

LEVERAGING LIQUID BIOPSY IN LUNG CANCER

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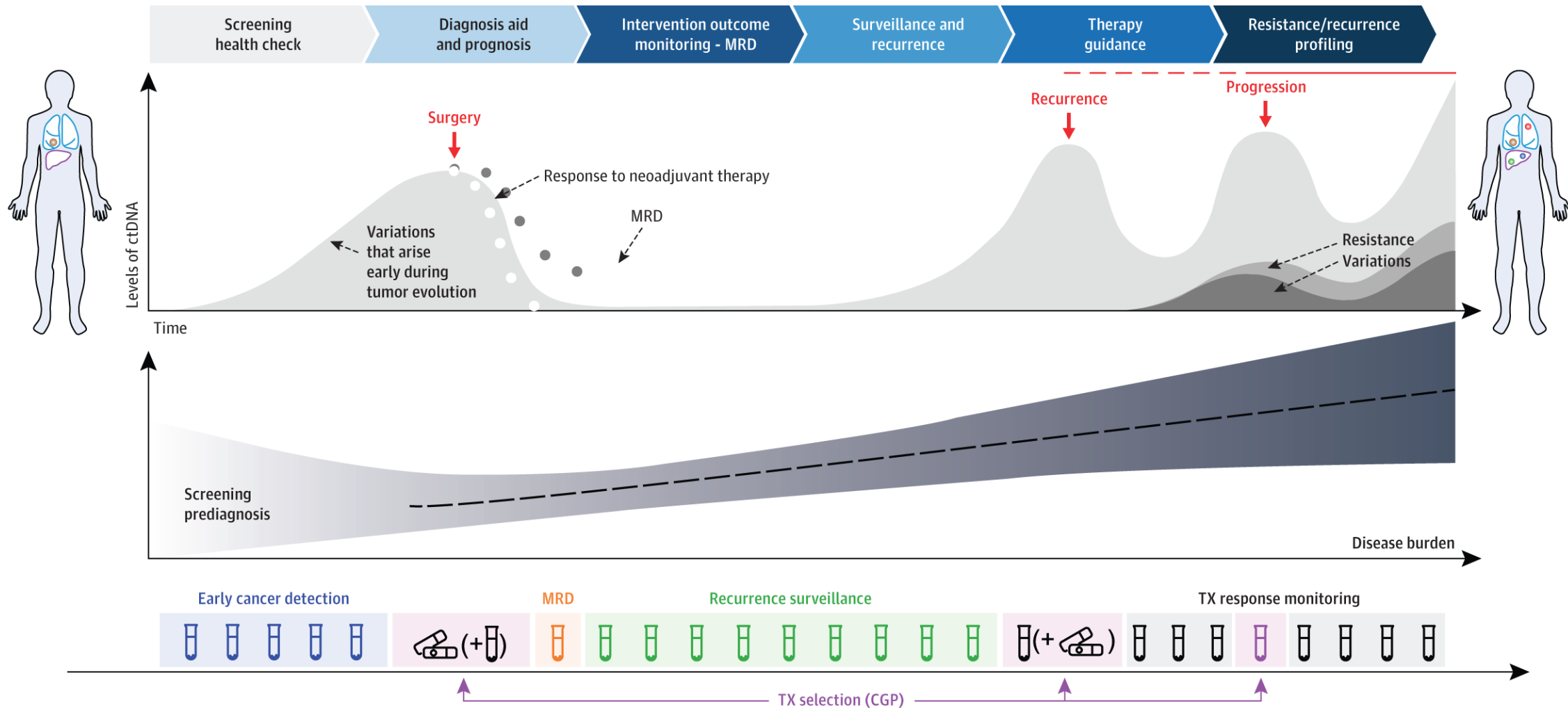


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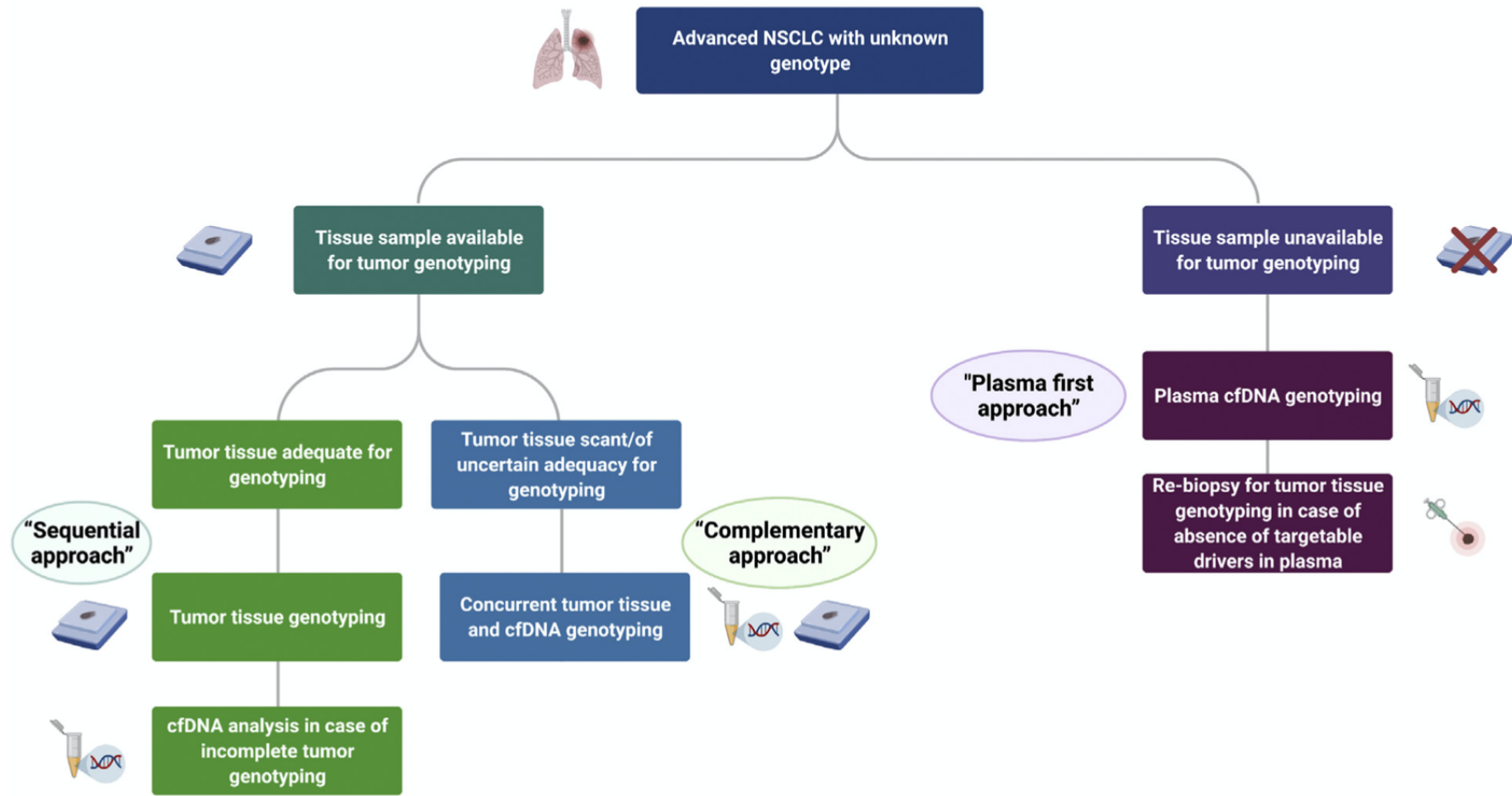




Krebs et al (Rolfo), JAMA Oncology OCT 2022

What we are doing currently... or expected

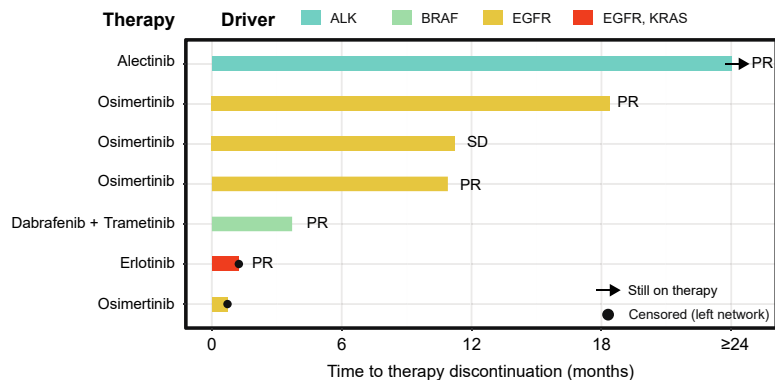
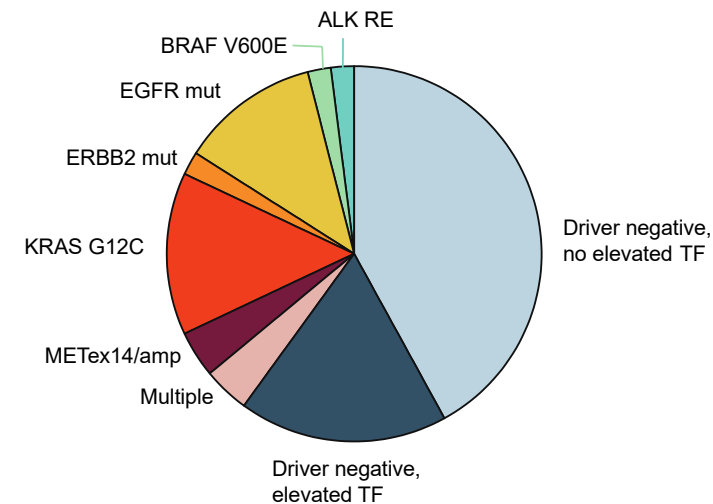
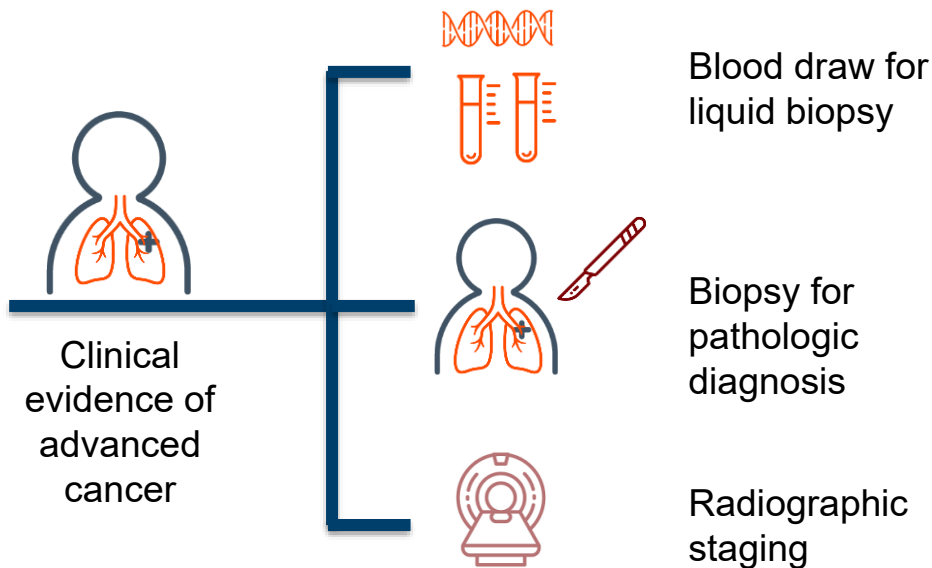
Diagnostic algorithm for liquid biopsy use in treatment-naive advanced/metastatic NSCLC



Rolfo et al, JTO 2021 Oct;16(10):1647-1662

How we can speed the process and access to treatment?

Stacking diagnostic steps may be able to shorten the diagnostic odyssey

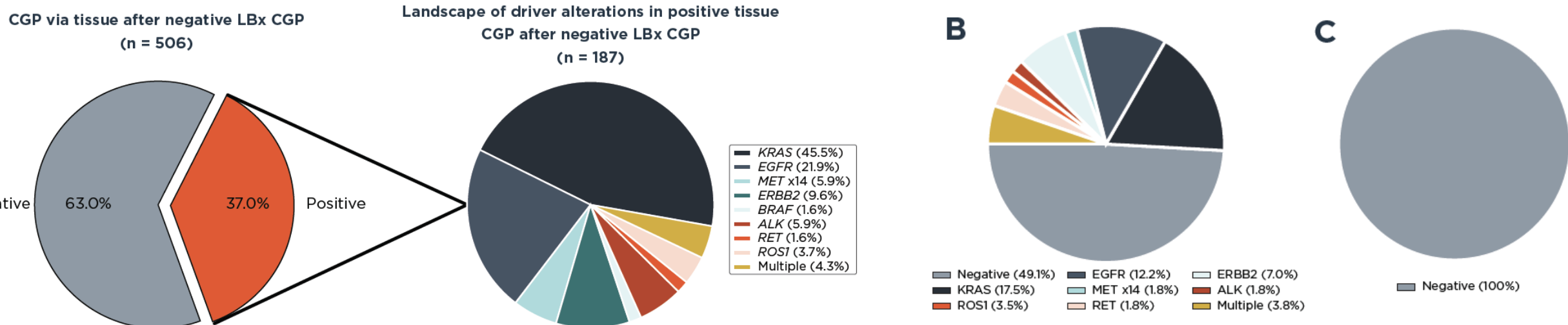


36% of early LBx samples were positive for an actionable NCCN driver

Russo A. et al (Rolfo C.) JCO PO, Feb 2024

How we identify *non shedders* than non informative LB?

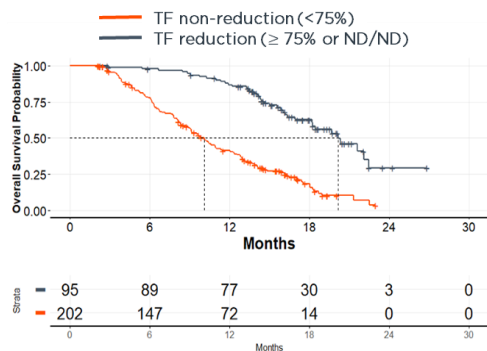
Tumor Fraction Identifies Informative Negative Liquid Biopsy Results



Patients with lung cancer with negative LBx and ctDNA TF $\geq 1\%$ are unlikely to have a driver detected on confirmatory tissue testing; such informative negative results may benefit instead from prompt treatment initiation.

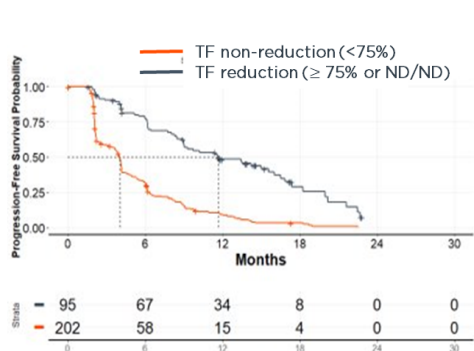
Tumor Fraction a potential Biomarker? Predictive, Prognostic?

B.) FILCDx Tumor Fraction Kinetics Associated OS



20.2 vs. 10.1 months median
HR = 3.93 [2.73 - 5.67]

E.) FILCDx Tumor Fraction Kinetics Associated rPFS



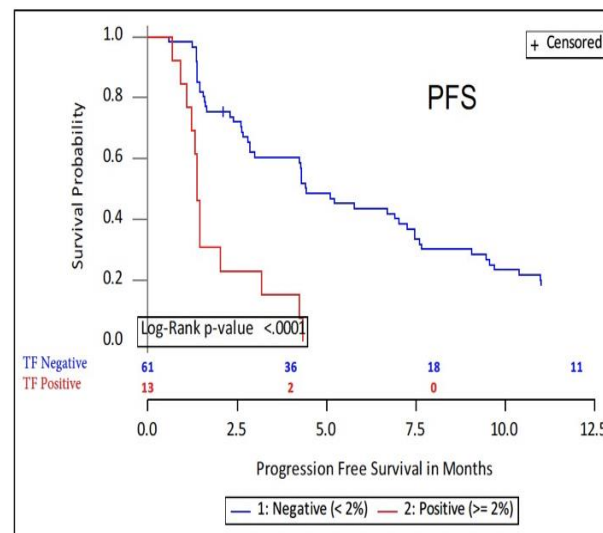
11.8 vs. 4.0 months median
HR = 3.61 [2.66 - 4.90]

C.) PSA Response Associated OS

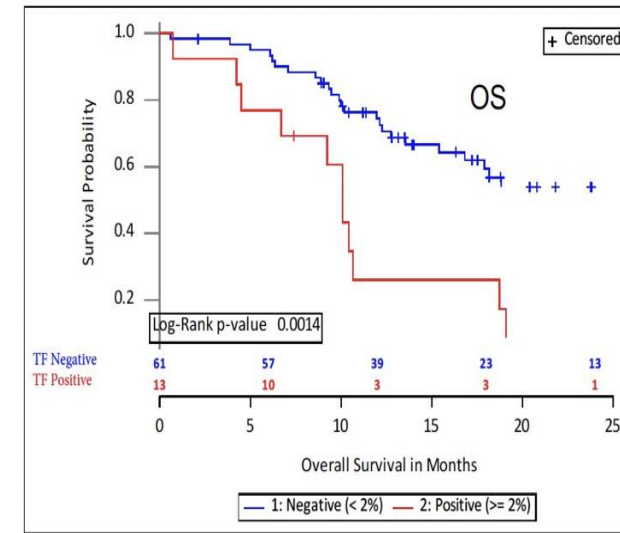
20.2 vs. 11.7 months median
HR = 2.82 [1.87 - 4.26]

F.) PSA Response Associated rPFS

11.4 vs. 4.1 months median
HR = 2.60 [1.86 - 3.63]



mPFS 4.4 vs 1.4



mOS 25.5 vs 10.1

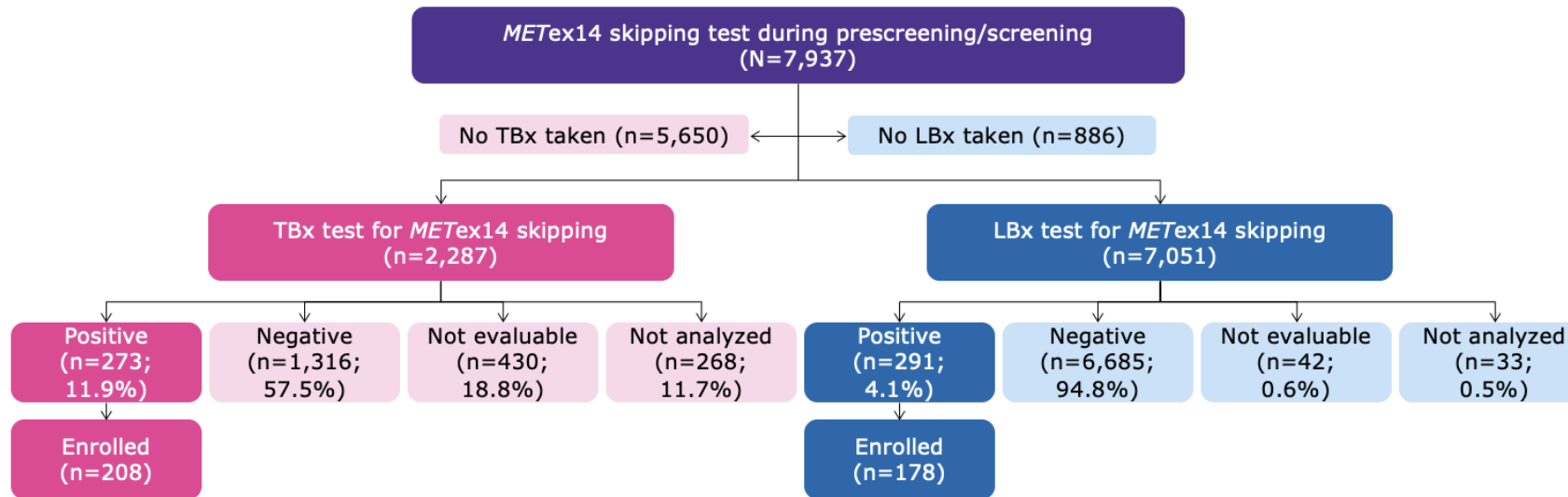
IMbassador250, metastatic castrate-resistant prostate cancer

TF and survival in advanced NSCLC treated with maintenance durvalumab in the UNICANCER SAFIR02-Lung/IFCT1301 trial.

AACR 2023, Sweeney et al. ; Dall'Olio et al, ASCO 2023

How we integrate LB in Clinical trials Design?

Phase II VISION study of tepotinib in MET exon 14 Skipping mutation

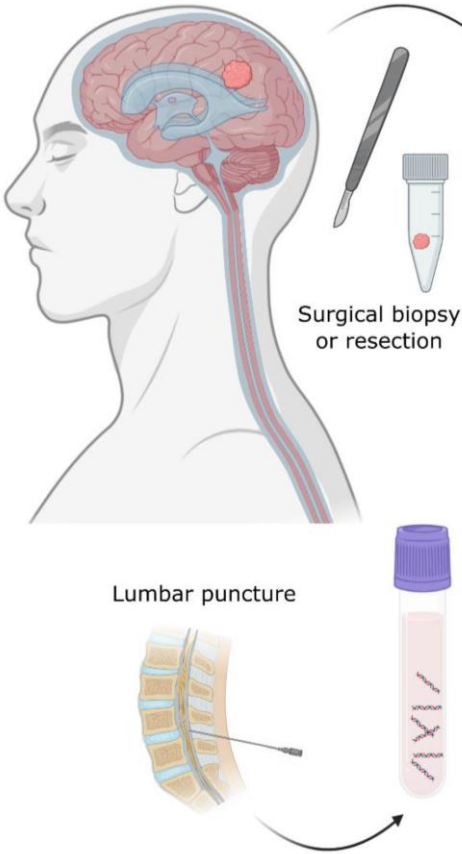
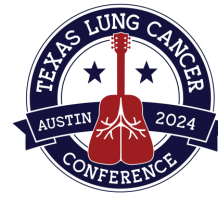


IRC	1L		+2L	
	T+/L- (n=52)	T+/L+ (n=42)	T+/L- (n=54)	T+/L+ (n=32)
ORR, % (95% CI)	57.7 (43.2, 71.3)	64.3 (48.0, 78.4)	44.4 (30.9, 58.6)	53.1 (34.7, 70.9)
mDOR, months (95% CI)	ne (10.4, ne)	19.4 (7.6, ne)	12.6 (5.1, 20.8)	9.9 (4.4, 15.4)
mPFS, months (95% CI)	22.1 (14.8, ne)	12.1 (7.8, 49.7)	13.8 (8.2, 24.9)	8.2 (5.5, 13.7)
mOS, months (95% CI)	32.7 (15.3, ne)	28.5 (14.2, ne)	20.8 (15.6, 32.5)	19.8 (10.0, 26.5)

Rolfo et al, ASCO 2023, in press

Special Situations: Brain metastasis in TKI resistance

CSF Demonstrates Superiority of Cell-Free DNA over Cell Pellet Genomic DNA for Molecular Profiling



Solid biopsy (tumour specimen)

Advantages
Allow histological diagnosis

Limitations
Very invasive and risky procedure
Sometimes not feasible due to tumour anatomical location
Not representative of tumour heterogeneity
Static snapshot

Liquid biopsy (CSF ctDNA)

Advantages
Less-invasive and easier to obtain than a tumour biopsy
CSF obtained as SOC for some patients
Concordance with tissue characterisation
Representative of intratumour and interlesion heterogeneity
Longitudinal real-time monitoring

Limitations
No histological characterisation
Lack of standardisation
Contraindications for lumbar puncture
Limited sensitivity

Effective in establishing CNS involvement:

- >97% cases with mutational profile matching primary tumor
- >70% of cases profiled had mutations

New findings compared with primary tumor in >17% demonstrating:

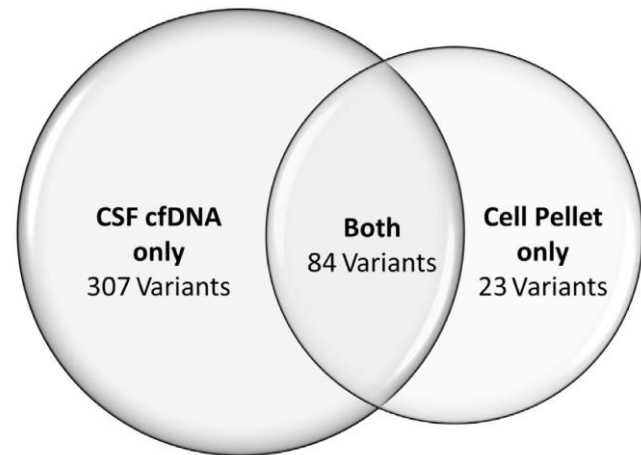
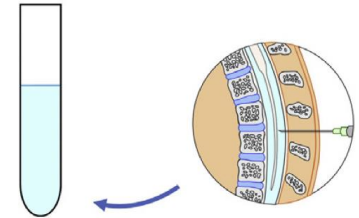
- Resistance mechanisms
- Clonal evolution
- New primary diagnoses

More informative than tumor cell profiling from same CSF sample

- Higher success
- More variants detected
- Higher variant frequency

Meaningful results generated even in samples with:

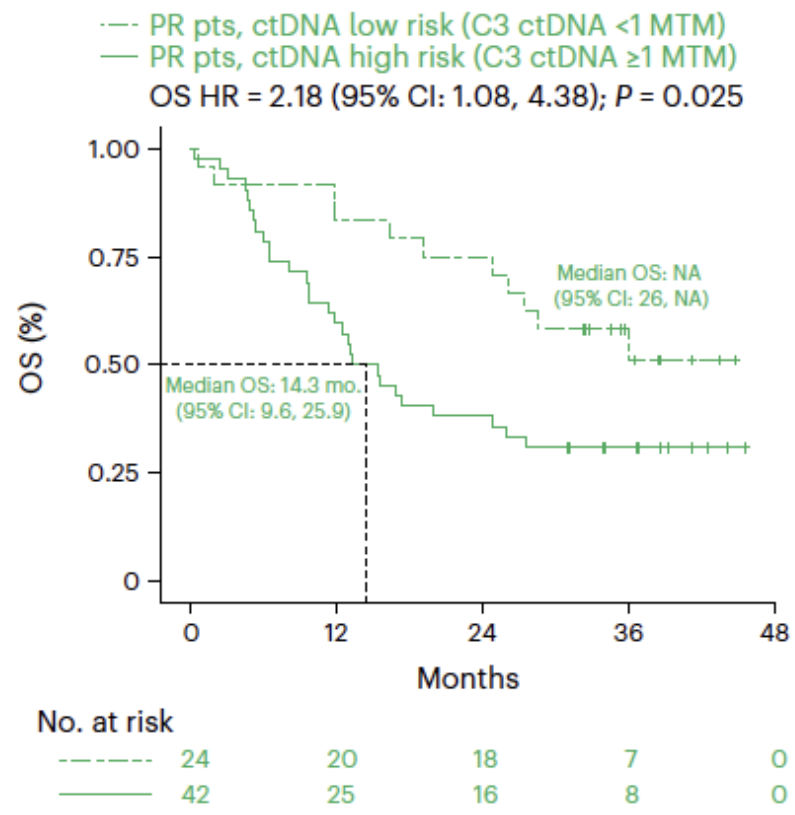
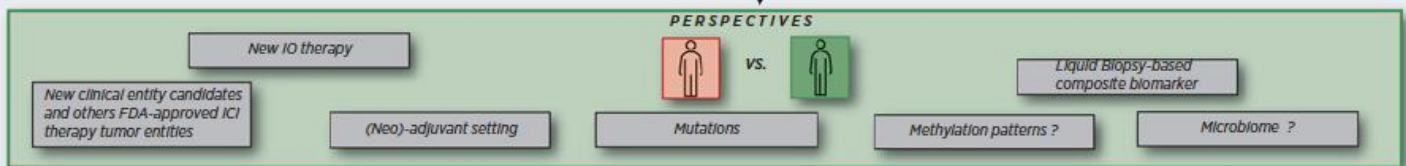
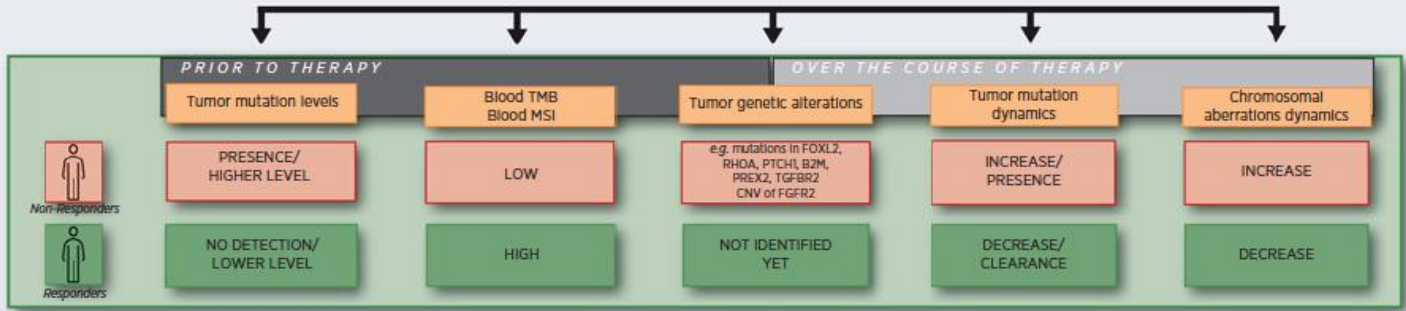
- Very Low input DNA
- Normal CSF cytology



Escudero et al, *Cancers* 2021, 13(9), 1989; Bale et al (Arcila M.) *J Mol Diagn* . 2021 Jun;23(6):742-752

Use of Liquid Biopsy in Immunotherapy

Dynamics, Clearance and more...



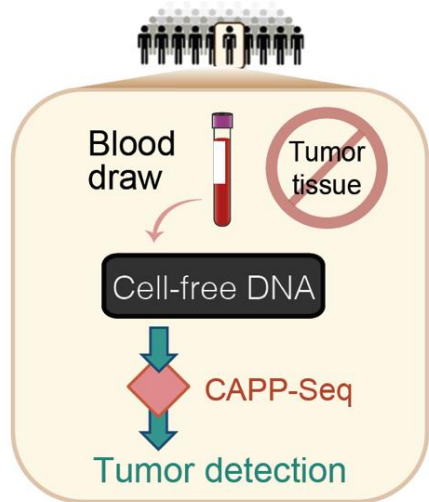
Important implications in new clinical trials design: escalation and de-escalation

Stadler J, et al. *Cancer Res* 2022 ; Assaf ZJF, et al. *Nat Med.* 2023;29(4):859-868.

Different types of ctDNA MRD Assays

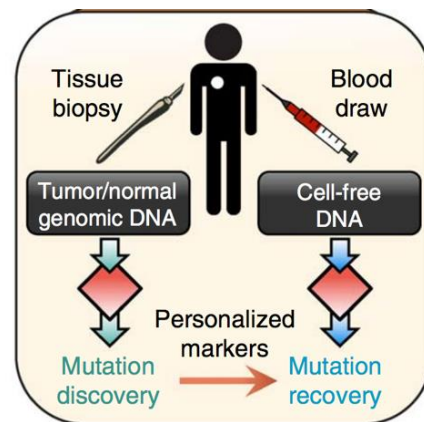
And different sensitivity....

Tumor-naive



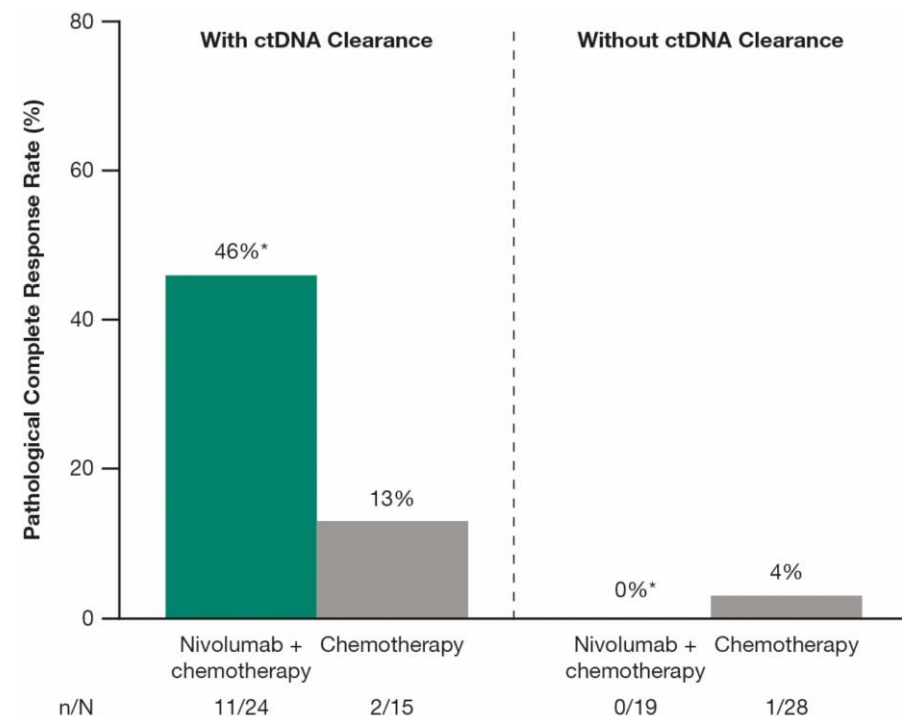
- Genotyping with no knowledge of tumor mutations (“off the shelf”)
- Faster, less expensive
- Limit of detection ~0.1%

Tumor-informed



- Tracking multiple known mutations (bespoke or personalized)
- Requires tumor tissue, time, \$\$
- Limit of detection ~0.01%

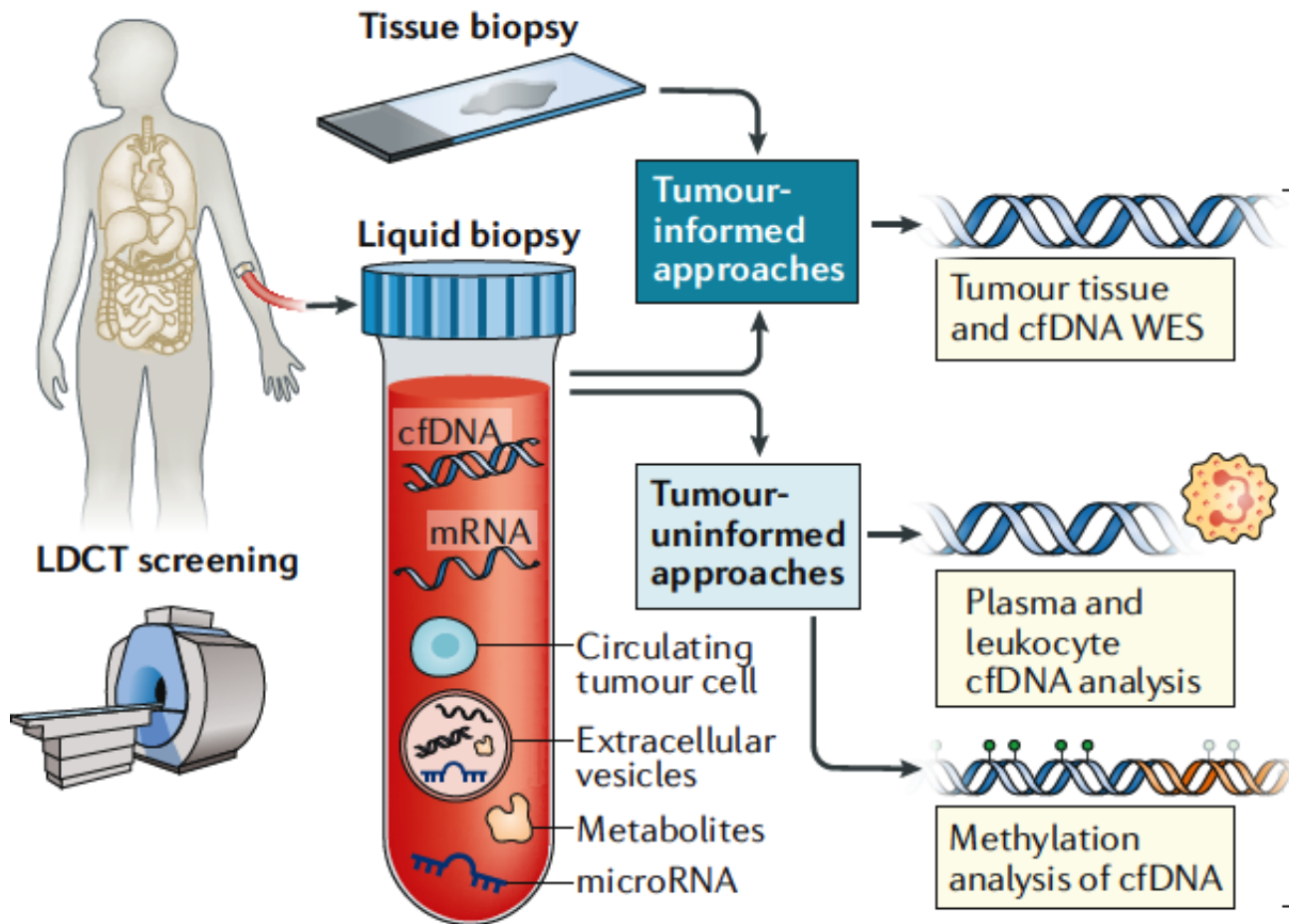
Use in Early Stage perioperative



Forde PM, NEJM 2023

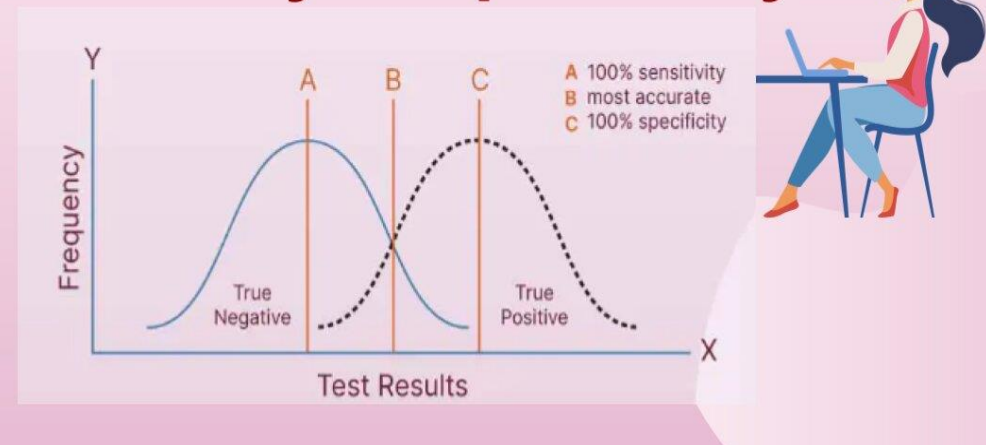
Courtesy Dr. Natasha Leighl

Are we **really** ready for LB in Early Detection?



To Remember...

Difference Between Sensitivity & Specificity

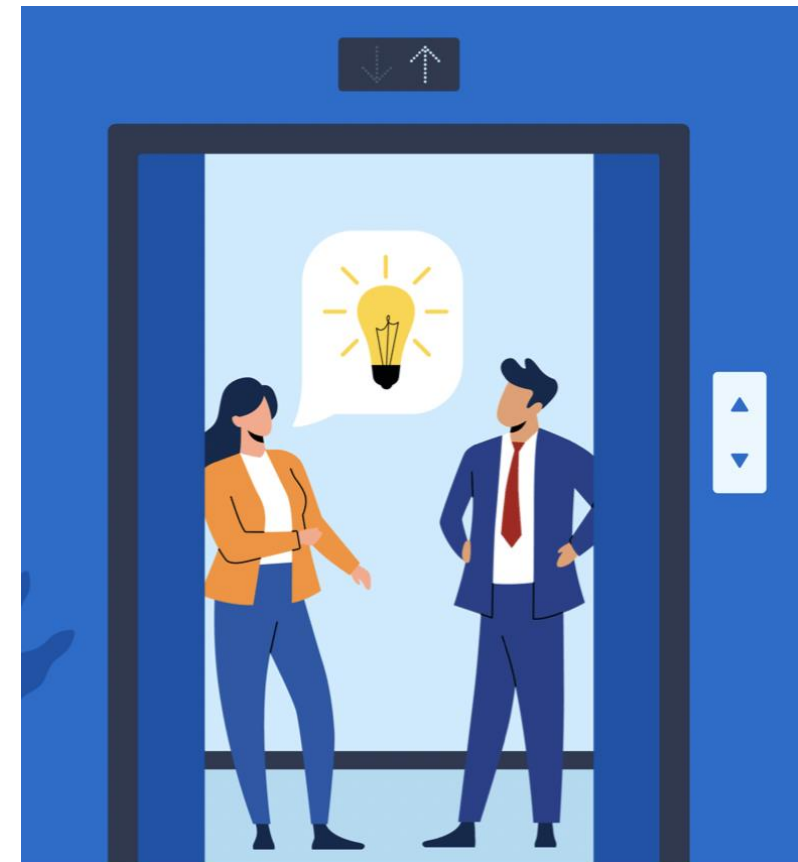


References *Rolfo C & Russo A. Nat Rev Clin Oncol 2020*

Take Home message... My elevator pitch

- **Liquid Biopsy is a perfect tool for Advance Disease, MRD**
- **Important opportunity for LB in Immunotherapy treatment**
- **Detecting MRD is crucial to improve survival and disease control rates (knowing differences between assays and sensitivity it's also crucial!)**
- **Integrating liquid biopsy in clinical trials is a necessity**
- **Early detection: good intentions, we are not when we would like to be yet.**

References





6TH ANNUAL CONGRESS
Liquid Biopsy
November 23-25, 2024 • Denver, Colorado, USA

See You at

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in Denver, Colorado, USA

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