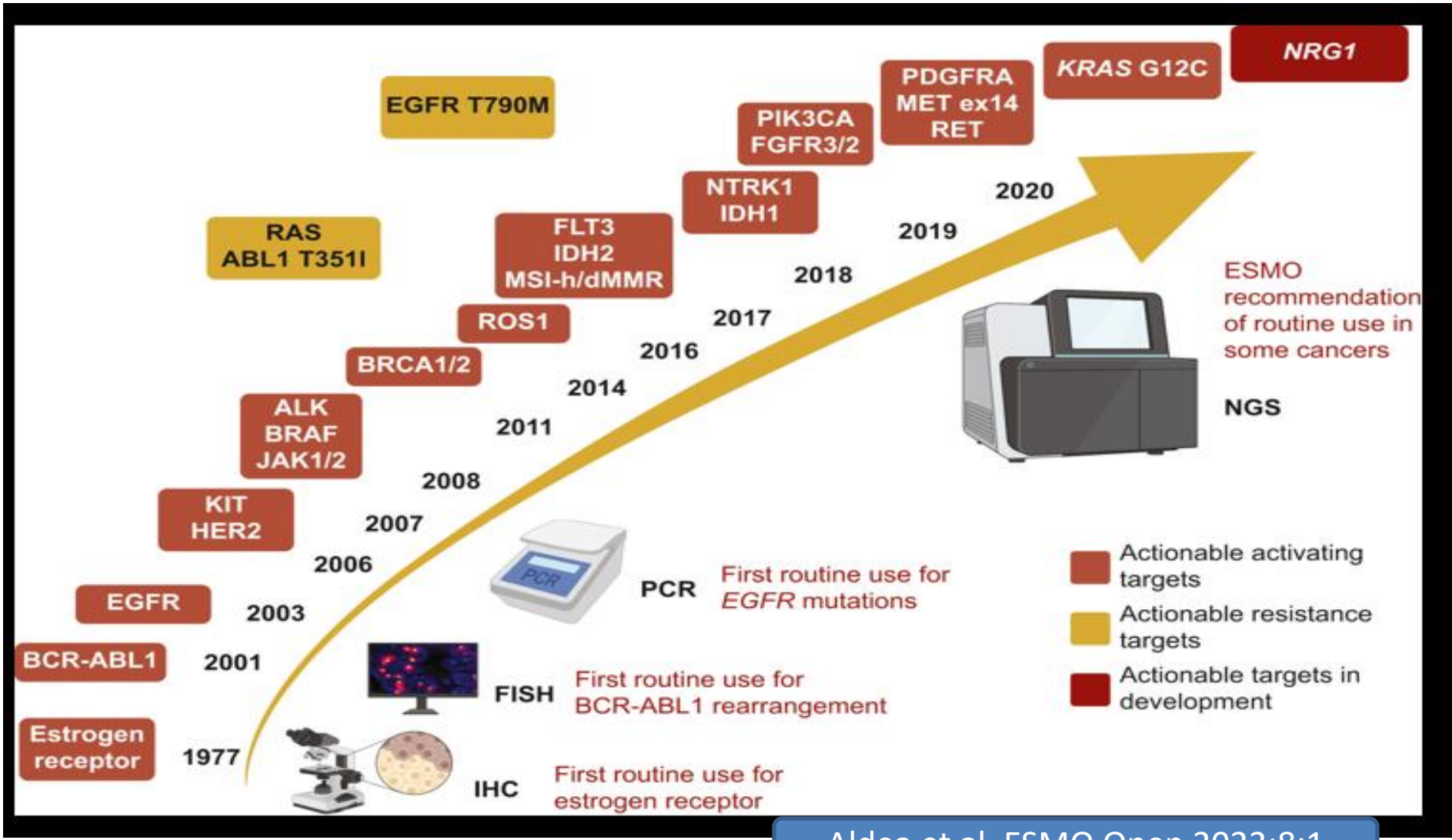
Garcai-Muriallas et al, Ann Oncol 2025;36:673

- **Use of ctDNA in predicting response to therapy**

Why We Need Therapy Predictive Biomarkers in Oncology

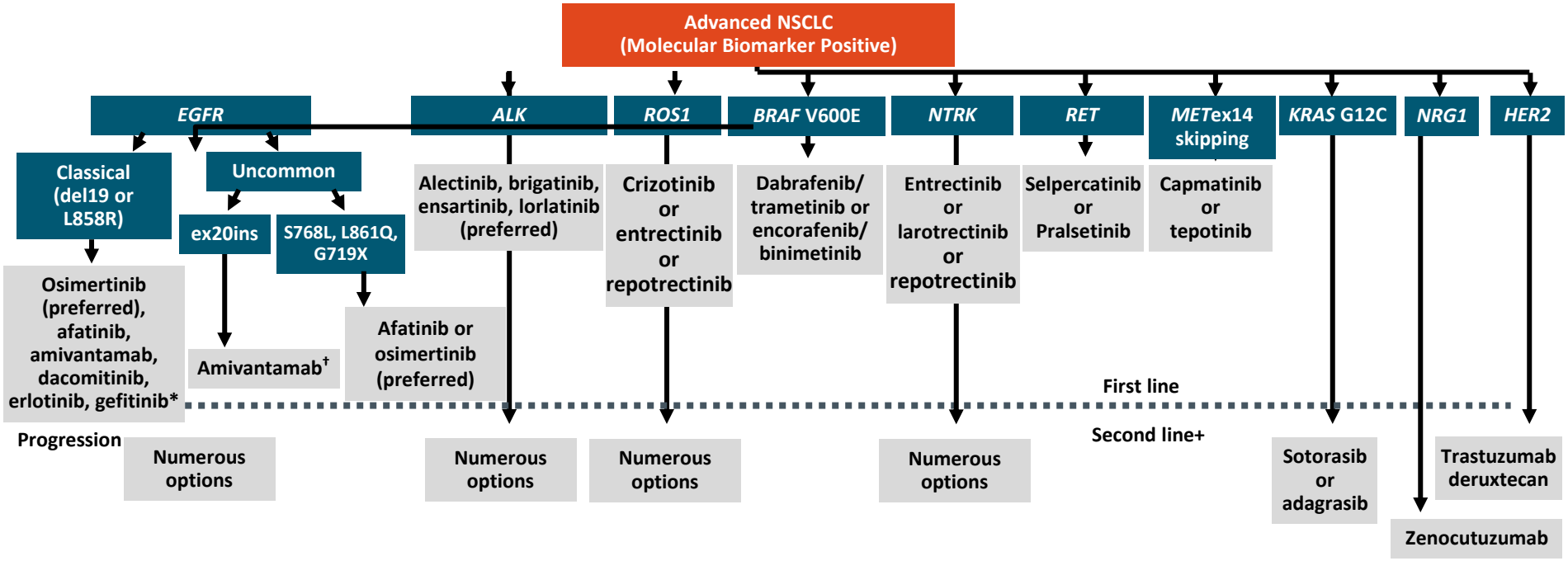
- Most anti-cancer therapies effective in a minority of patients treated
- Most anti-cancer therapies have adverse side effects
- Cancer therapies, especially the new treatments (targeted therapy, immunotherapy) are highly expensive

Therapy Predictive Biomarkers for Oncology Drugs



Aldea et al, ESMO Open 2023;8:1

Biomarker Testing and Targeted Treatment in Advanced NSCLC



*Amivantamab (other recommended) in combination with lazertinib; erlotinib alone or in combination with ramucirumab or bevacizumab. †With CT.

NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2025.

Slide credit: clinicaloptions.com

Tissue: Gold Standard Method for Predictive Biomarkers But Has Problems

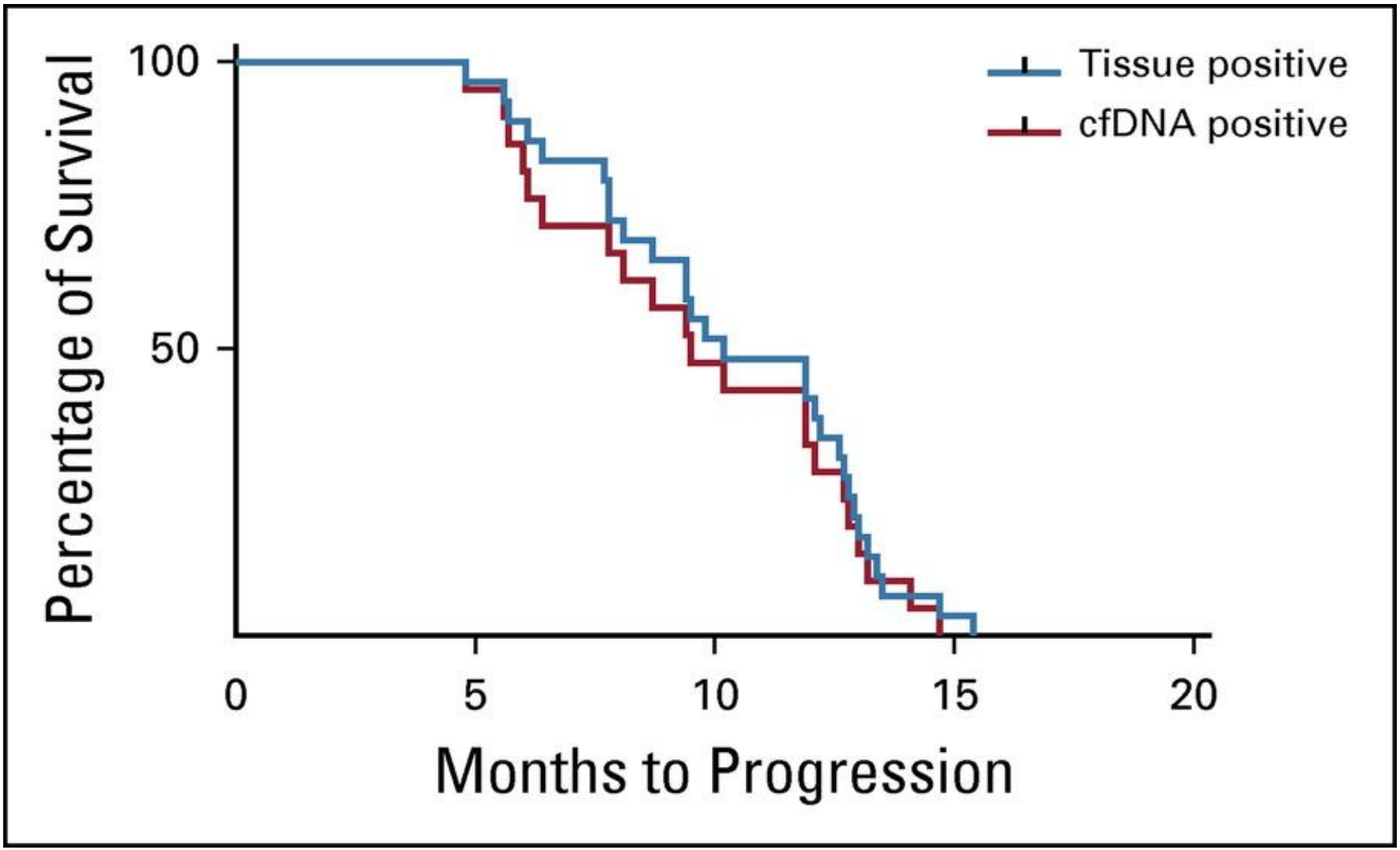
- Invasive (harmful, uncomfortable)
- May not be possible in all patients
- May not capture tumor heterogeneity
- Difficult to do serial measurements

Duffy & Crown, J Person Med 2022

Advantages of ctDNA vs Tissue

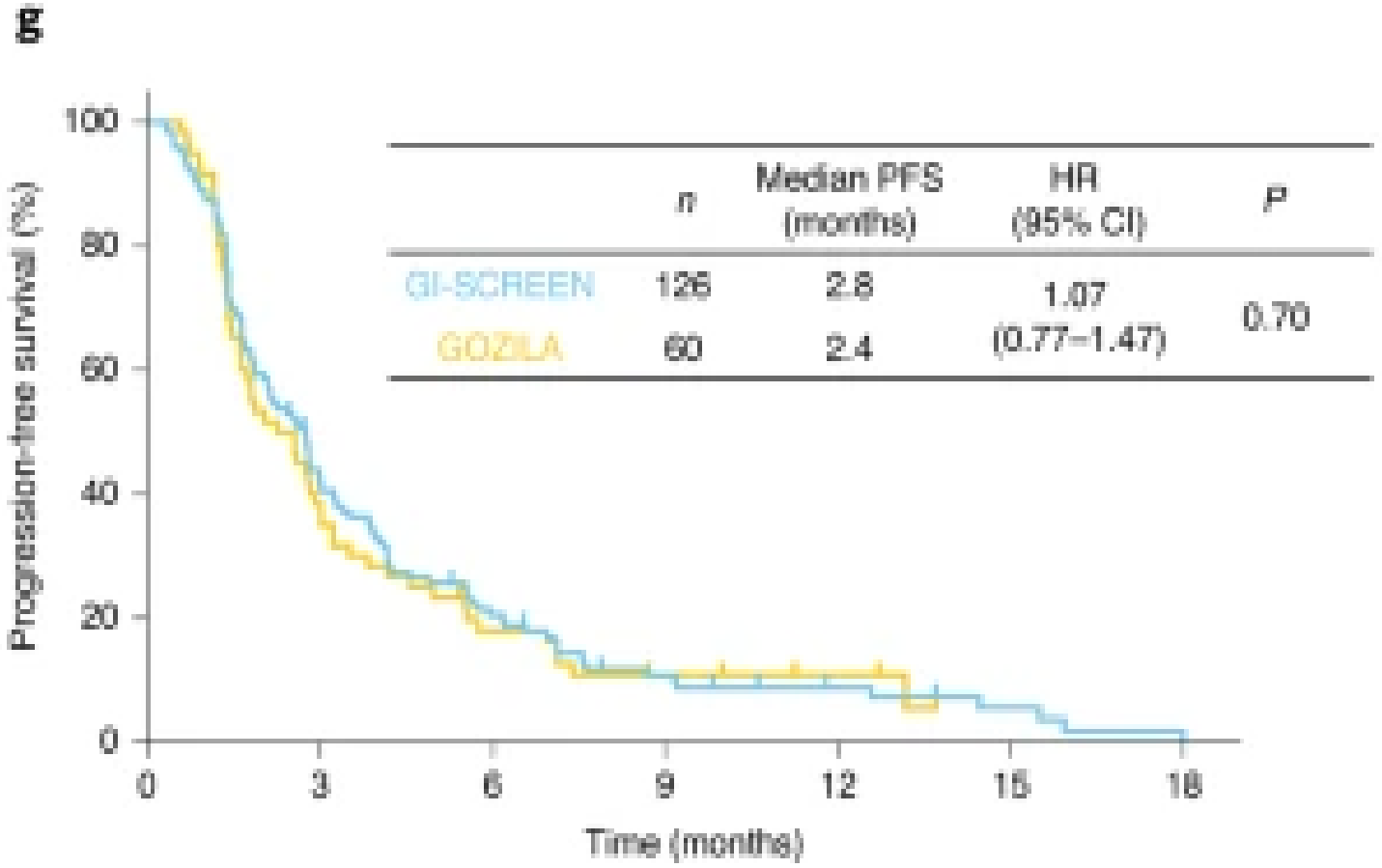
Advantage	Benefit to Patient
Minimally invasive	Safer, cheaper and more convenient
Allows serial monitoring	Provides real-time data as regards response to therapy
Faster TAT	More rapid availability of new therapy
Minimizes problem of tumor heterogeneity	Provides more global picture of mutations in primary and metastatic tumor(s)

Tissue vs ctDNA in NSCLC: Patient Outcome



Palmero et al, JCO Prec Oncol 2021;5:93

Predicting Outcome in Advanced GI Cancers; ctDNA vs Tissue Analysis



Nakamura et al, Nature Med 2020;26:1859

Problems With Clinical Use of ctDNA Assays

- Time consuming
- Expensive
- Difficult to automate
- Lacks standardization
- Additional training of lab staff
- Additional infrastructure

"ctDNA is here to stay and transform our practice, and we haven't even tapped into most of the potential."

PEDRAM RAZAVI, MD, PHD

SABCSMeetingNews.org

- Thank you