Novel Platforms for Lung Cancer Screening *(and Earlier Diagnosis)* using Liquid Biopsy

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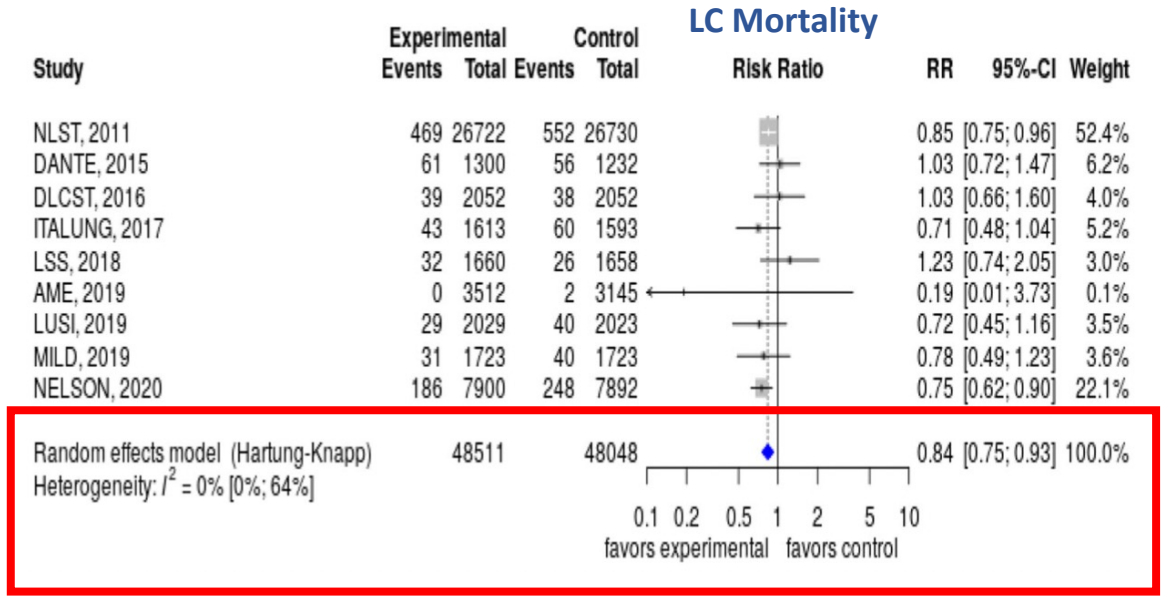
Objectives

- To review emerging novel platforms for lung cancer screening using liquid biopsy
- To highlight the current applications of liquid biopsy in patients with lung cancer in clinical practice
  - Genotyping in advanced NSCLC patients
- To highlight potential to accelerate molecular diagnosis

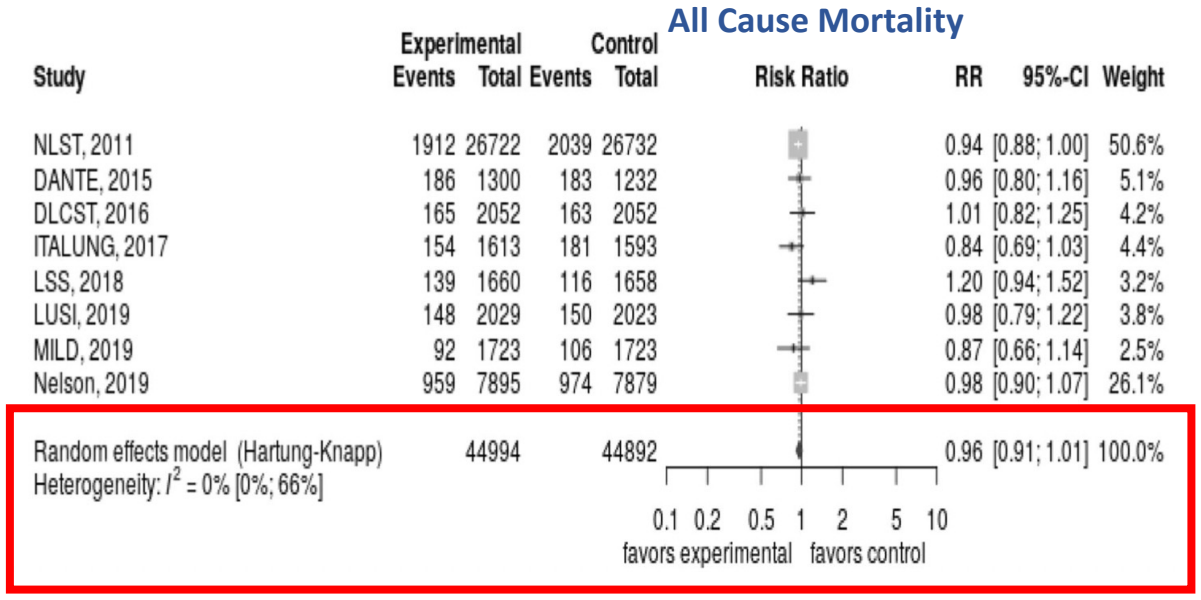
Lung Cancer and Screening

- Lung cancer remains the leading cause of cancer mortality and cancer care costs globally including in the US
  - 5-year survival 22% → Need Prevention, Early Detection
- Screening with low-dose CT reduces lung cancer-related mortality [I,A].

LC Mortality

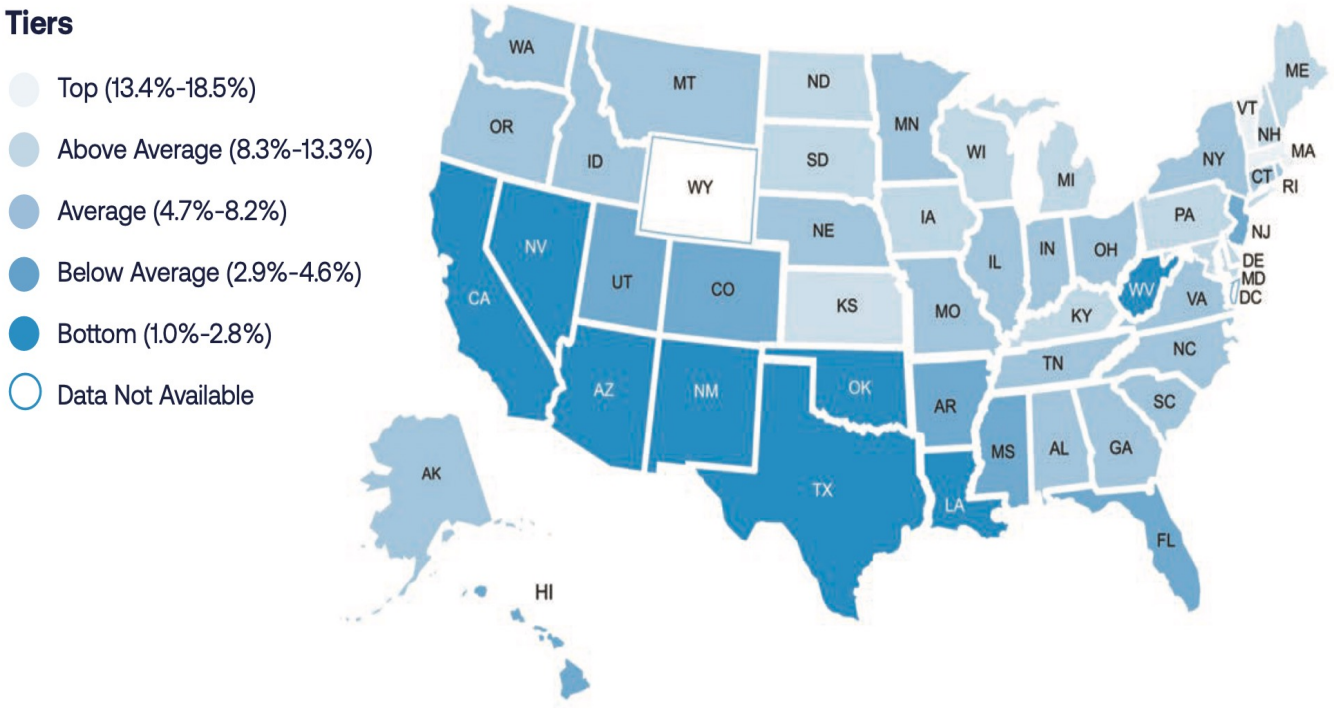


All Cause Mortality



Sung H, et al. CA Cancer J Clin. 2021;71(3):209-249; Siegel RL et al. CA Cancer J Clin 2022;72:7-33

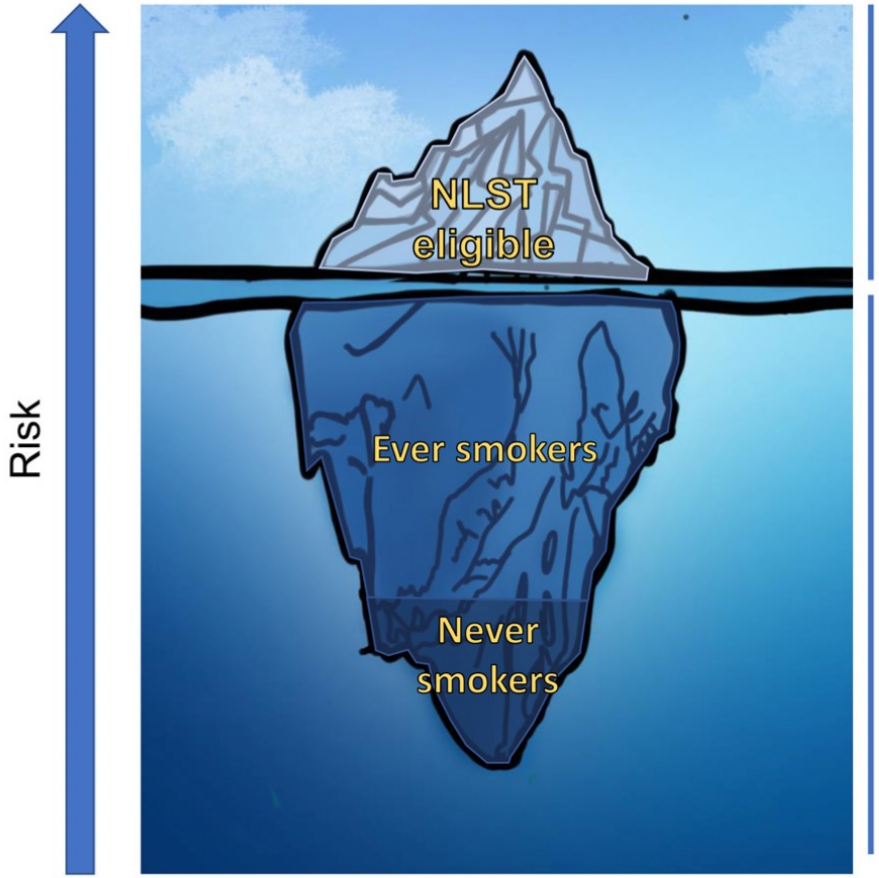
Lung Cancer Screening in the US



- In **US, only 5.7%** of those at high risk screened
- Screening rates range from 1.0 to 18.5%
- Louisiana ranks 40th of 50 states at **3.3%**
- Only 21.6% of cases diagnosed at early stage (National average 24.5%, Louisiana ranks 43rd of 50); 17.6% undergo surgery (National average 20.7%)
- USPSTF 2021– expanded screening population: 50-80 years old, current or former smokers (quit<15 yrs ago), >=20 pack year smoking history

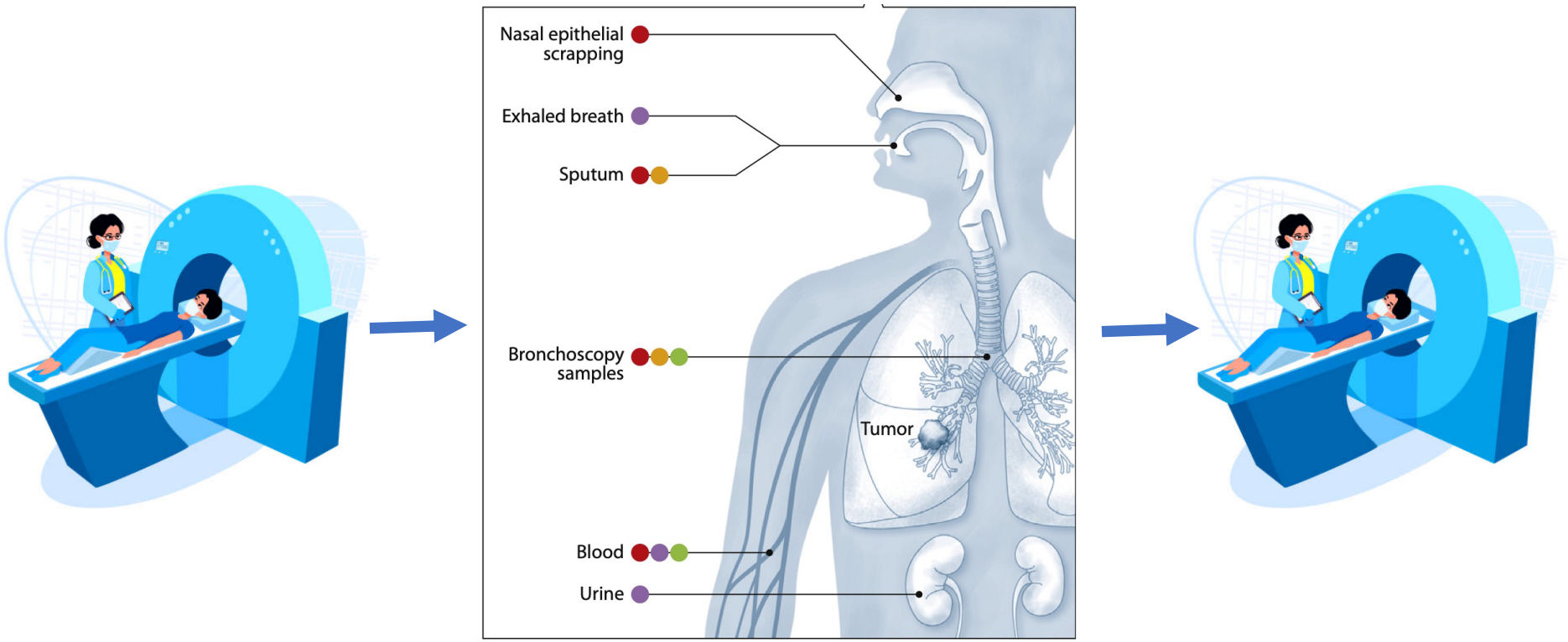
American Lung Association. State of Lung Cancer 2021. https://www.lung.org/research/state-of-lung-cancer (accessed 23 March 2022) USPSTF JAMA. 2021;325(10):962-970

What are some challenges with lung cancer screening?



- If we screened all NLST eligible patients, we would detect only 27% of all lung cancers
- With new criteria, this may increase by ~30%
- Even low dose CT (LDCT) not perfect…
- ~27% had “positive” screen, most (96%) did not have cancer
- 2.7% of those without cancer underwent at least 1 invasive procedure
- Definition of “positive” test improving, e.g. Lung RADS criteria, but still need to improve positive predictive value

Ostrin et a. Cancer Epidemiol Biomarkers Prev. 2020; NLST Research Team New Engl J Med 2011.

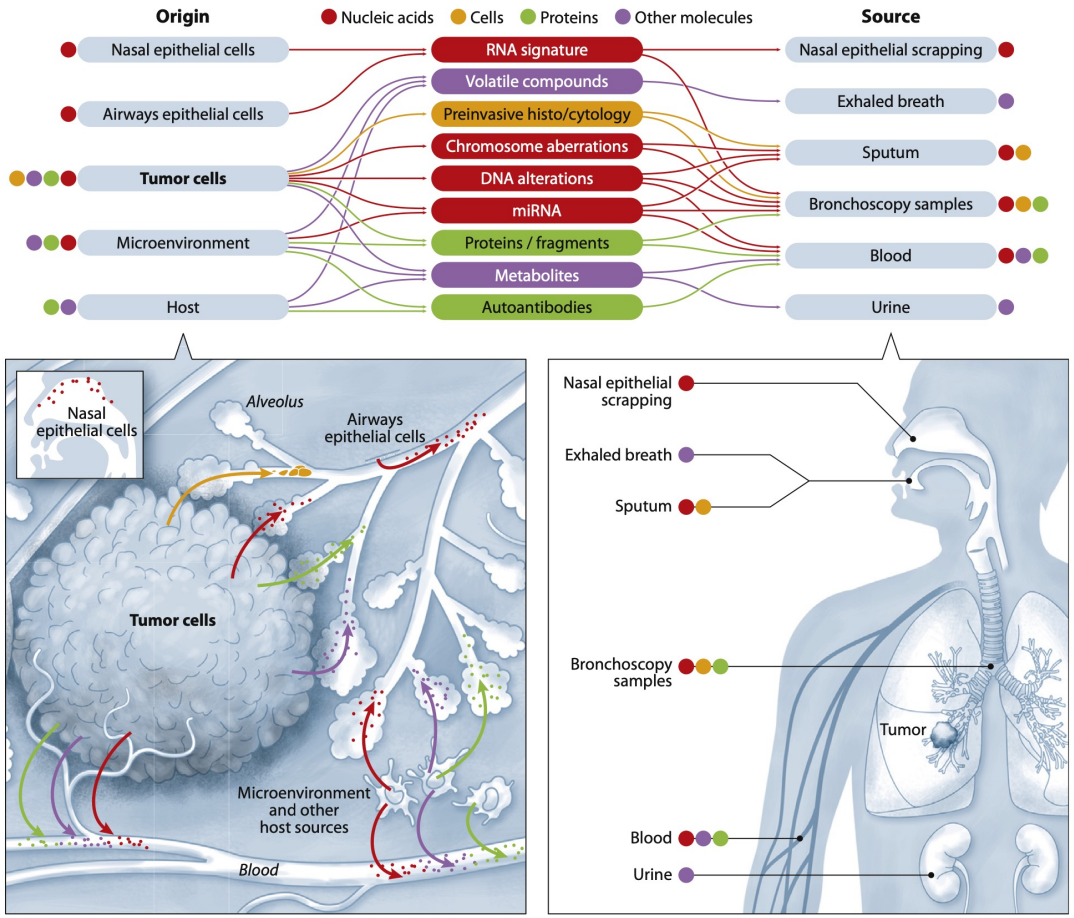


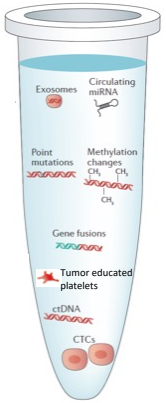
Enhance detection in those with positive LDCT screen

OR screen population with novel biomarker → further investigation in those deemed at risk

Illustration from Seijo et al. J Thorac Oncol 2019

Many candidate biomarkers under investigation



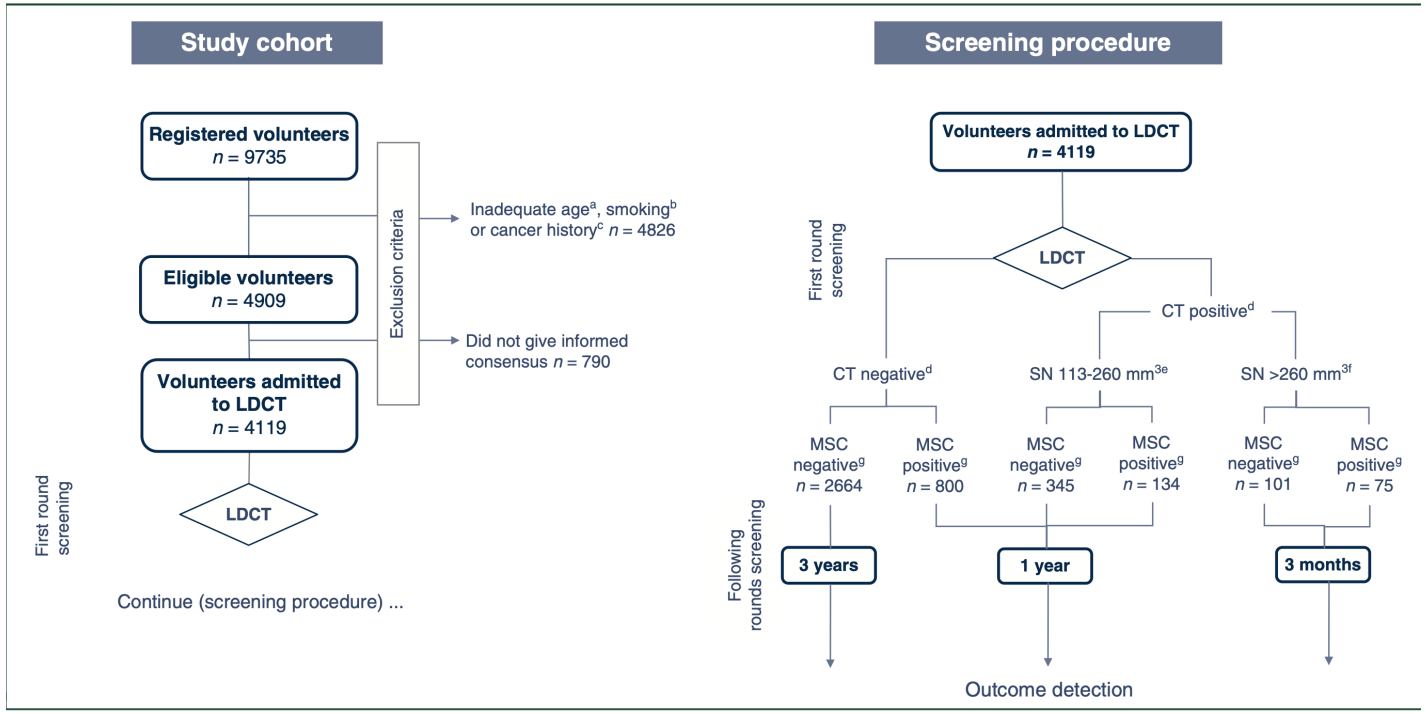


Blood Components	Biomarkers	Tests
Candidate Blood-Based Biomarkers for the Early Detection of Lung Cancer		
Plasma	Circulating free DNA	NGS (large panels)
Plasma/serum	MicroRNAs/ exosomes	RT-PCR, NGS
Plasma	Proteins/ autoantibodies	ELISA
Whole blood	CTCs	ISET, ScreenCell, CellSearch, other
Platelets (TEPs)	Nucleic acids	NGS, RNA sequencing
Candidate Blood-Based Biomarkers for the Prediction of Lung Cancer Occurrence		
Plasma	Circulating free DNA	Gene methylation, DNA fragmentation assessment
Plasma/serum	MicroRNAs	RT-PCR
Plasma	Proteins	ELISA
Whole blood	CTCs	ISET, ScreenCell

Abbreviations: CTC, circulating tumor cell; ELISA, enzyme-linked immunoadsorbent assay; ISET, Isolation by Size of Epithelial Tumor Cell; NGS, next-generation sequencing; RT-PCR, reverse transcriptase–polymerase chain reaction; TEP, tumor-educated platelet.

Seijo et al J Thorac Oncol 2019; Herath et al Front Oncol 2022

bioMILD: LDCT + plasma miRNA signature classifier (MSC)



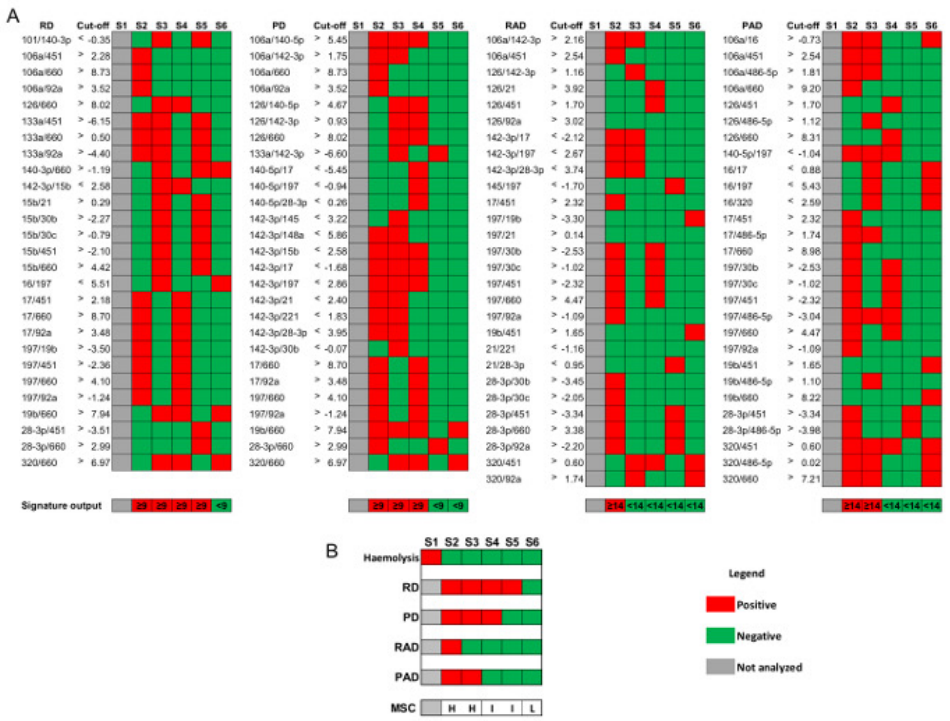
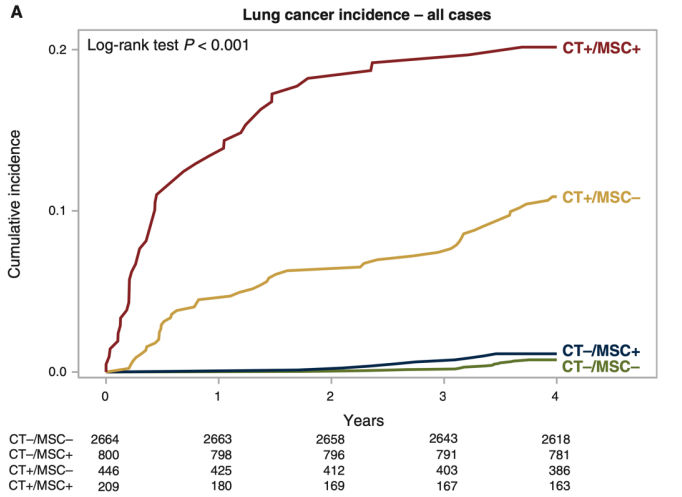
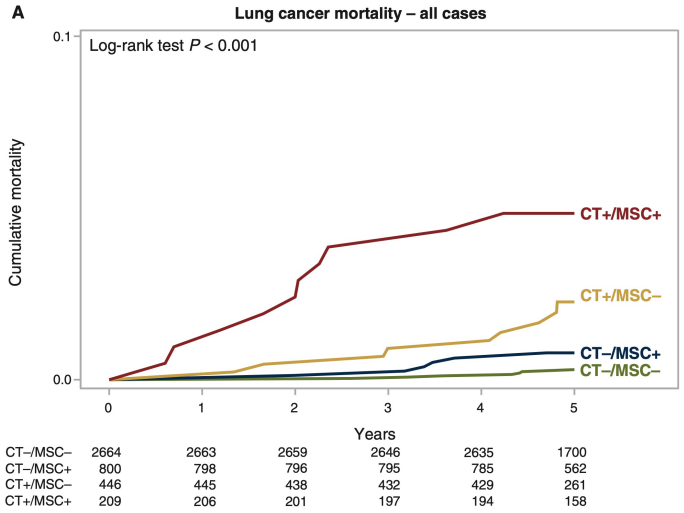


Figure 1. CONSORT diagram of the BioMILD screening trial.
LDCT, low-dose computed tomography; LC, lung cancer; MSC, micro RNA signature classifier; SN, solid nodules.
[a]Volunteers aged ≤50 or ≥75 years.
[b]Never smokers or former smokers who quit for 10 years or more or current smokers with <30 pack-years or current smokers with <20 pack-years without chroni obstructive pulmonary disease and/or family history of lung cancer.
[c]Volunteers in whom a neoplasm was diagnosed in the past 5 years.
[d]Negative LDCT: no nodule, or nodule with calcification pattern, or solid nodules <113 mm^3, or non-solid nodules <5 mm; positive LDCT: solid nodules ≥113 mm^3, o part-solid. nodules, or non-solid nodules ≥5 mm.

Pastorini et al. Ann Oncol 2022; Sozzi et al J Clin Oncol 2014; Mensah et al J Vis Exp 2017

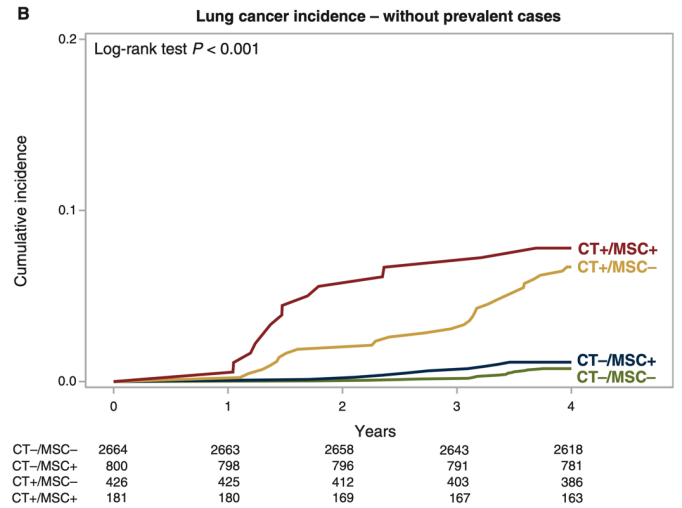
bioMILD: LDCT + plasma miRNA signature classifier (MSC)

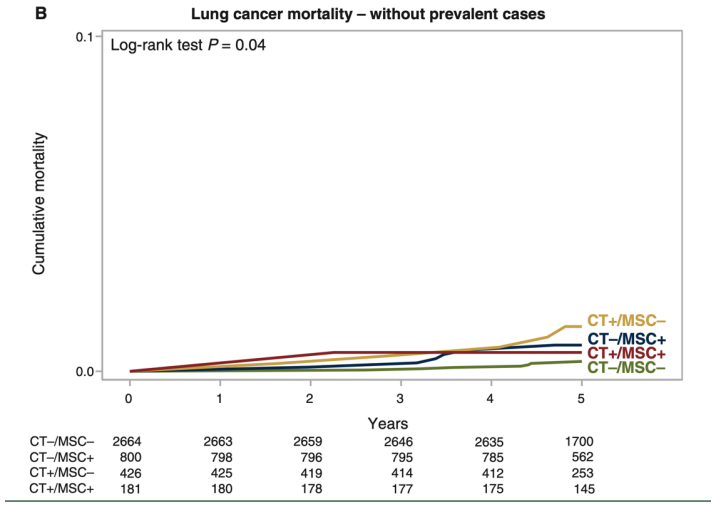




At first screen, MSC + associated with 2 fold risk of lung cancer diagnosis in those with LDCT + screen

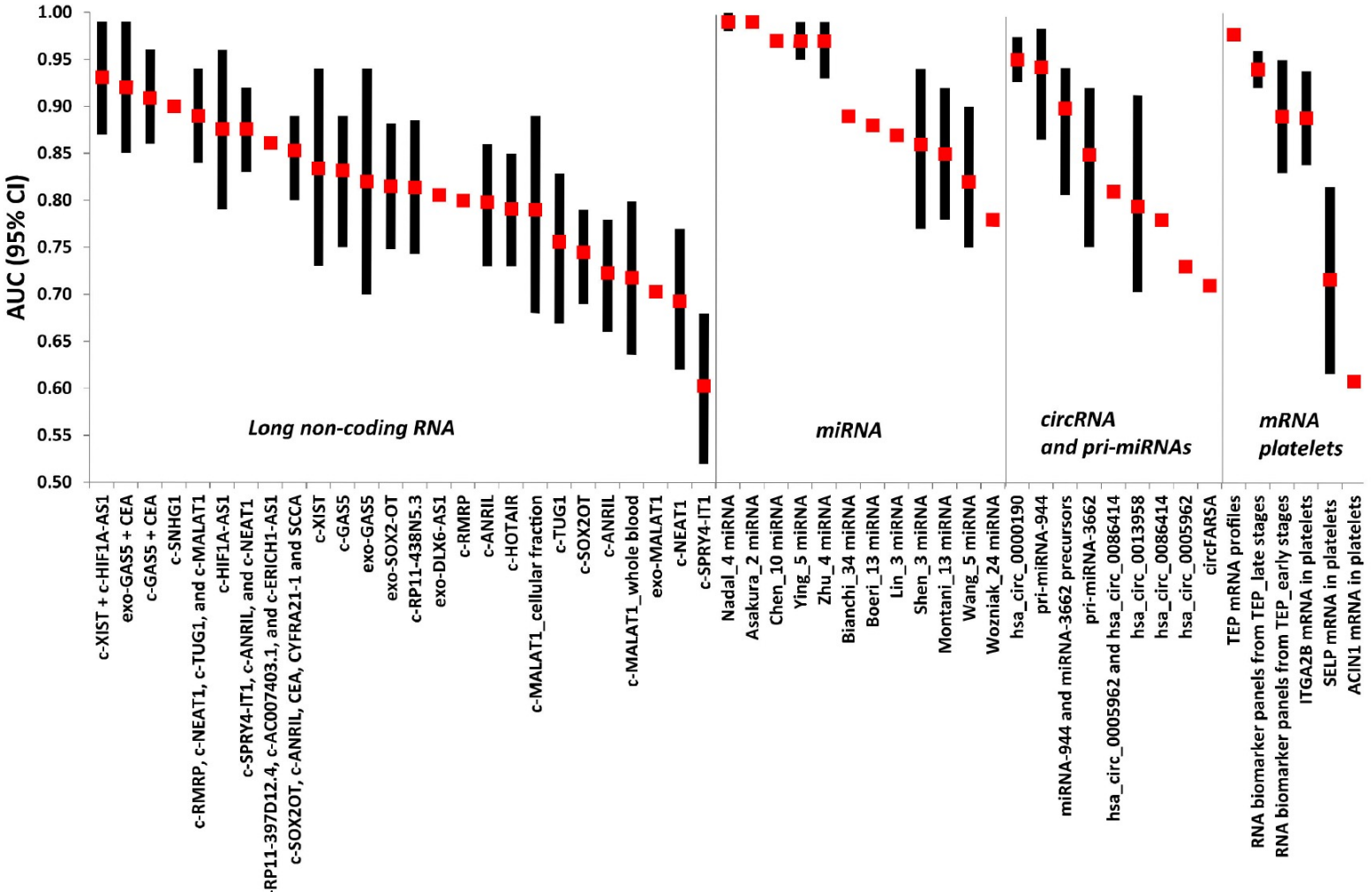
Benefit of MSC in subsequent follow up less clear but may help inform less frequent follow up intervals for low risk group (LDCT- MSC-)





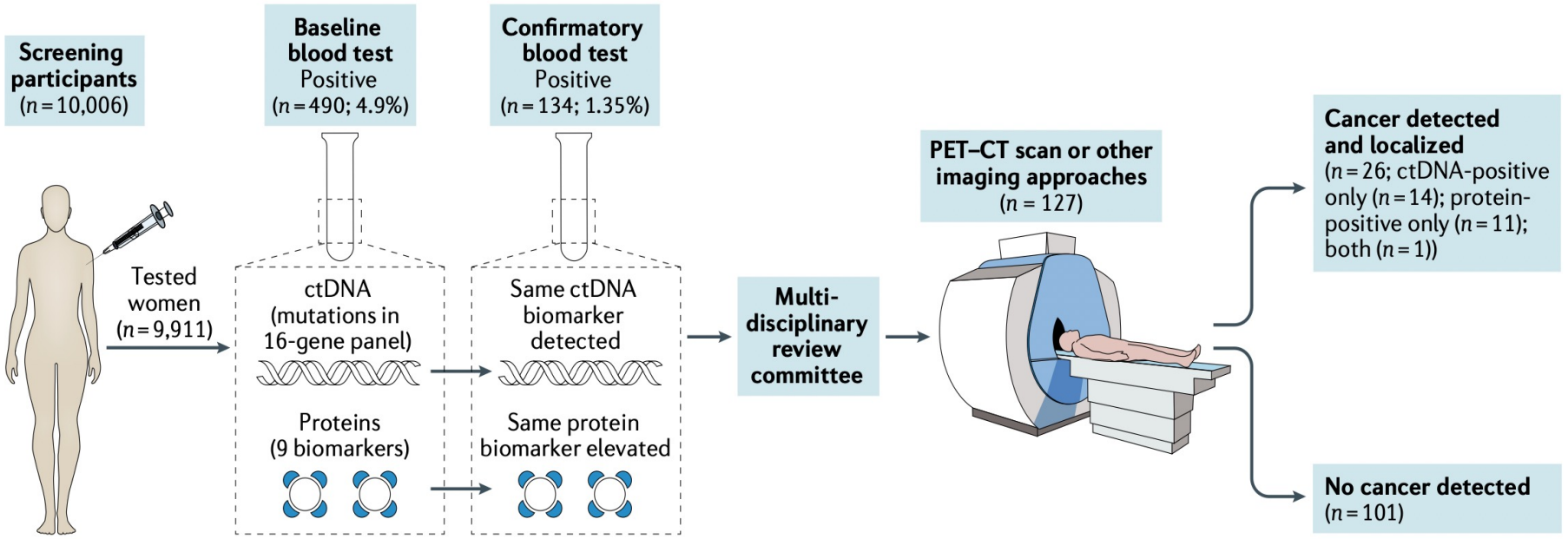
Pastorini et al. Ann Oncol 2022

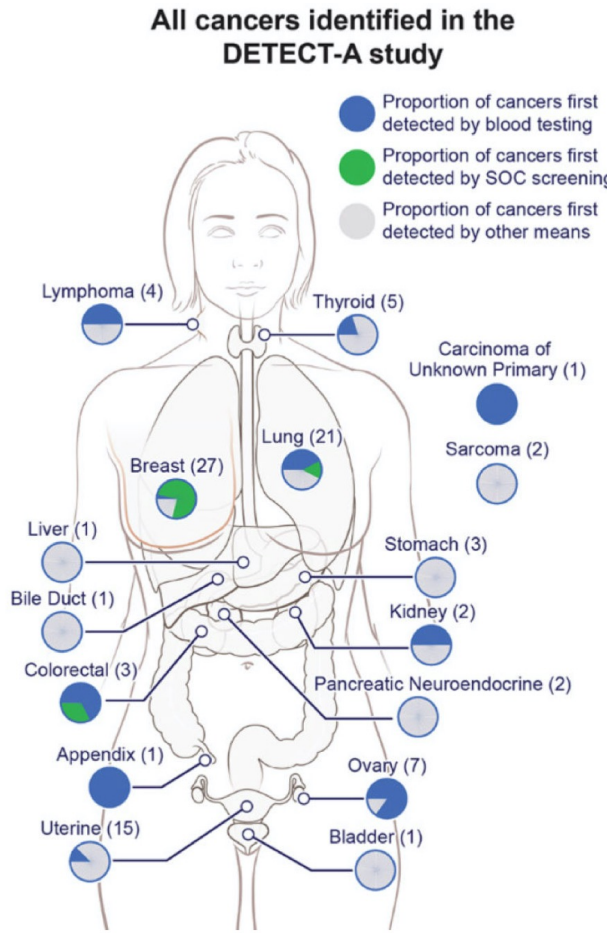
Blood-based RNA signatures promising



Dama et al Cancers 2021

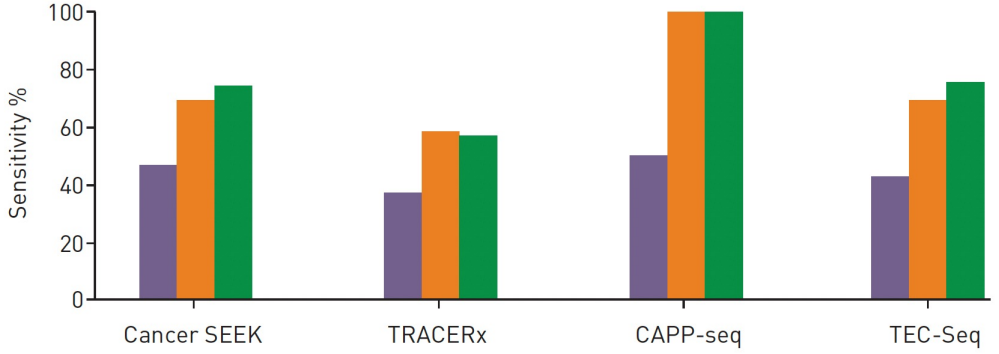
Multi-cancer early detection assays





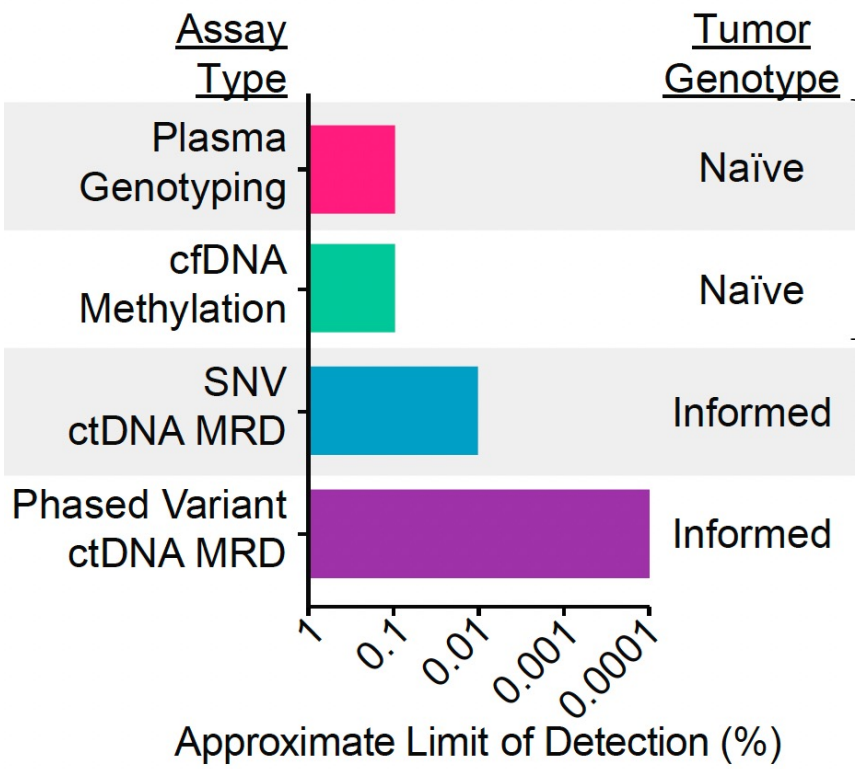
Lennon et al Science 2020

Key challenge of ctDNA assays in screening, minimal residual disease identification is the limit of detection



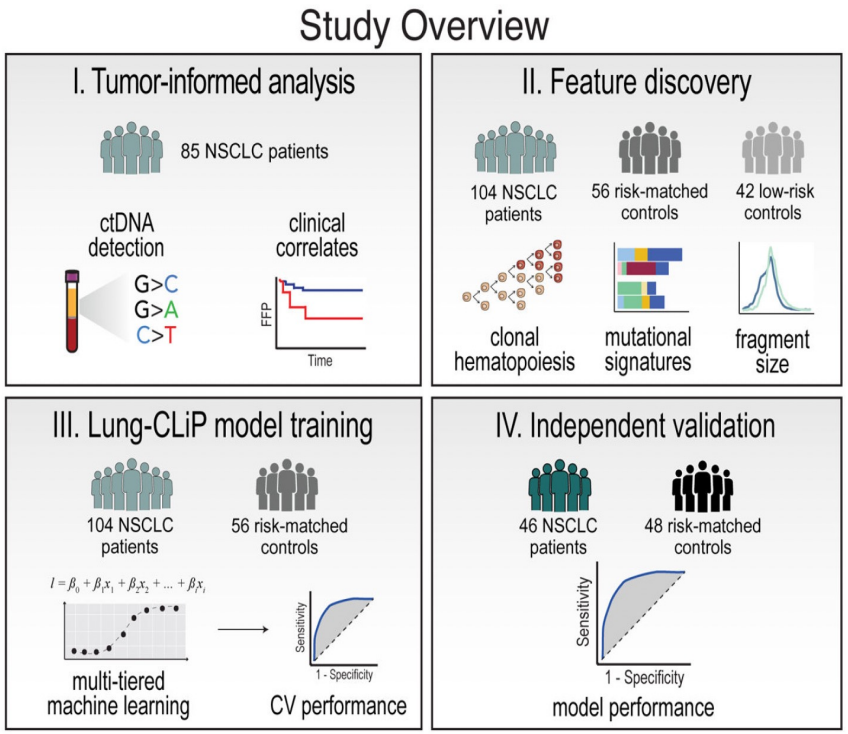
	Cancer SEEK[#]	TRACERx[¶]	CAPP-seq[+]	TEC-Seq[§]
Stage I	43	37	50	45
Stage II	69	59	100	72
Stage III	74	57	100	75

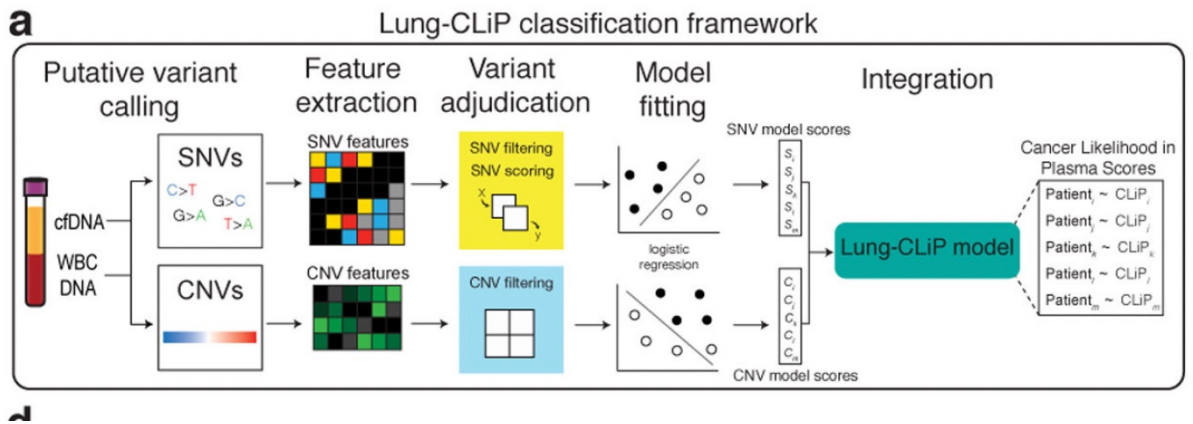
FIGURE 2 Summary of the technical properties and performances of the four main plasma genotyping platforms studied for early stage nonsmall cell lung cancer detection. [#]: early stages: hybrid capture, plasma next-generation sequencing (NGS) (16 genes) and 8 protein markers. [¶]: minimal residual disease (MRD): plasma NGS, patient-specific multiplex PCR (10 to 22 single-nucleotide variations), subclonal evolution. [+]: early stage MRD: hybrid capture, plasma NGS (139 genes). [§]: early stage MRD: hybrid capture, plasma NGS (58 genes).

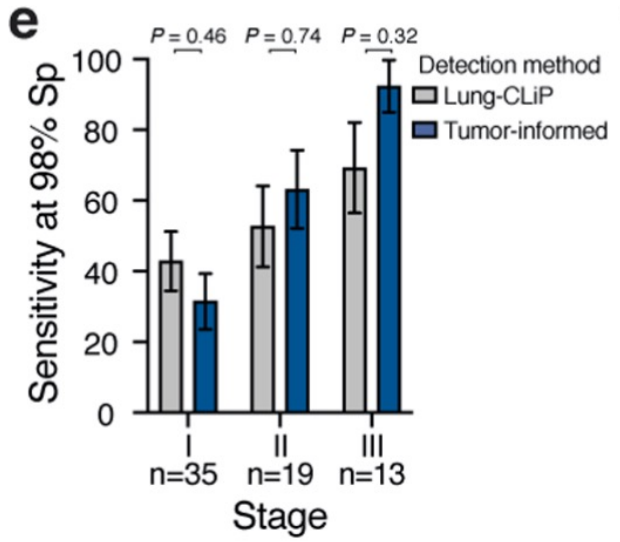


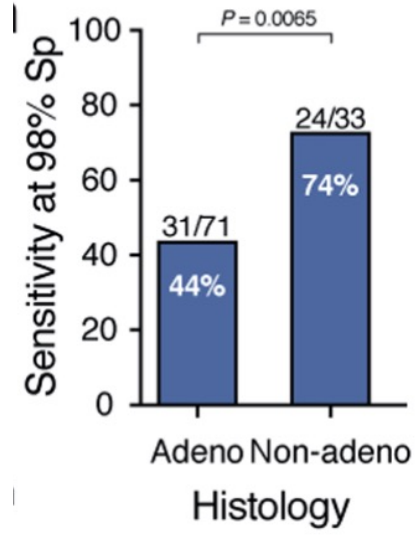
Guibert et al Eur Resp Rev 2020; Dr. Max Diehn, ESMO Applications of Liquid Biopsy Series – Lung Cancer, October 2021
Chin et al Mol Diagn Ther; Moding et al Canc Discov 2021

Lung Cancer Likelihood in Plasma (Lung CLiP assay)









Chabon et al. Nature 2020

The PATHFINDER Study: Assessment of a Multi-Cancer Early Detection Test In Clinical Practice

Prospective, multicenter, interventional, return-of-results study (NCT04241796)

Study Objectives

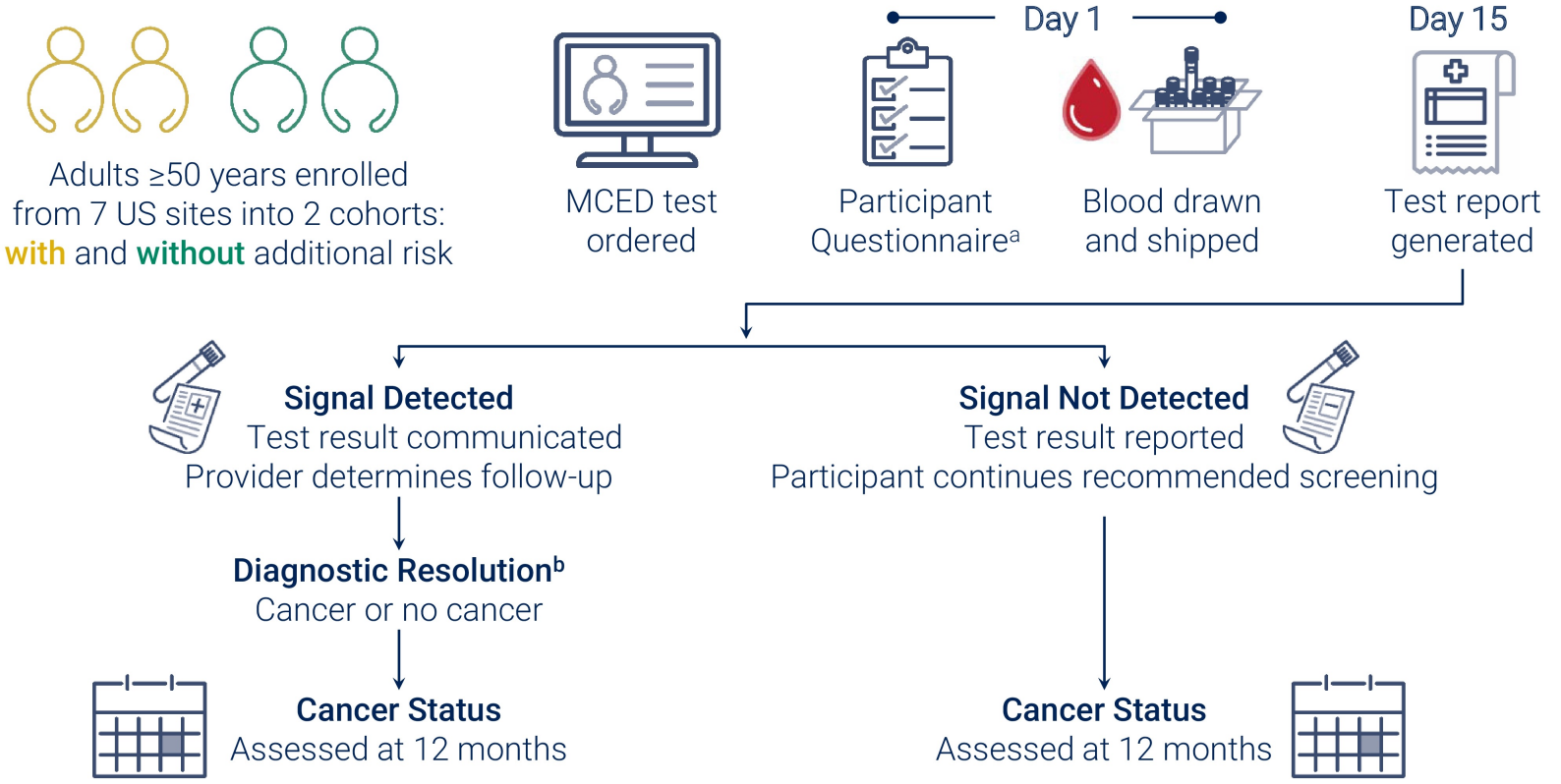
Primary

- Assess extent of diagnostic testing required to achieve diagnostic resolution following a "signal detected" test result

Secondary

- Evaluate test performance
- Assess participant-reported outcomes and perceptions of the MCED test

Study Design



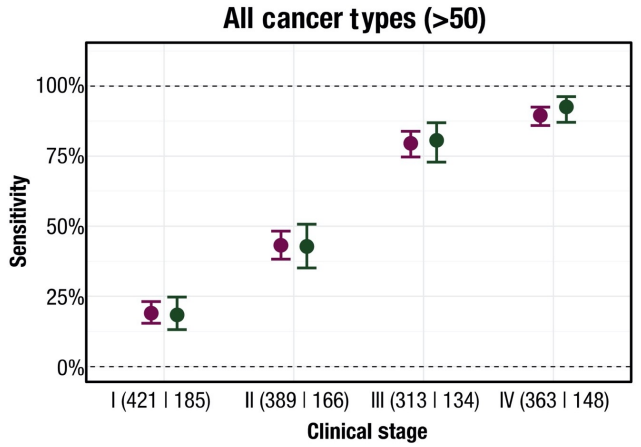
[a]Also collected at other timepoints during the study.
[b]Defined as date when study team determines to end diagnostic evaluation triggered by a "signal detected" test result.
MCED, multi-cancer early detection.

Presented By: **Tomasz M. Beer**
OHSU Knight Cancer Institute, Portland, OR

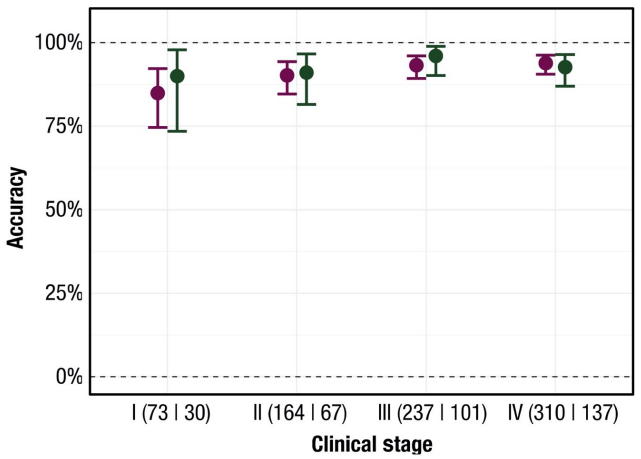
2021 ASCO ANNUAL MEETING

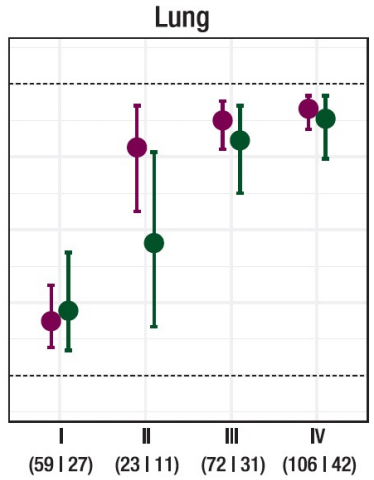
Background

- Early detection via screening improves cancer-specific survival for some cancers
- GRAIL's Multi Cancer Early Detection (MCED) Test is a methylation-based cell-free DNA blood test that can detect multiple types of cancers
- A case control study demonstrated 18-81% sensitivity in stage I-III and >99% specificity
- Accuracy for predicting tissue of origin was 93%



Note in Lung Cancer, sensitivity lower for early stages – which we need to identify in order to cure lung cancer

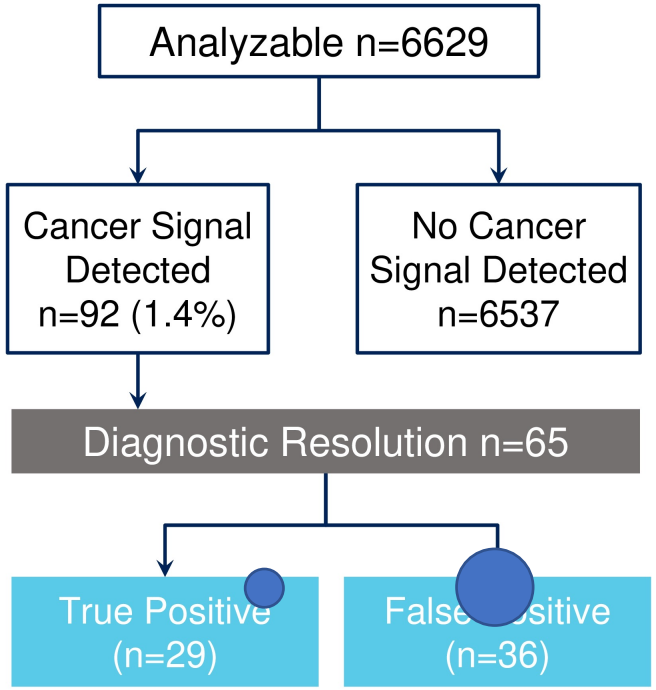




Liu M, et al. *Ann Oncol.* 2020

Adapted from Dr. Diehn, ASCO 2021; Liu et al Ann Oncol 2020; purple = training set, green = validation set

Interim Primary Outcome: Extent of Diagnostic Testing



Median (Q1, Q3)	True Positive n=27*	False Positive n=36	Total (n=63*)
All Imaging/Invasive Procedures	2.0 (1.5, 3.0)	1.5 (1.0, 2.2)	2.0 (1.0, 3.0)
All Imaging Tests	1.0 (1.0, 1.5)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Functional	1.0 (		1.0)
Anatomic			
All Invasive Proce			
Minimally Invasi			
Surgical			
ical Lab T			
Days to Resolu			

52% lymphoid cancers; 1 lung cancer
85% accuracy for tissue of origin
PPV 49% (39-67%)
40% stage I, II
? Are plasma tests better at picking up micrometastatic cases rather than more curable early stage?

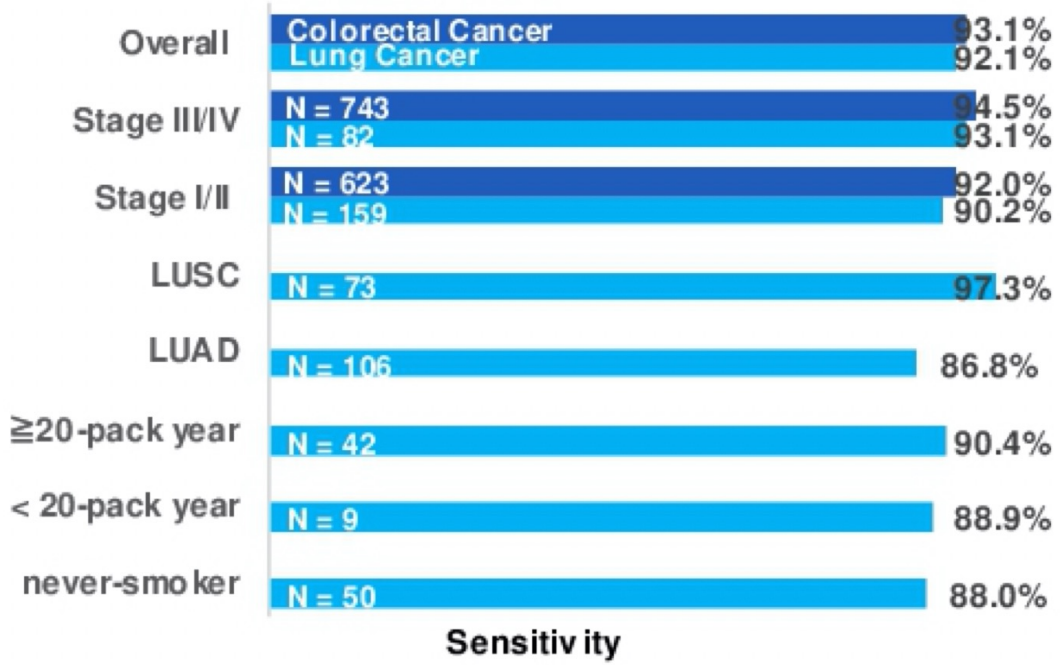
Most participants with diagnostic resolu
More true positives (21/27; 78%) than false positives (
Most invasive procedures were minimally invasiv
sive procedure

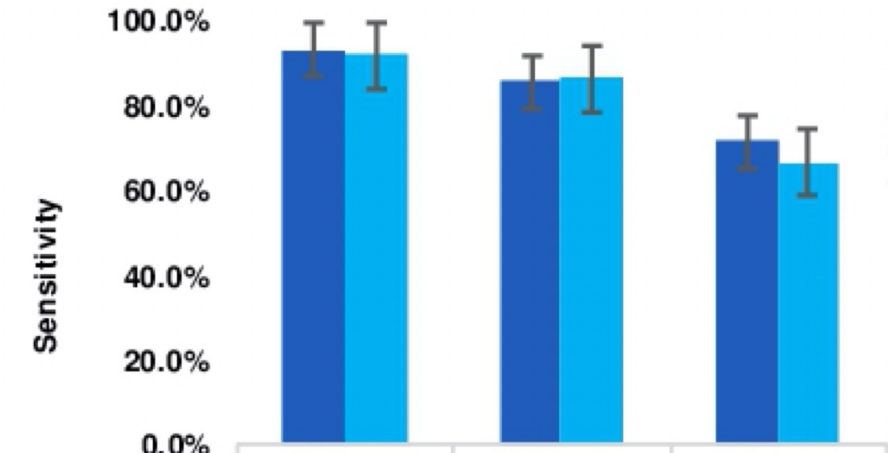
*2 participants with 'signal detected' MCED test result (true positives) were excluded from the diagnostic workup analysis because diagnostic testing was initiated before MCED test results were returned. As of March 2021, 30 participants had ≥1 invasive procedure (26 minimally invasive, 2 surgical, 2 both).

Presented By: **Tomasz M. Beer**
OHSU Knight Cancer Institute, Portland, OR

Other plasma methylation assays in clinical trials

Cohort Demographics				
		Cancer-free (N = 3,298)	Colorectal Cancer (N = 1,366)	Lung Cancer (N = 241)
Cancer Stage	I / II	-	54%	34%
	III / IV	-	46%	66%
Age (years)	Median (Range)	57 (18 – 86)	65 (19 – 93)	67 (23 – 93)
Number of unique cohorts		17	12	6

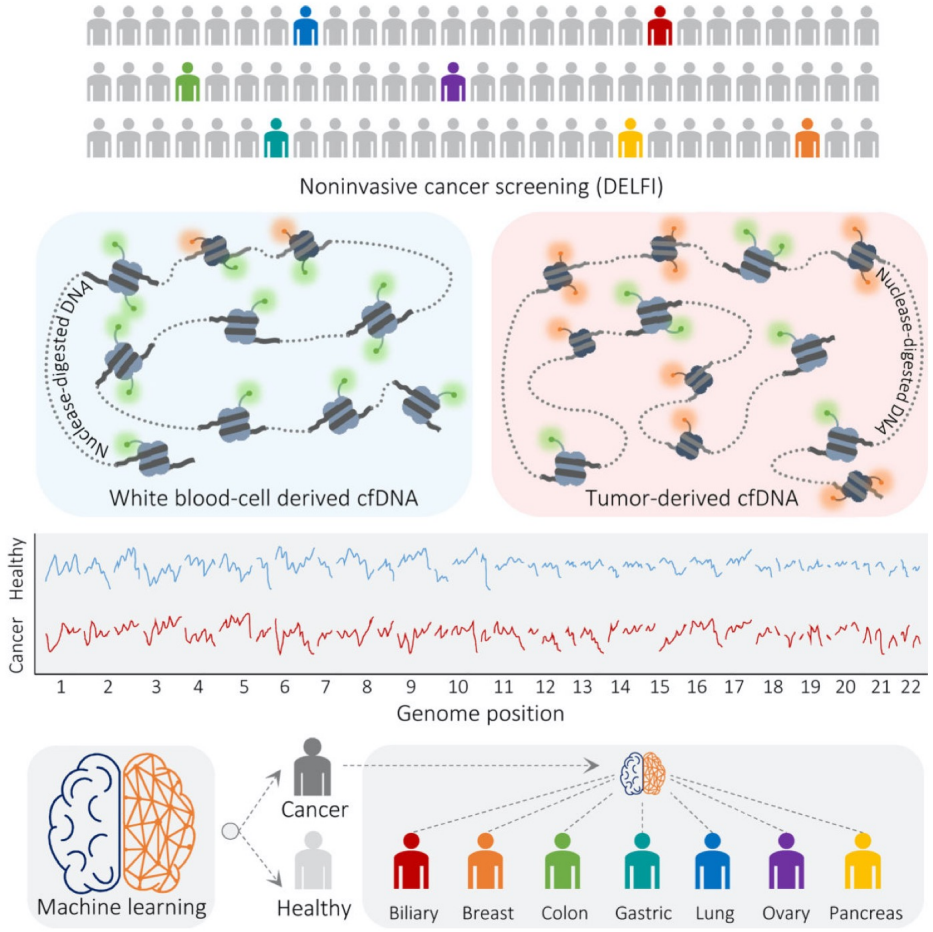


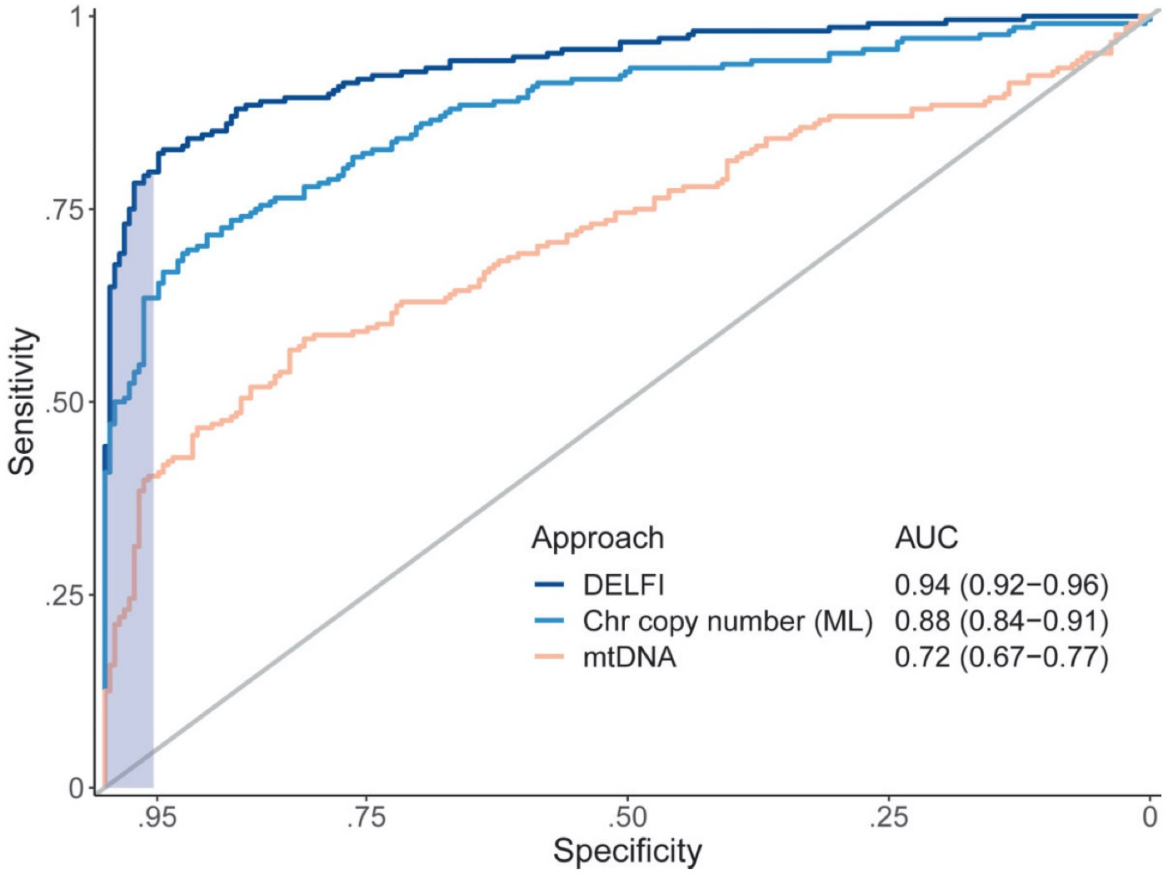


Specificity	90%	95%	98%
CRC	93.1%	85.7%	71.6%
Lung Cancer	92.1%	86.3%	66.4%

Valouev et al. ASCO 2022 TPS1602; SHIELD NCT05117840

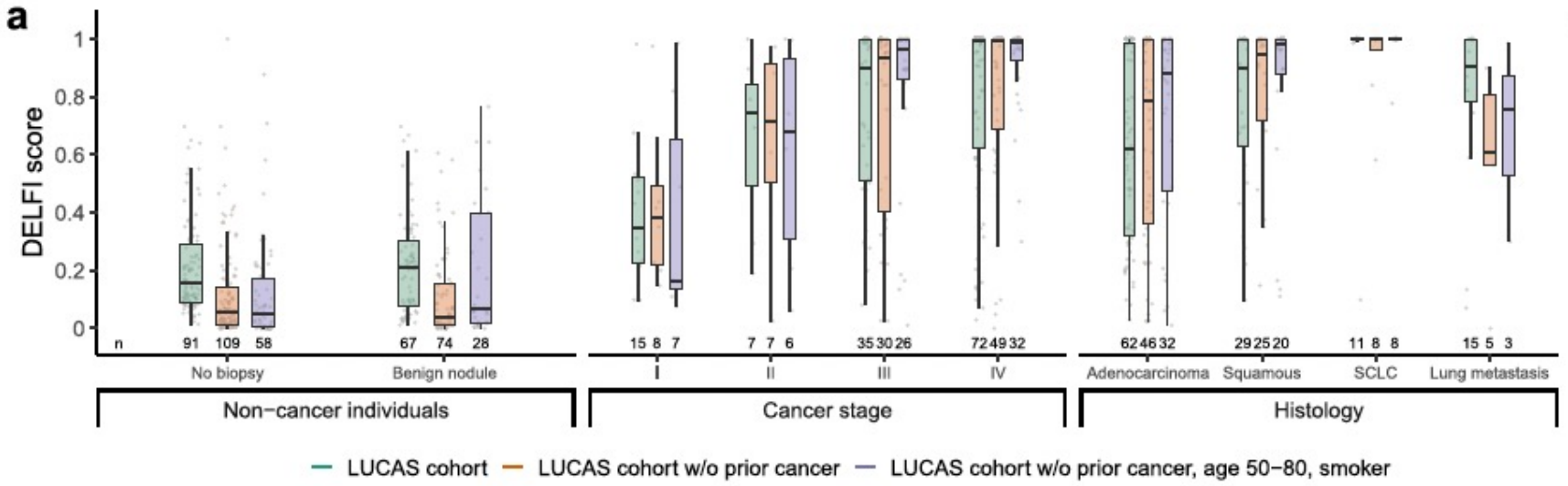
Cancer diagnosis using Genome Wide ctDNA Fragmentation

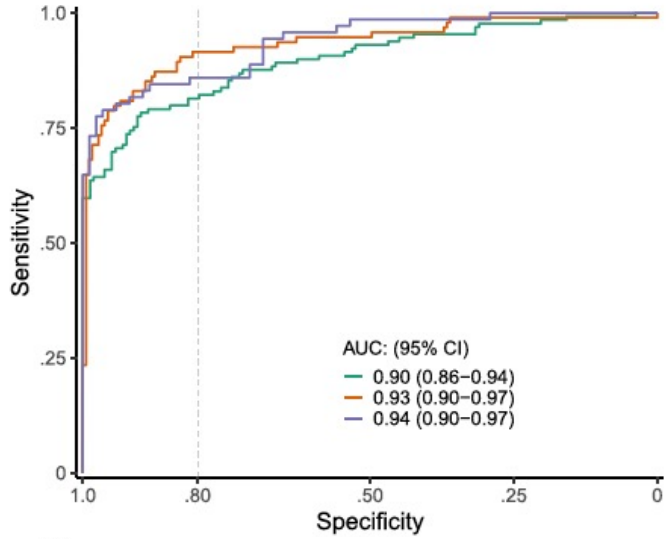


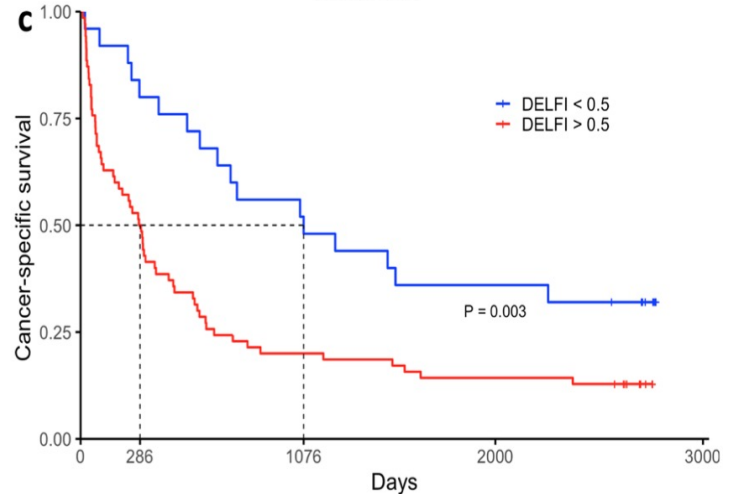


Cristiano et al Nature 2019

Higher DELFI scores in those with lung cancer

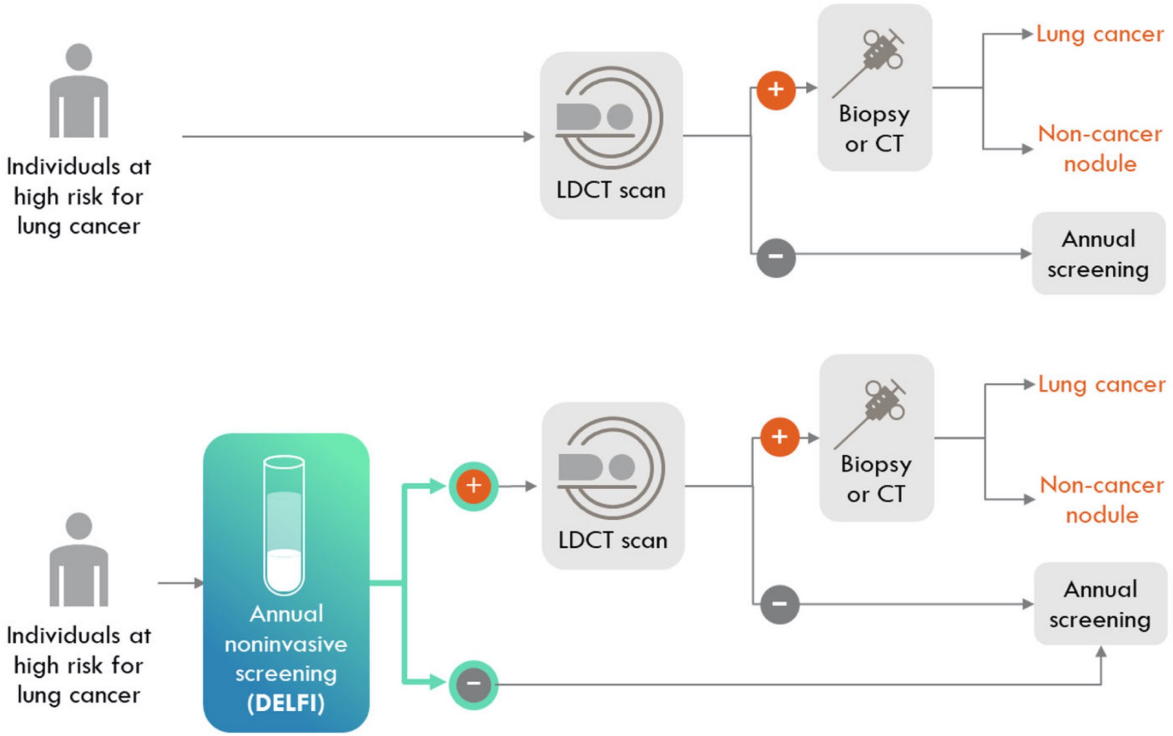


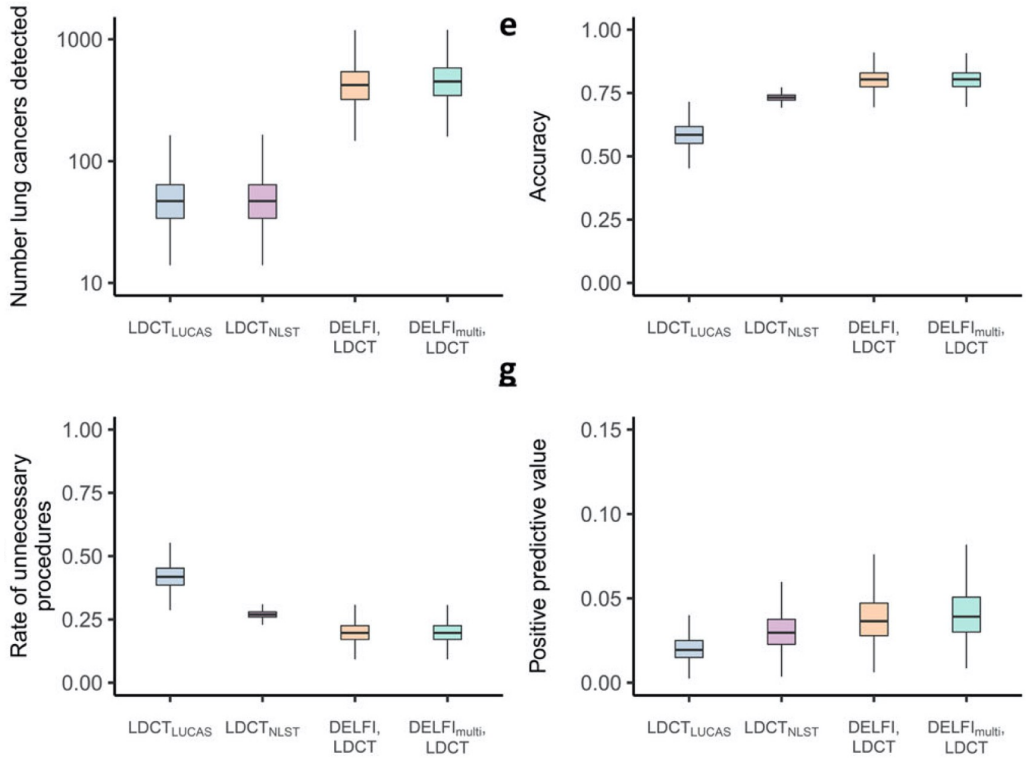




Mathios et al Nature Comm 2021

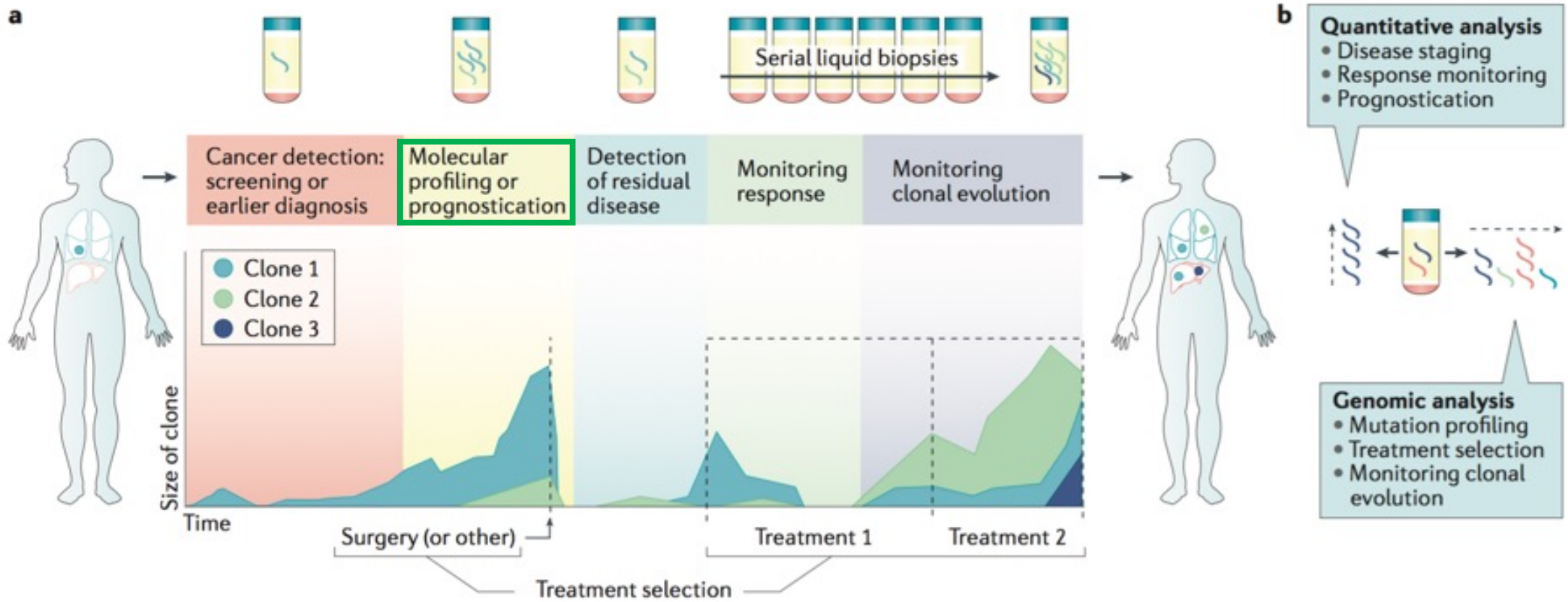
The future? Hypothesized potential improvement with adding shallow whole genome sequencing (DELFI) to LDCT





Mathios et al Nature Comm 2021

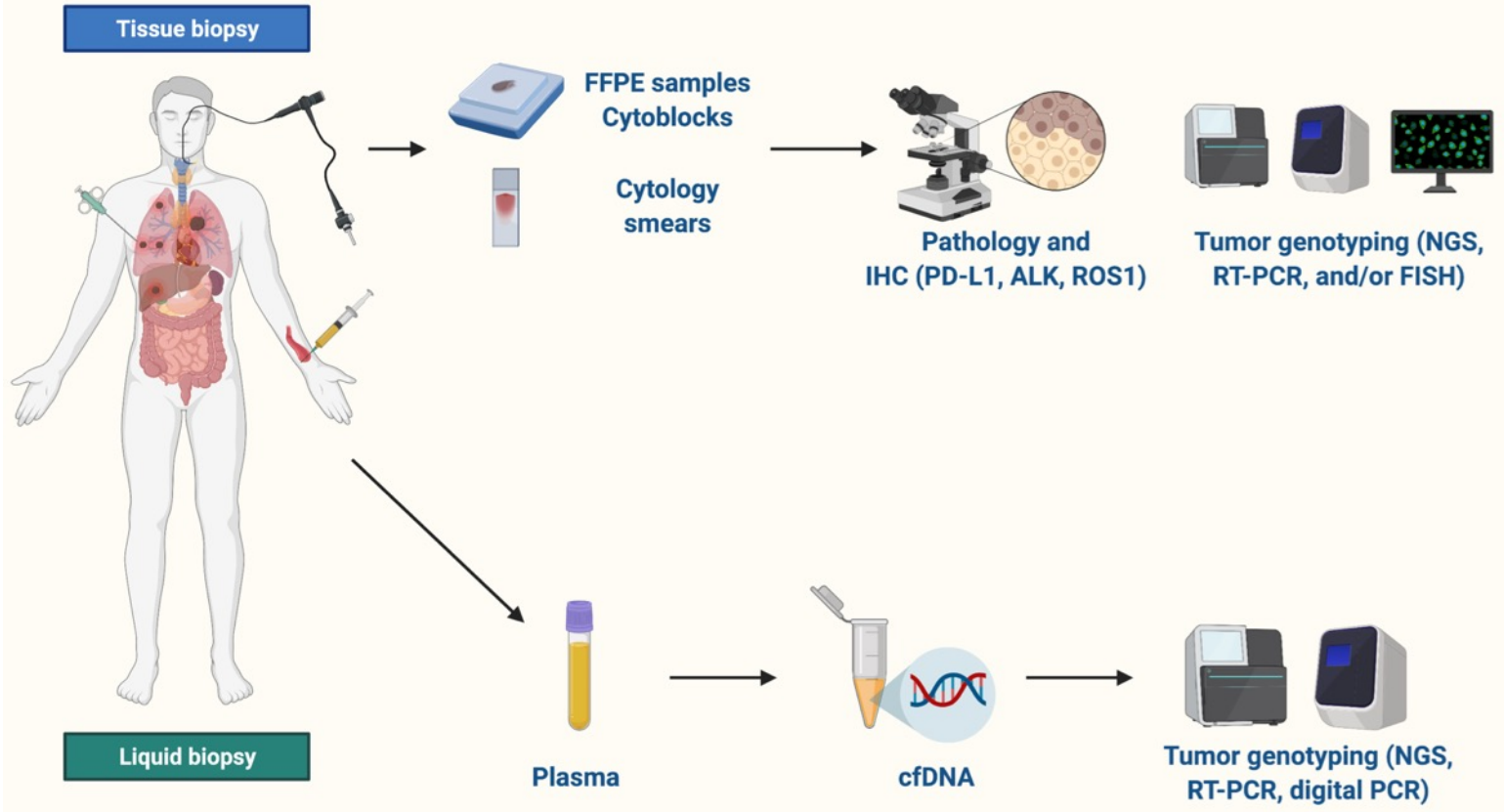
Current Roles of Liquid Biopsy in Lung Cancer in Clinic



Wan et al. Nat Rev Cancer 2017

Liquid Biopsy in Advanced NSCLC: 2021 IASLC Consensus Statement

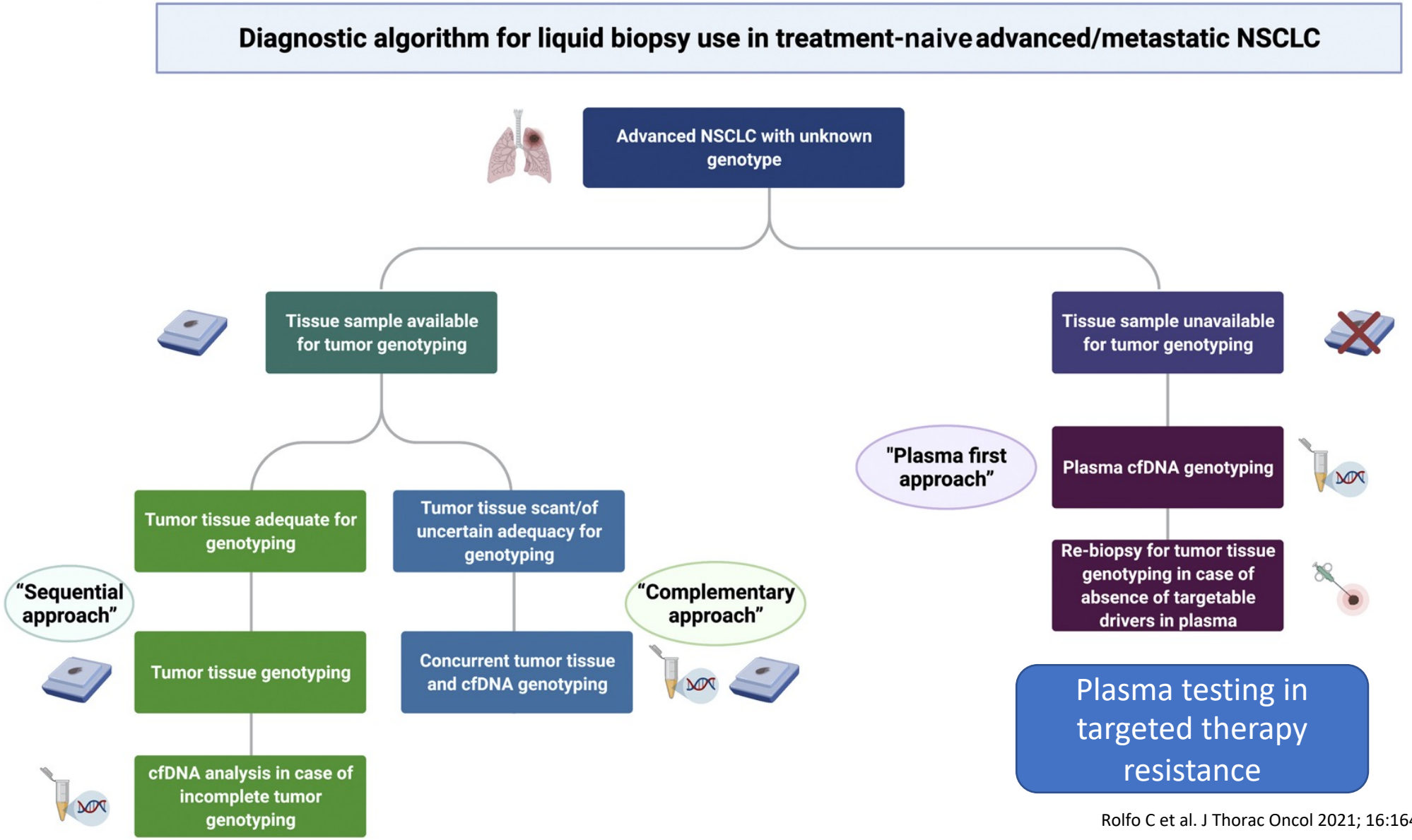
Tissue vs. Liquid Biopsy



	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; 16:1647-1662.

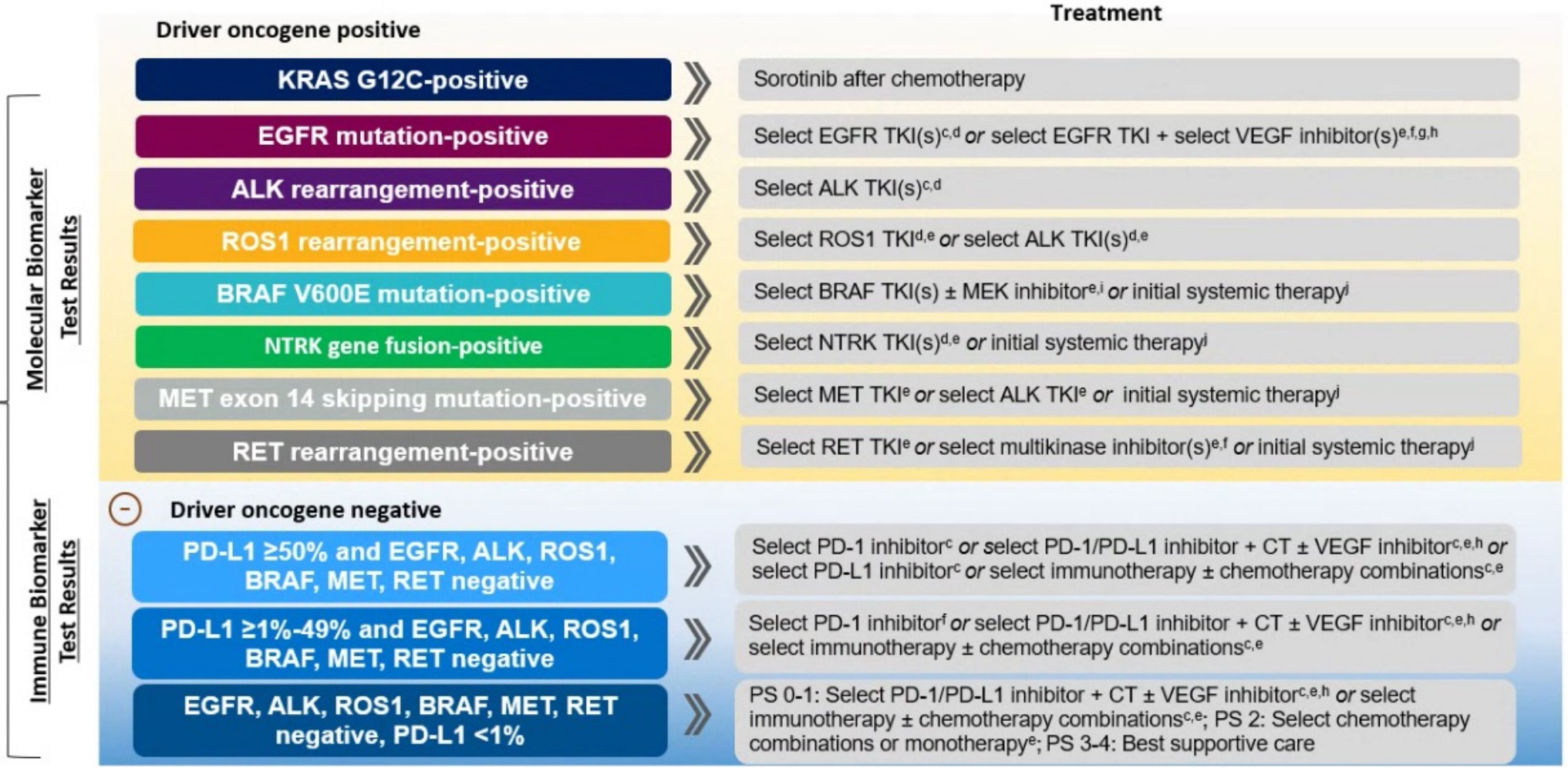
Plasma cfDNA testing can be used in genotyping of patients with advanced NSCLC



Rolfo C et al. J Thorac Oncol 2021; 16:1647-1662.

Actionable driver oncogenes in metastatic lung cancer (2022)

ASCO/OH, NCCN Guidelines® recommend biomarker testing for eligible patients with mNSCLC and treating patients based on results[a,b]

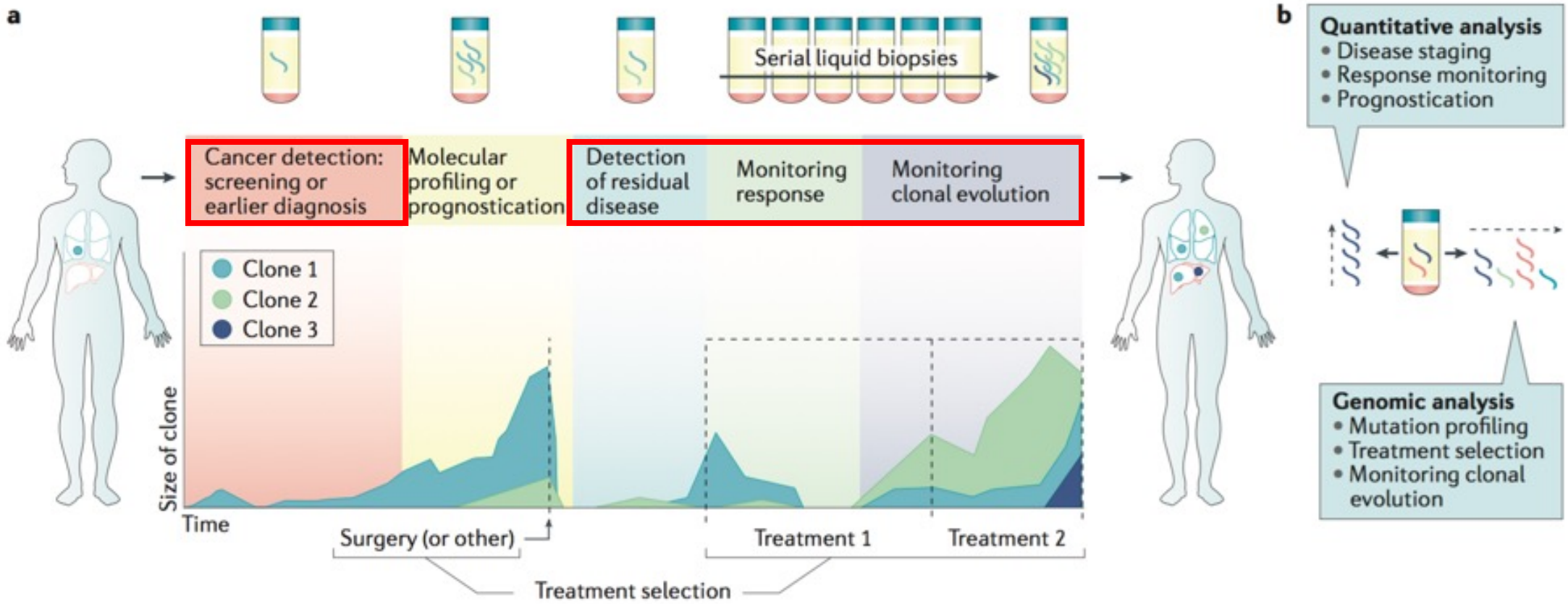


[a]Refer to the NCCN Guidelines® for specific treatment recommendations for each setting. Not all agents in a drug class are recommended for all settings. [b]The NCCN NSCLC Panel recommends molecular testing and strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. [c]Category 1. [d]For PS 0-4. [e]Category 2A. [f]Category 2B. [g]Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. [h]An FDA-approved biosimilar is an appropriate substitute for bevacizumab. [i]Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated. [j]Category 1 or category 2A.

ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CT, chemotherapy; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase; MET, MET proto-oncogene, receptor tyrosine kinase; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2021. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data become available.

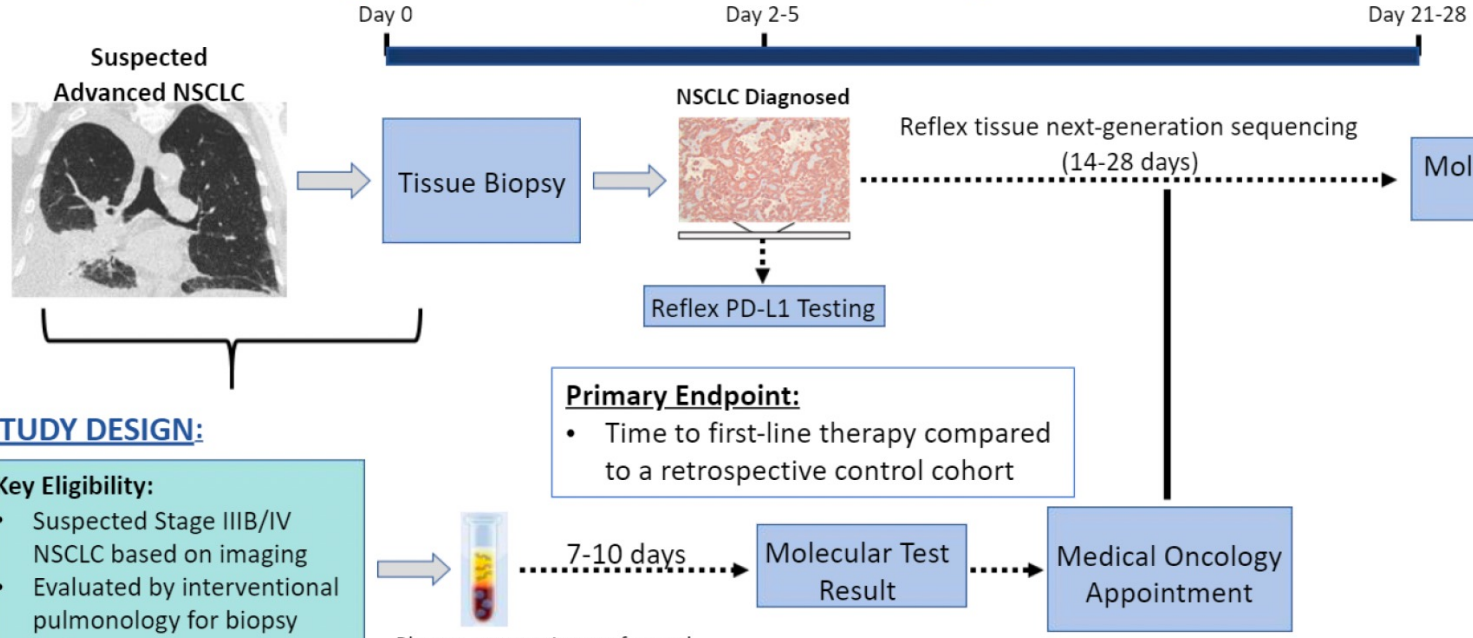
Slide adapted from Dr. Xiniung Le, MD Anderson Cancer Centre

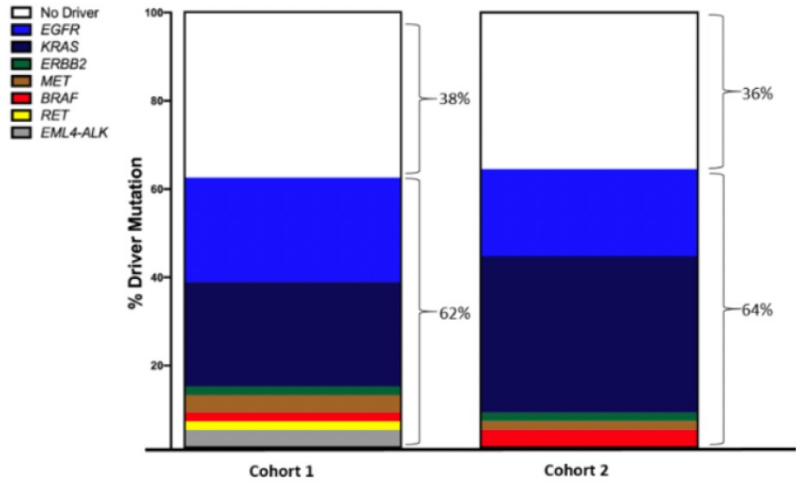
Future Roles of Liquid Biopsy



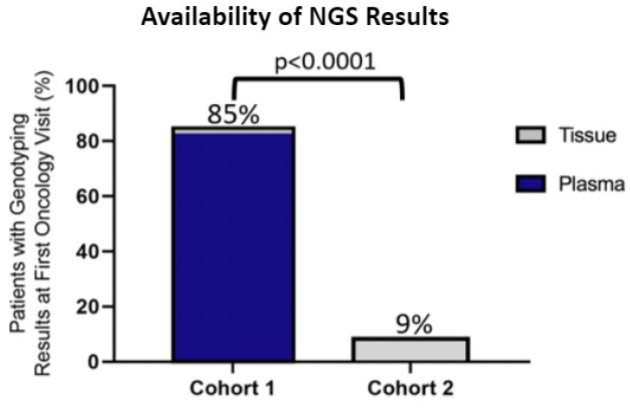
Wan et al. Nat Rev Cancer 2017

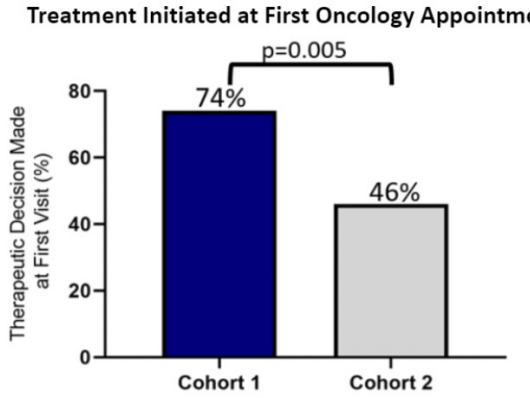
Thompson, et al (Abstract 405)

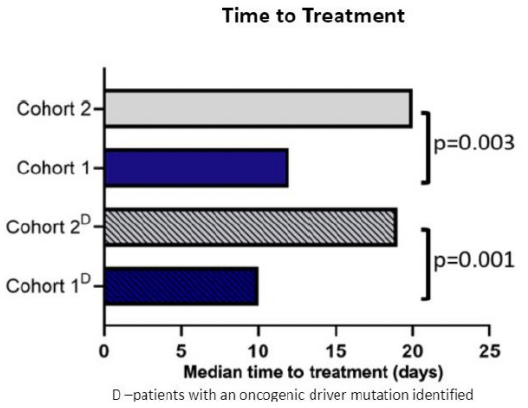




N=55 prospective pts
N=55 retrospective "controls"



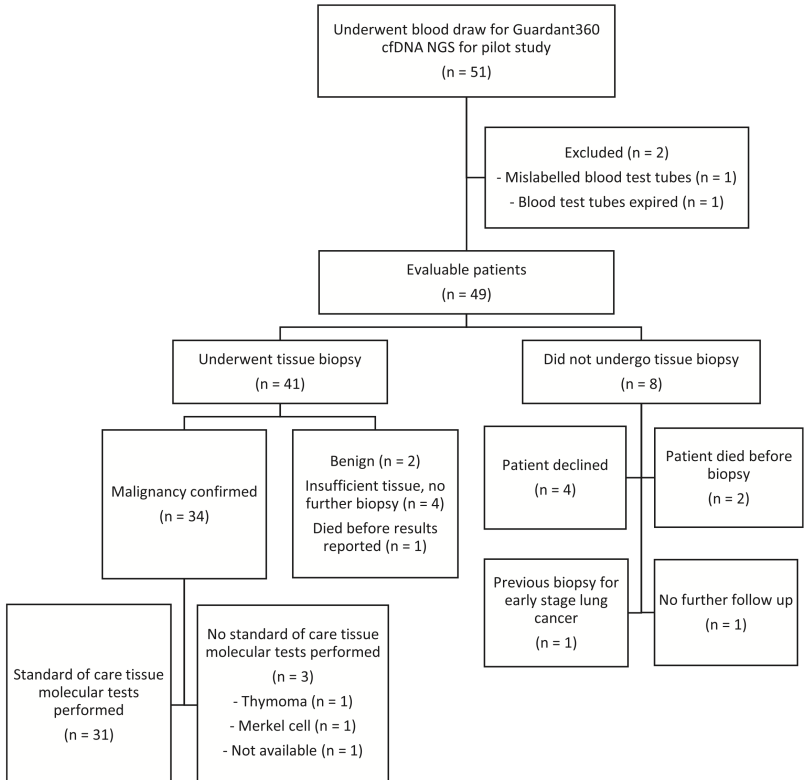


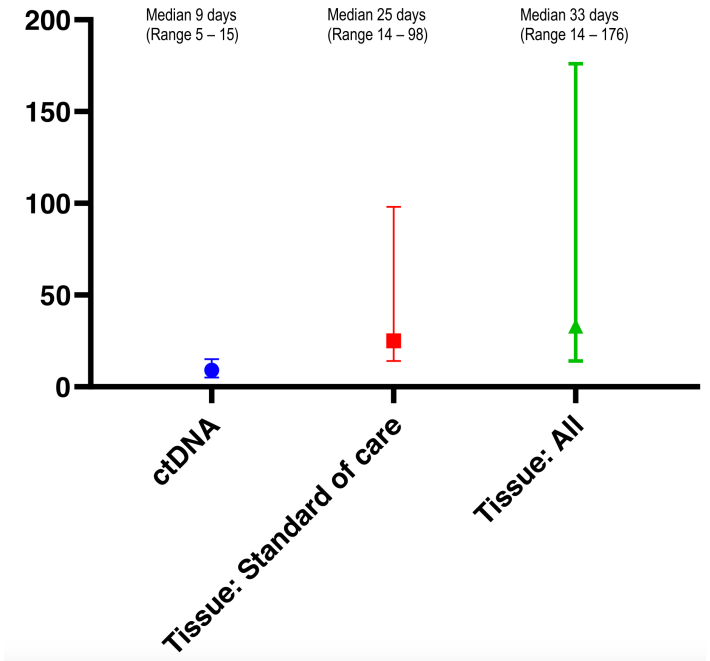


Thompson JC et al. JTO Clin Res Rep. 2022 Mar 8;3(4):100301.

UK Study: Plasma testing for suspected advanced lung cancer (n=51)

- Liquid biopsy taken when tissue biopsy taken
- 30 (61%) had actionable alterations (tier 1 variants ASCO/AMP/CAP) identified
- 20 alterations identified in plasma only, 3 alterations identified in tissue only
- 11 (22%) started targeted therapy based on plasma results before tissue available





Cui et al Lung Cancer 2022; 165:34-42.

ACCELERATE: Preliminary Results (N=60)

Liquid Biopsy first

REFERRAL to RAPID DIAGNOSTIC PROGRAM

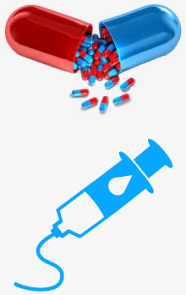
2 days

7 days

Molecular Diagnosis

25 days including tissue biopsy

Treatment



Faster time to results
(9 versus 36-46 days, P<0.0001)

Shorter time to treatment
(34 versus 62 days, P<0.0001)

More patients received targeted therapy (49% v. 29%)

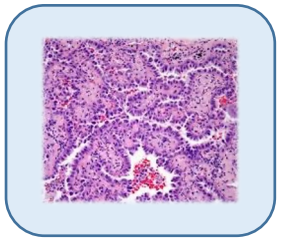
27% of patients started therapy based on plasma testing before tissue results available

Tissue Biopsy standard of care pathway

REFERRAL to RAPID DIAGNOSTIC PROGRAM

10-25 days

Tissue Biopsy

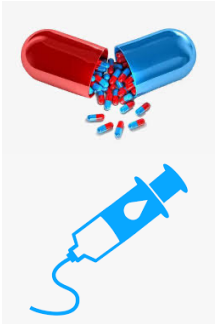


21-26 days

Molecular Diagnosis

16-26 days

Treatment



Times for tissue pathway based on study data and historical data

Garcia-Pardo M et al.. Leighl NB. Proc ASCO 2022. J Clin Oncol 2022; 40(Suppl 16), abstr 3039
NCT04863924

Where we are today in lung cancer?

- Molecular diagnosis

If actionable target in blood → treat
If none → profile tissue or repeat biopsy
For histologic transformation → biopsy

- Monitoring

ctDNA levels correlate with outcomes – clinical utility studies ongoing

- MRD

Presence of MRD is prognostic –
Ongoing trials to demonstrate utility

- Screening

Many exciting novel biomarkers under study
- miRNA, ctDNA, methylation, multimodal assays, metabolomics…
- Ongoing trials to demonstrate utility, cost effectiveness

Thank you!