ctDNA in Lung Cancer: Current State and Future Perspectives

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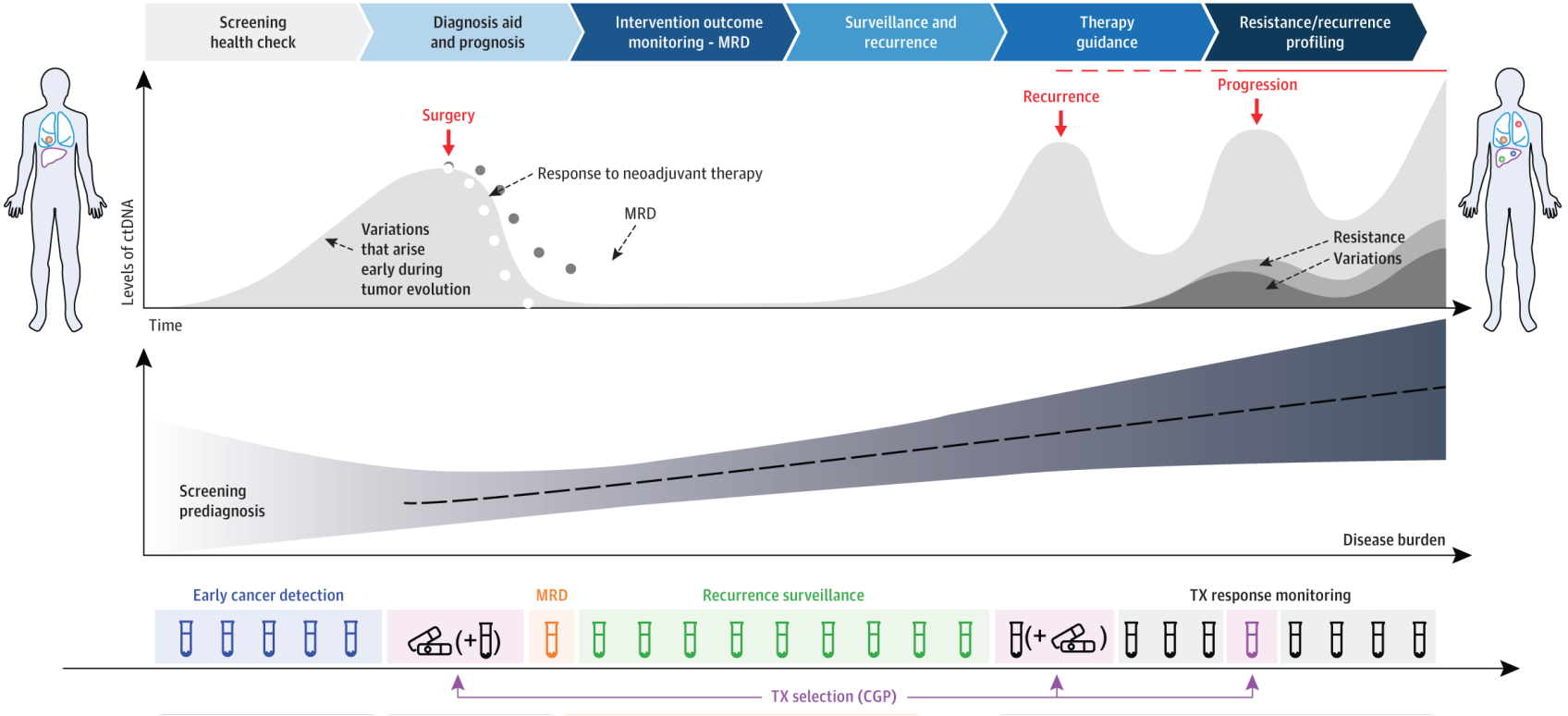
ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

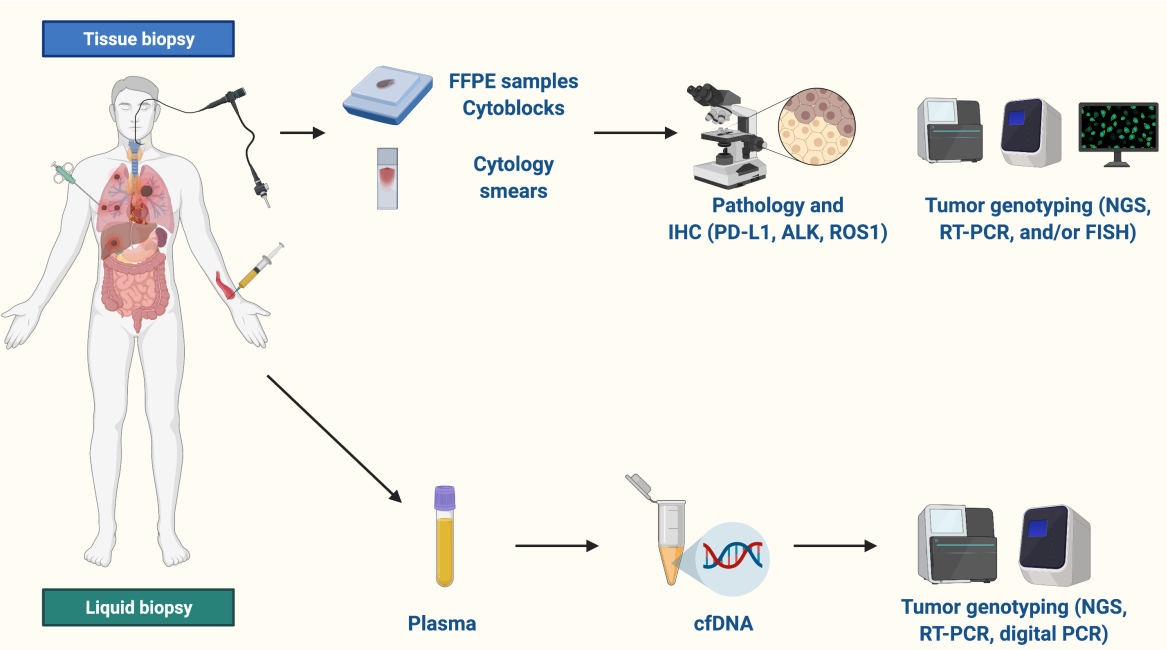
Center for Thoracic Oncology

Mount Sinai
The Tisch Cancer Institute



Krebs et al (Rolfo), JAMA Oncology OCT 2022

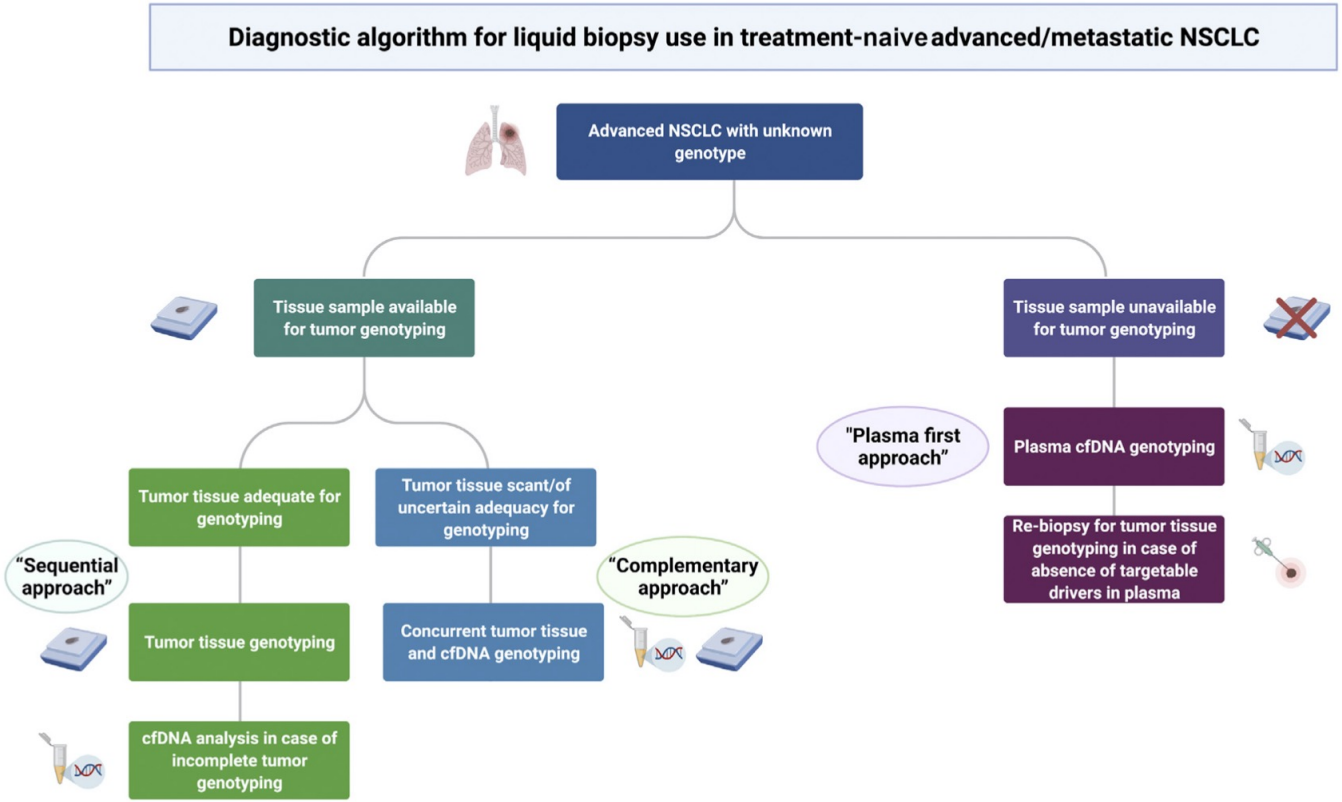
Tissue vs. Liquid biopsy



	Advantages	Disadvantages
Tissue biopsy	✓Pathology information ✓Assessment of DNA and non-DNA biomarkers ✓PD-L1 assessment	✓Longer TAT ✓Limited tissue quantities ✓Invasive ✓At PD, re-biopsy not always feasible ✓Tumor heterogeneity
Liquid biopsy (cfDNA)	✓High concordance rate ✓ Rapid TAT ✓Minimally invasive ✓Repeatable over time ✓Better capture tumor hetereogenity and clonal evolution	✓Non-DNA biomarkers not evaluable ✓Increased costs if used concurrently with tissue testing ✓False negatives

Rolfo C, *et al. J Thorac Oncol* 2021;16(10):1647-1662.

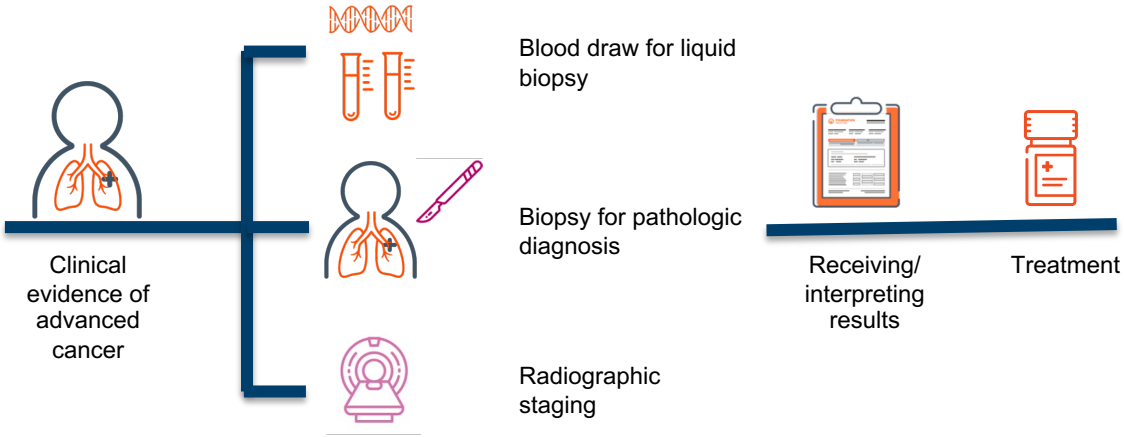
What we are doing currently… or expected

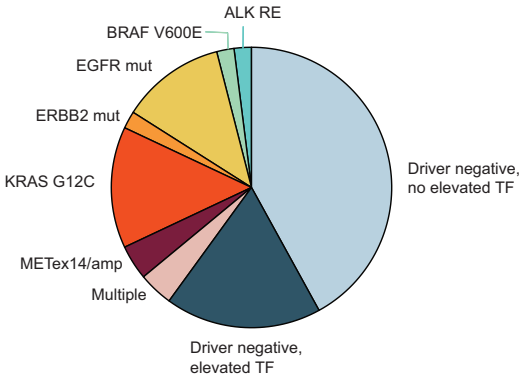


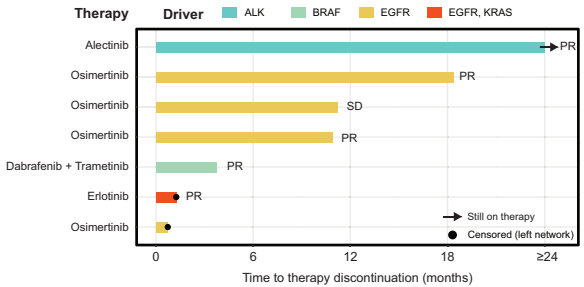
Rolfo et al, JTO 2021 Oct;16(10):1647-1662

How we can speed the process and access to treatment?

Stacking diagnostic steps may be able to shorten the diagnostic odyssey







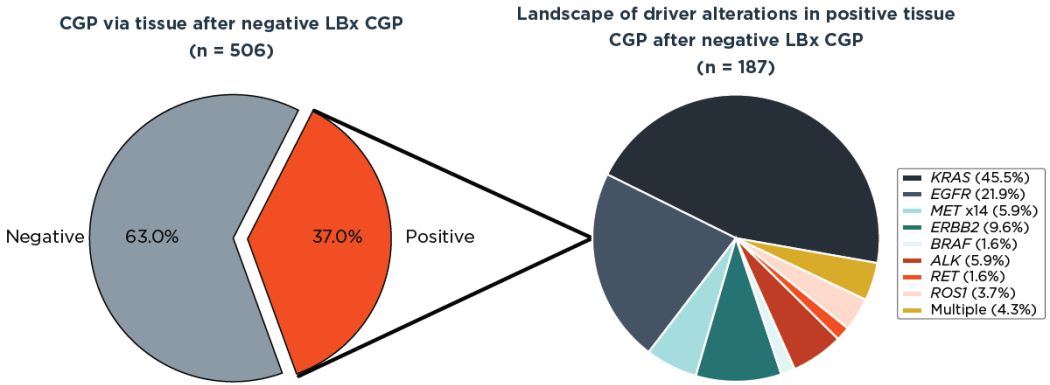
36% of early LBx samples were positive for an actionable NCCN driver

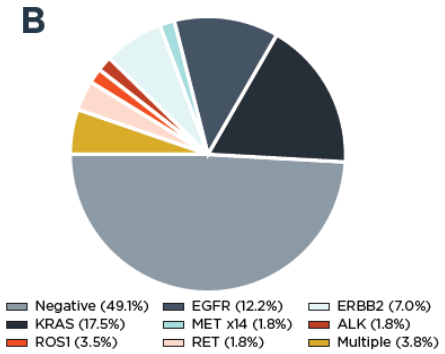
References

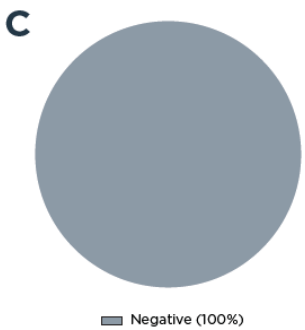
Russo A. et al (Rolfo C.) JCO PO, Feb 2024

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

Tumor Fraction Identifies Informative Negative Liquid Biopsy Results





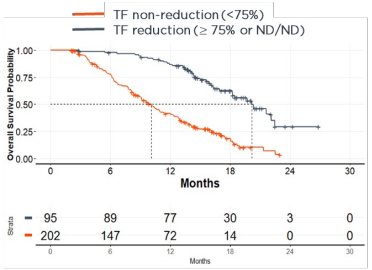


Patients with lung cancer with negative LBx and ctDNA TF ≥1% are unlikely to have a driver detected on confirmatory tissue testing; such informative negative results may benefit instead from prompt treatment initiation.

References : Rolfo C et al, Clin Cancer Research, April 10, 2024

Tumor Fraction a potential Biomarker? Predictive, Prognostic?

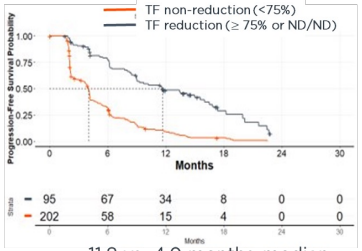
B.) F1LCDx Tumor Fraction Kinetics Associated OS



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

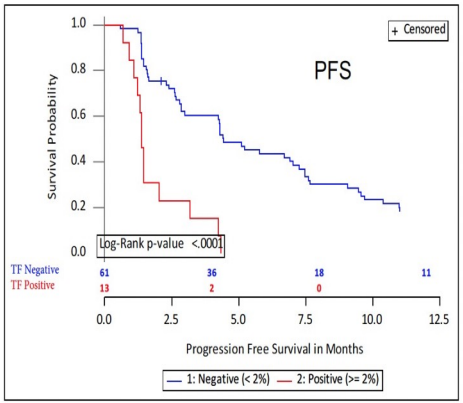
C.) PSA Response Associated OS
20.2 vs. 11.7 months median
HR = 2.82 [1.87 -4.26]

E.) F1LCDx Tumor Fraction Kinetics Associated rPFS

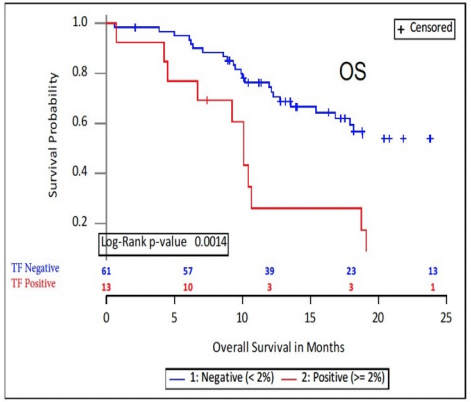


11.8 vs. 4.0 months median
HR = 3.61 [2.66 - 4.90]

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

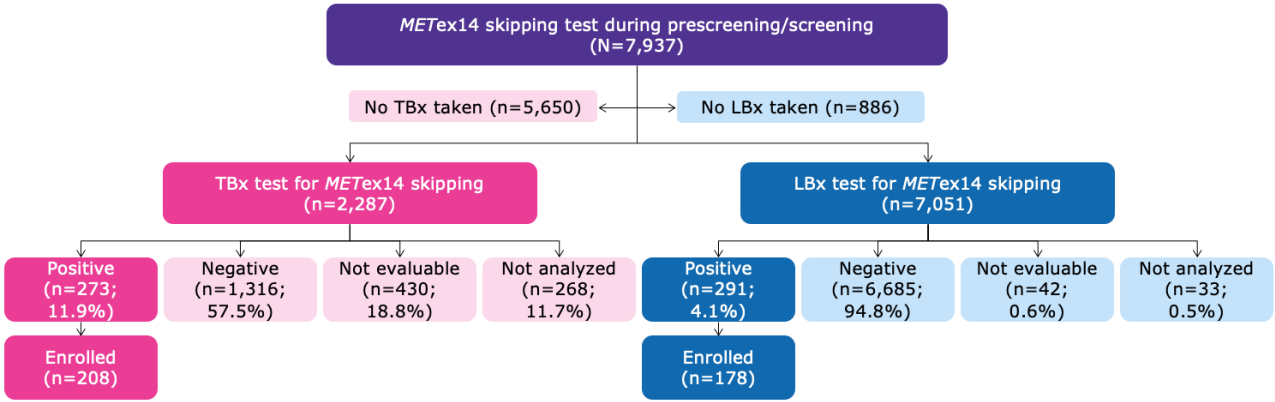
IMbassador250, metastatic castrate-resistant prostate cancer

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

References: 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

Liquid biopsy can capture the dynamic evolution of resistance mechanisms to EGFR TKIs

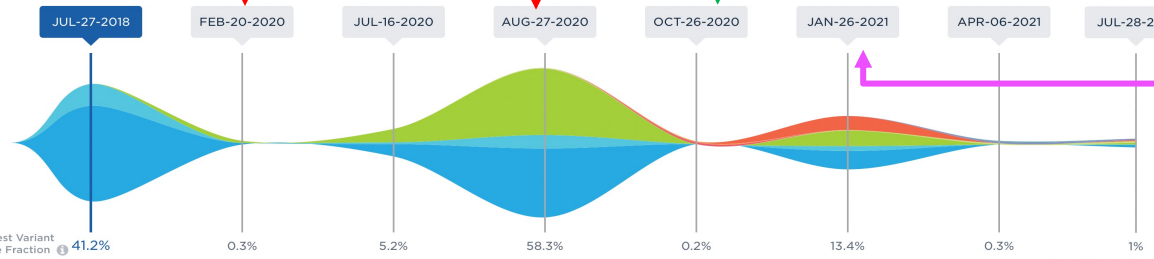
Osimertinib start with an intracranial CR and extracranial PR

After 18 mos oligo-PD (LN mets) → SBRT and continued osi

Further disease progression → osimertinib stopped; switch to erlotinib

PET/CT in Nov. 2020: CR

52-year-old never smoker female; diagnosed in July 2018 with cT4 N3 M1c lung adenocarcinoma (stage IVB).



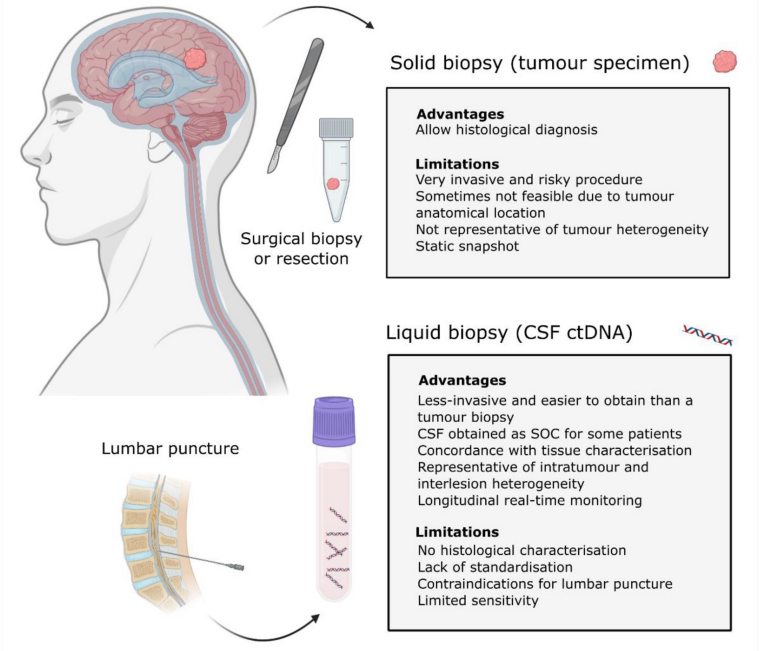
Erlotinib discontinuation → platinum-based chemo start

Genetic Alteration	% cfDNA or amplification							
EGFR E746_A750del	41.2%	0.3%	4.7%	58.3%	ND	13.4%	ND	1%
EGFR C797S	ND	0.3%	5.2%	55.6%	ND	10.7%	ND	0.7%
ARID1A Q456Q	ND	ND	ND	0.2%	ND	0.2%	0.3%	0.6%
EGFR T790M	ND	ND	ND	ND	ND	9.6%	ND	0.4%
TP53 C275Y	ND	ND	ND	ND	ND	ND	0.1%	0.2%
ARID1A F1728F	ND	ND	ND	ND	ND	ND	0.3%	0.2%
TP53 S127F	6.5%	ND	0.4%	7.6%	ND	2.6%	ND	0.2%
***BRAF* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND	ND	ND	ND
***NTRK2* L699L**	-	-	-	-	0.2%	ND	ND	-
***EGFR* N338N**	ND	ND	ND	ND	0.1%	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND	ND	ND	ND	0.1%	ND

Russo A (Rolfo C) et al. Clin Lung Cancer 2023

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

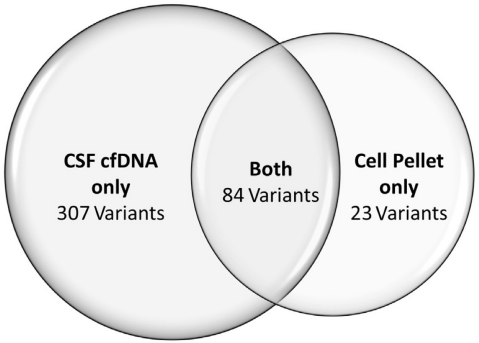
Limitations
No histological characterisation
Lack of standardisation
Contraindications for lumbar puncture
Limited sensitivity

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

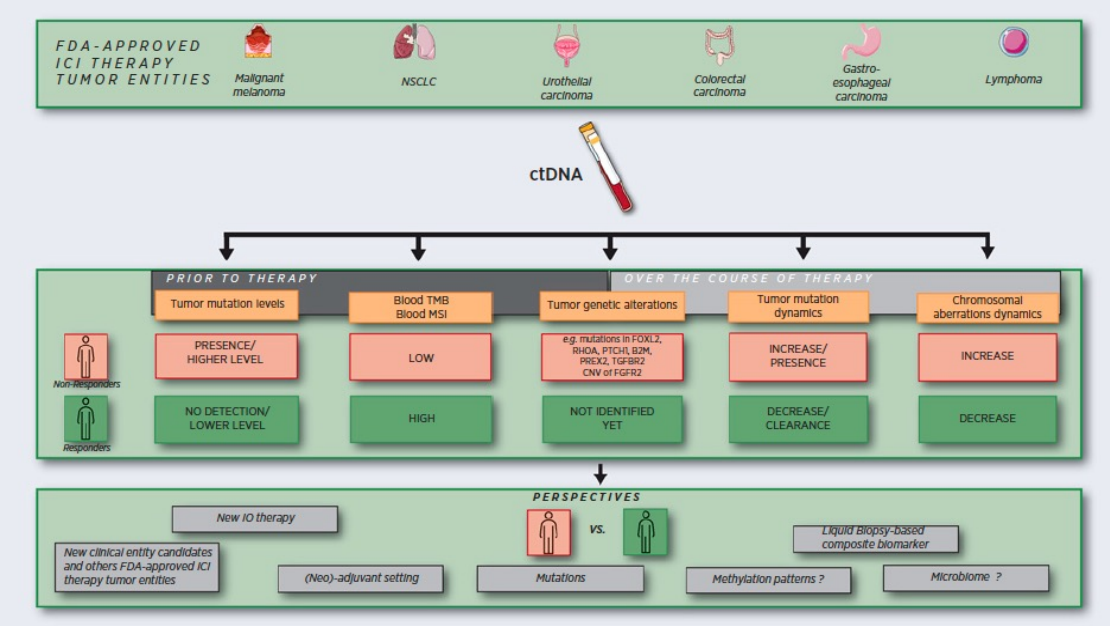
Meaningful results generated even in samples with:
- Very Low input DNA
- Normal CSF cytology



References *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

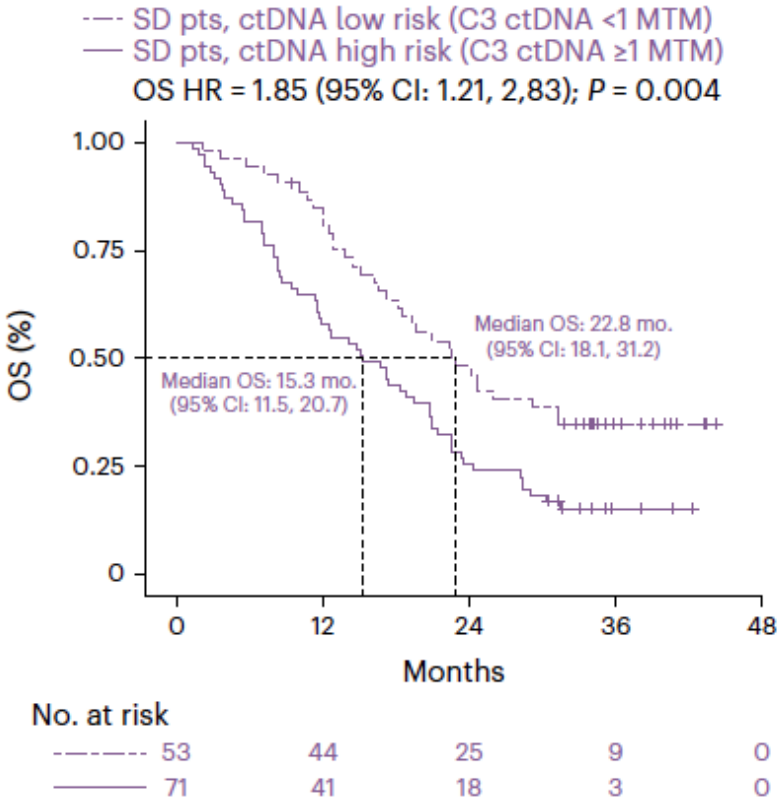
Dynamics, Clearence and more…

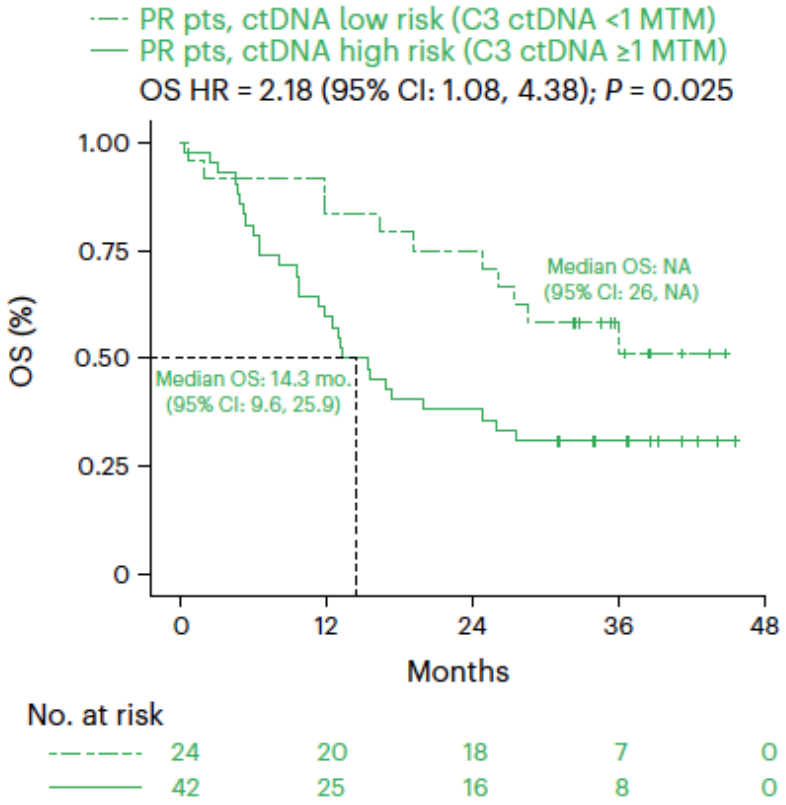


Important implications in new clinical trials design: escalation and de-escalation

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

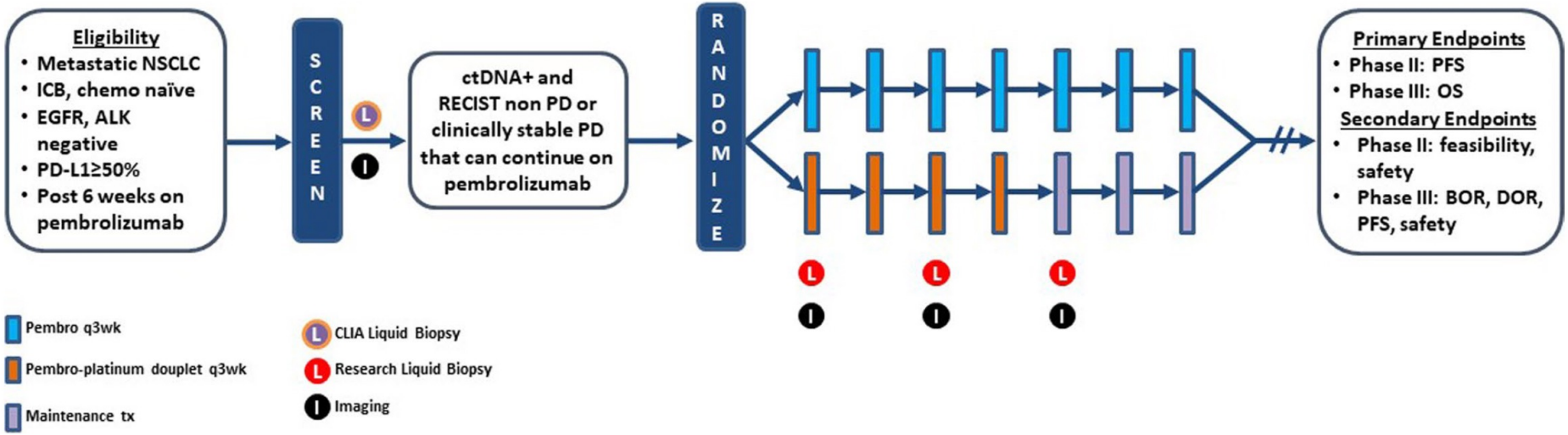
Lack of ctDNA Clearance Is Associated with Poorer Outcomes





Assaf ZJF, et al. *Nat Med*. 2023;29(4):859-868.

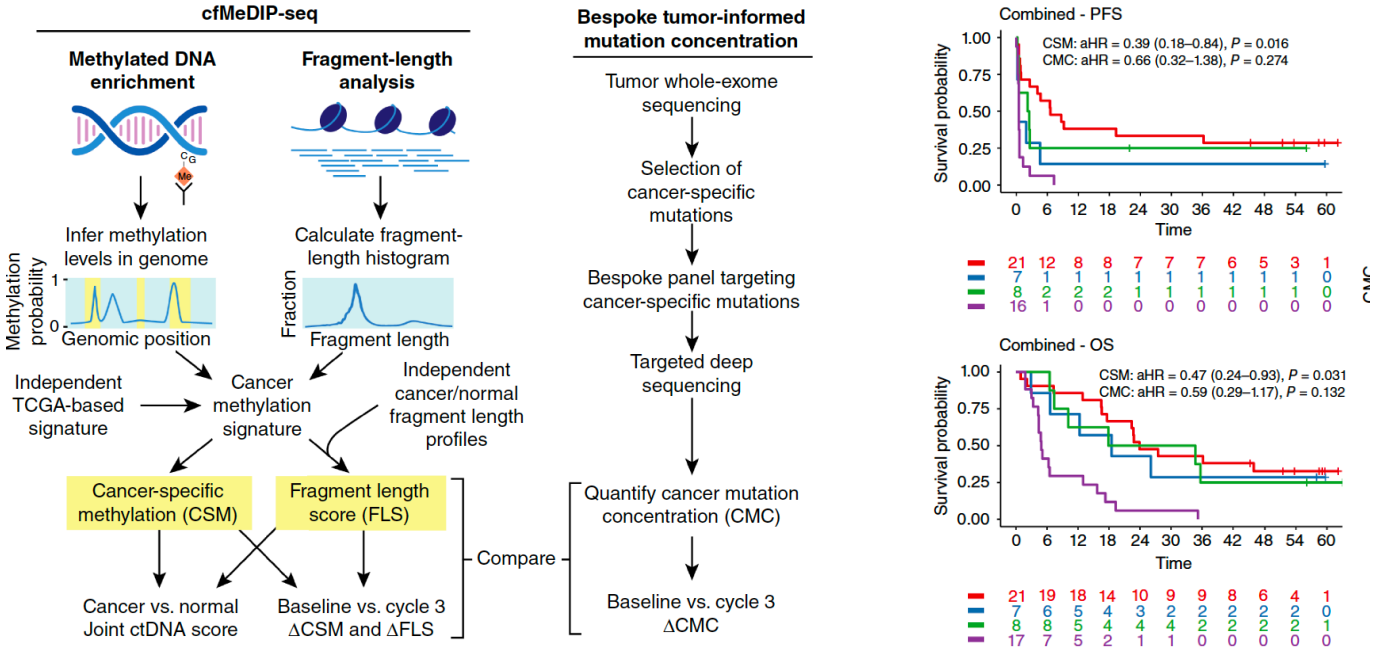
ctDNA for escalation/de-escalation therapeutic strategies: The randomized phase 2 BR36



tumor-agnostic, white blood cell (WBC) DNA-informed NGS approach

Anagnostou V, et al. Nat Med 2023

Early Changes in Tumor-Naive Cell-Free Methylomes and Fragmentomes Predict Outcomes in Pembrolizumab-Treated Solid Tumors



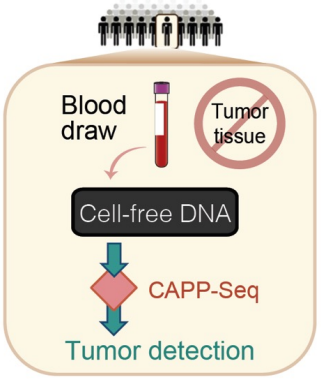
Analysis of methylation and fragment length in plasma using cfMeDIP-seq provides a tumor-naive approach to measure ctDNA with results comparable with a tumor-informed bespoke ctDNA.

Stutheit-Zhao et al (L. Siu), Cancer Discovery June 2024

Different types of ctDNA MRD Assays

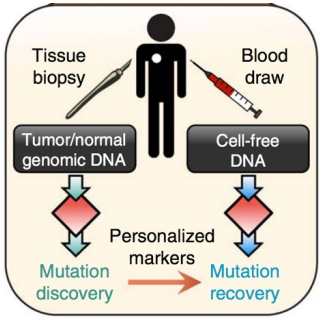
And different sensitivity….

Tumor-naive



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

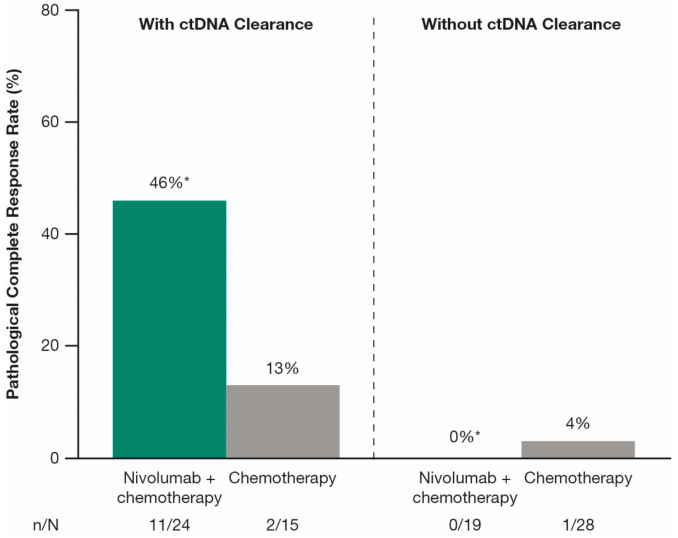
Tumor-informed



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

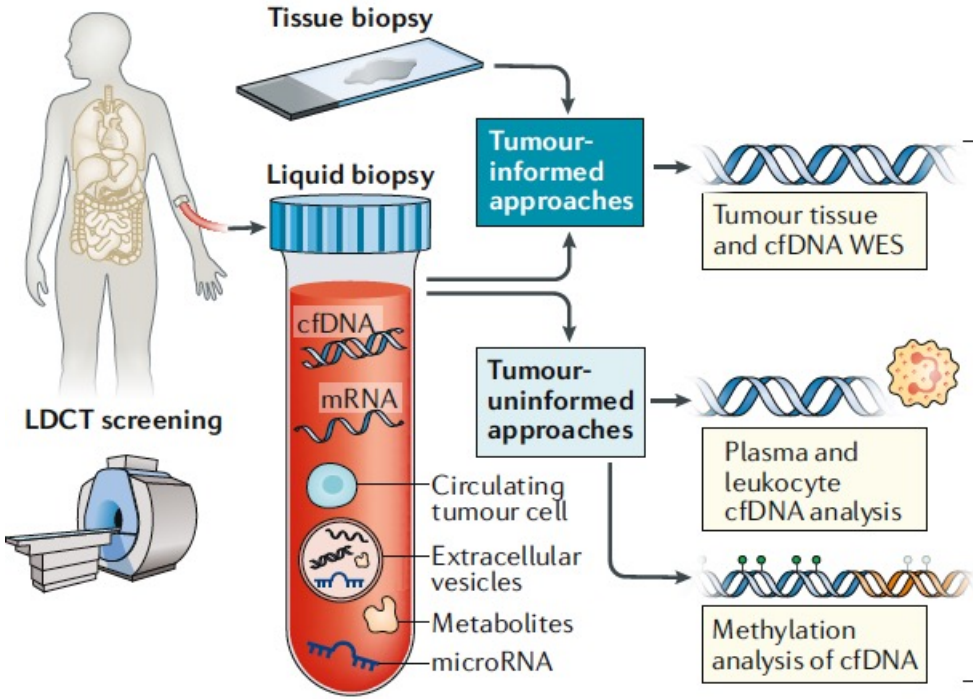
Courtesy Dr. Natasha Leighl

Use in Early Stage perioperatory

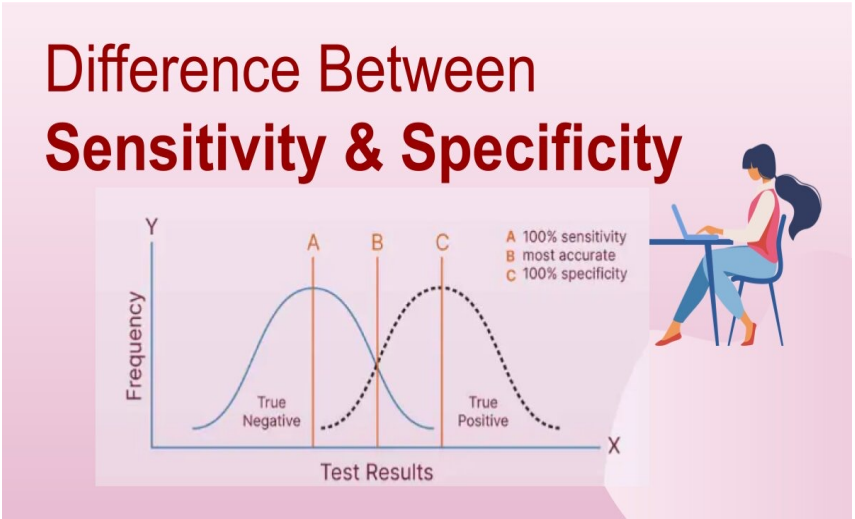


Forde PM, NEJM 2023

Are we really ready for LB in Early Detection?

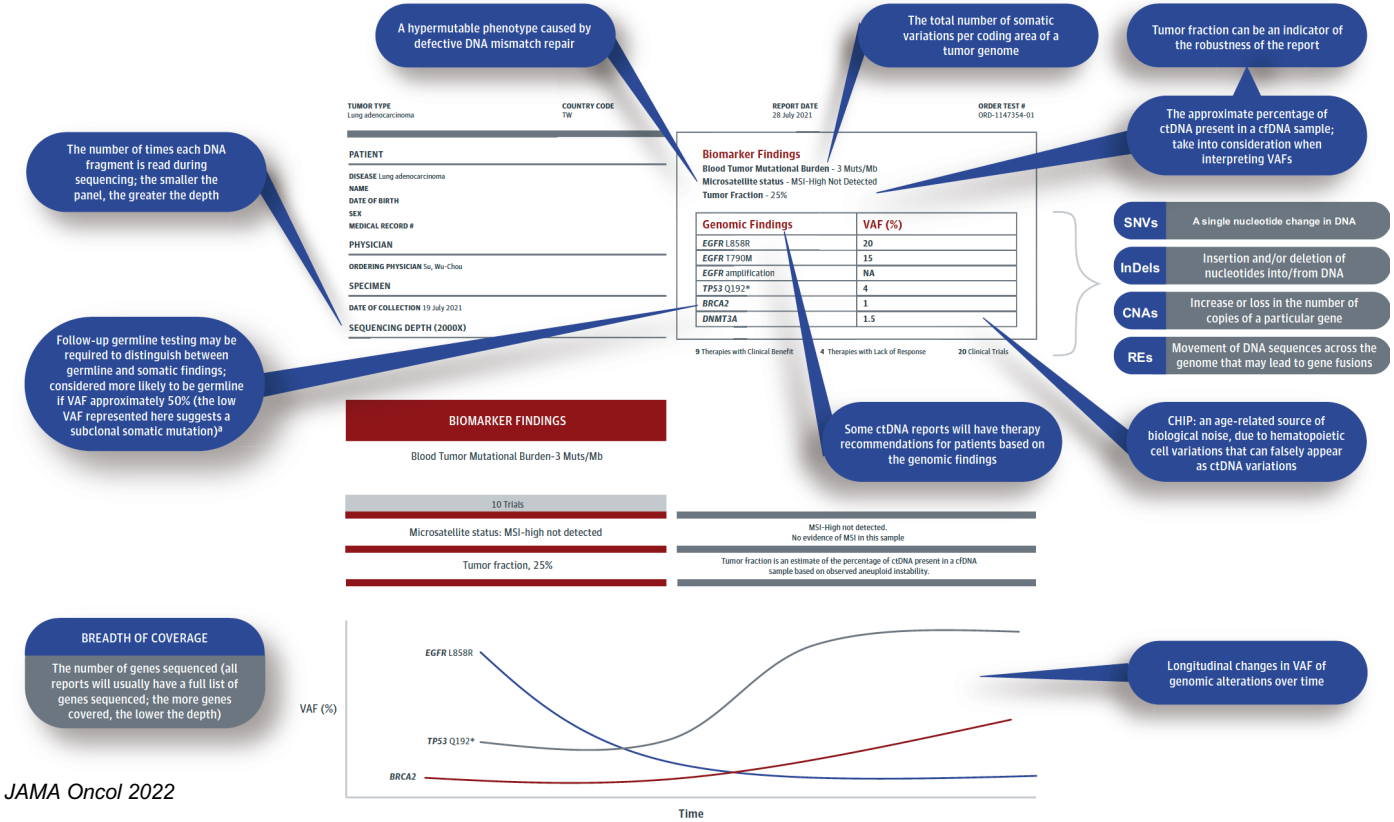


To Remember…

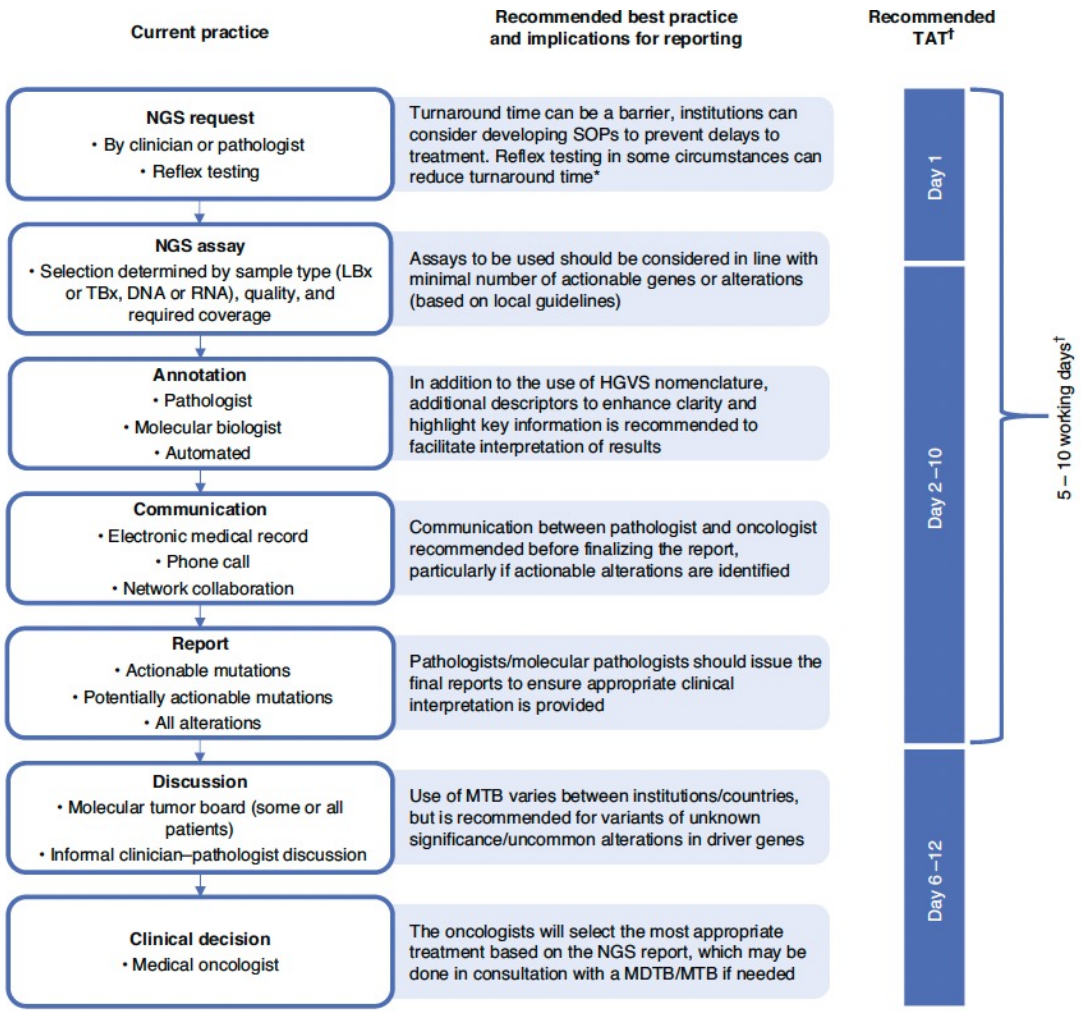


References *Rolfo C & Russo A. Nat Rev Clin Oncol 2020*

A sample of ctDNA report with key elements

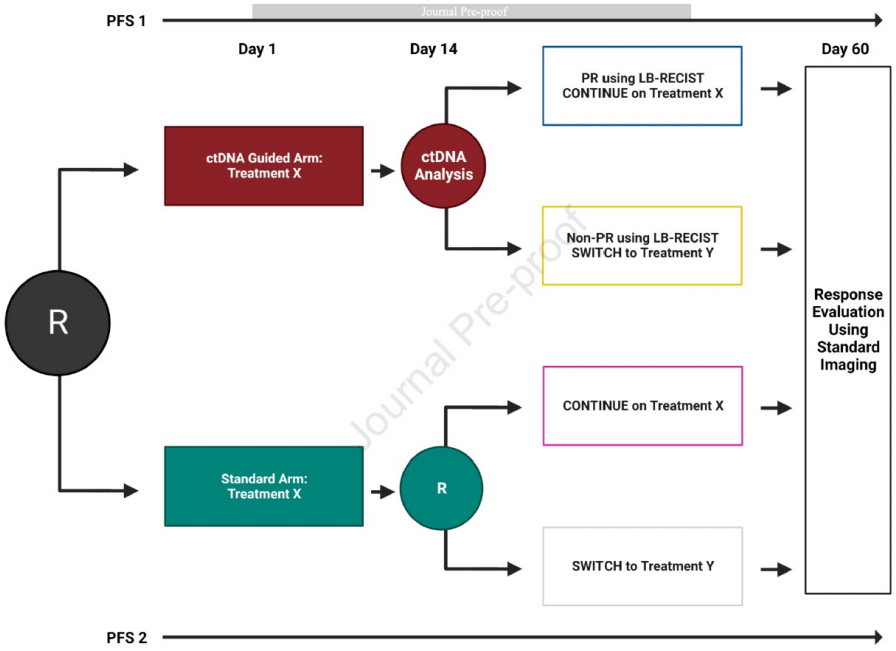


Krebs MG (Rolfo C) et al. JAMA Oncol 2022



Malapelle et al (Rolfo) BJC May 2024

Potential Study Design and *Different issues related to implementation of LB-RECIST*



Biological Issues

Shedding potential
Type of targets
Definition of cutoffs

Clinical Issues

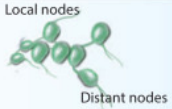
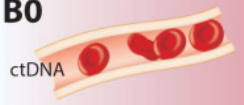
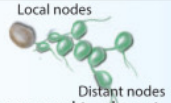
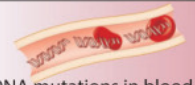
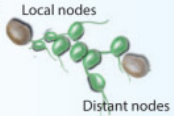
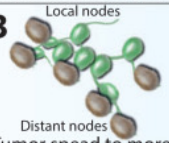
What?
Who?
When?
Why?
How?

Regulatory Issues

Validity of data
Totality of evidence
Sampling considerations
Assay validation

M. Gouda et al (Rolfo C. Subbiah V.), Annals of Oncology, Dec 2023

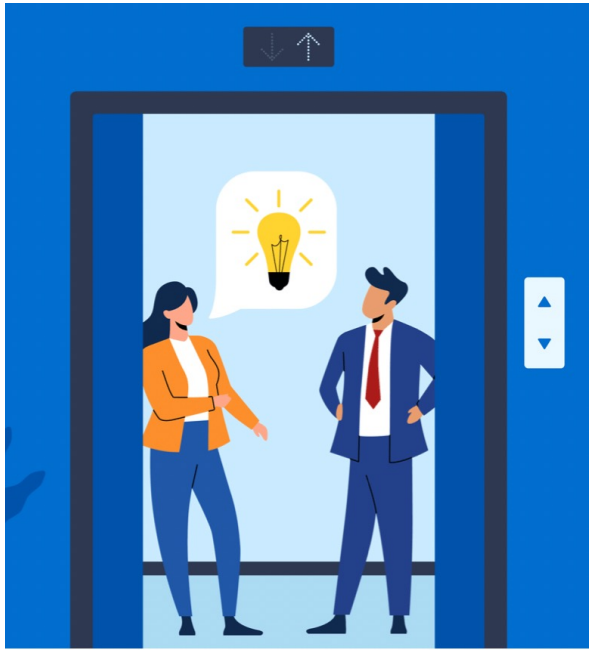
ctDNA incorporation into the hallmark cancer staging system as TNMB

T Tumor Size	N Lymph Node	M Metastasis	B Blood
T1  Tumor size/local invasion	**N0**  No regional lymph node invasion	**M0**  No distant metastasis	**B0**  No ctDNA mutations in blood
T2  Tumor size/local invasion	**N1**  Tumor spead to closest or small number of regional lymph nodes	**M1**  Distant metastasis	**B1**  ctDNA mutations in blood (can be further defined with more detailed quantification in the future)
T3  Tumor size/local invasion	**N2**  Tumor spead to an extent between N1 and N3		
T4  Tumor of any size that invades to other organs	**N3**  Tumor spead to more distant or regional numerous lymph nodes		

Yang et al, Annals of Oncology 29: 311–323, 2018

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

Acknowledgements team and collaborations

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UPMC HILLMAN CANCER CENTER

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

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