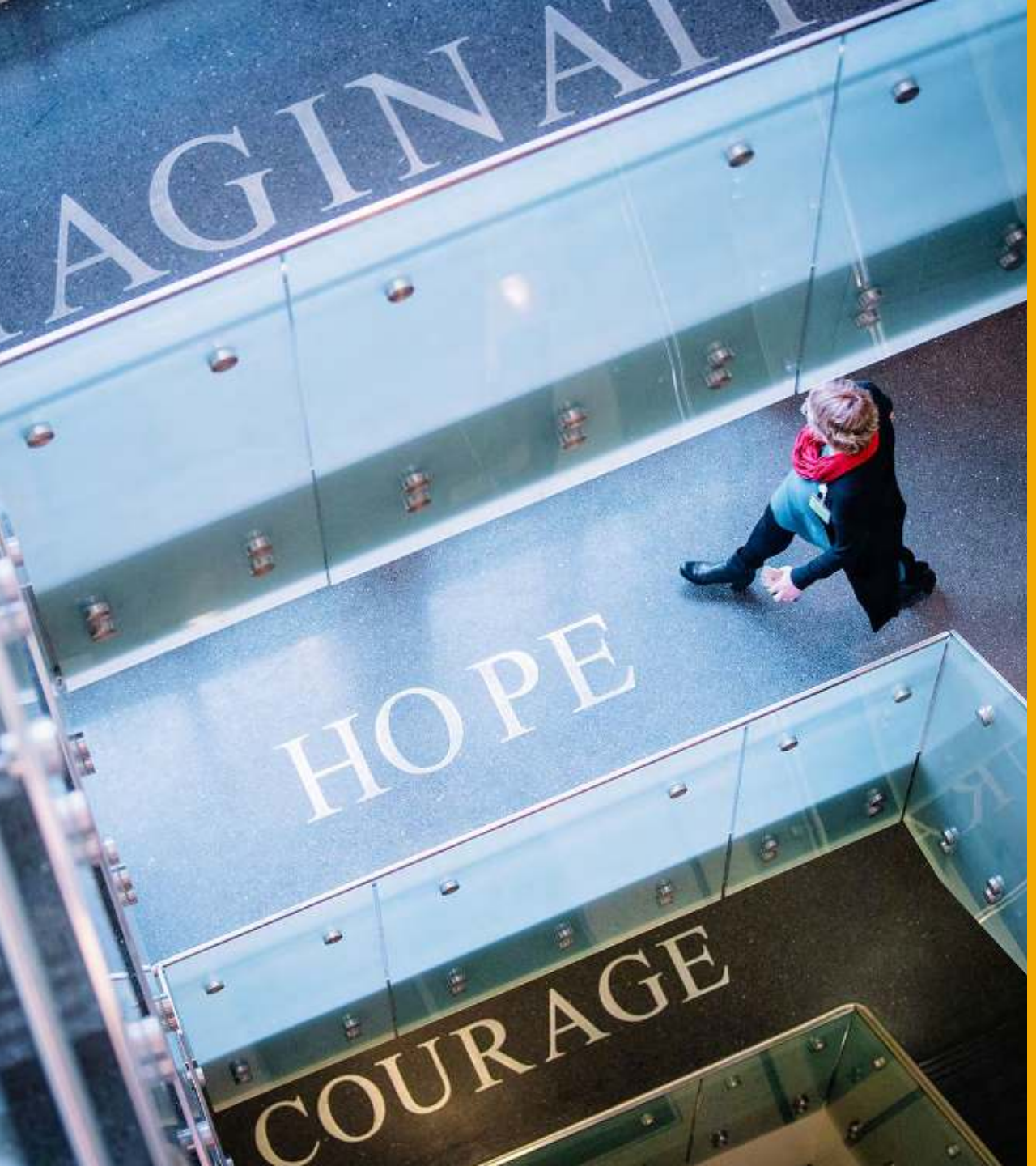


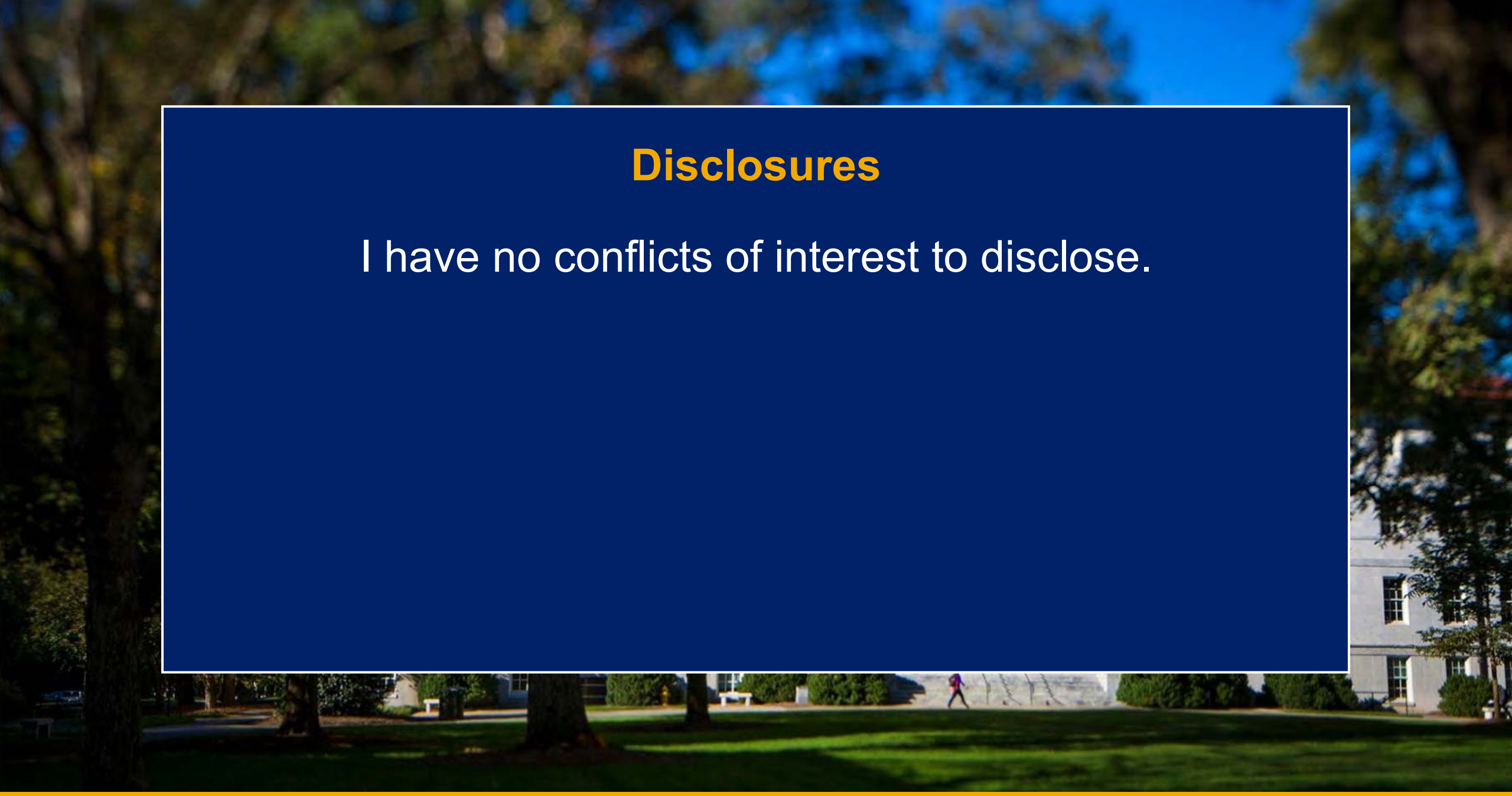
OPTIMAL NGS TESTING AT DIAGNOSIS OF ADVANCED NSCLC: TISSUE AND PLASMA

Jennifer W. Carlisle, MD

Assistant Professor
Winship Cancer Institute of Emory University
Emory University School of Medicine

EMORY WINSHIP CANCER INSTITUTE

NCI Designated Comprehensive Cancer Center



Disclosures

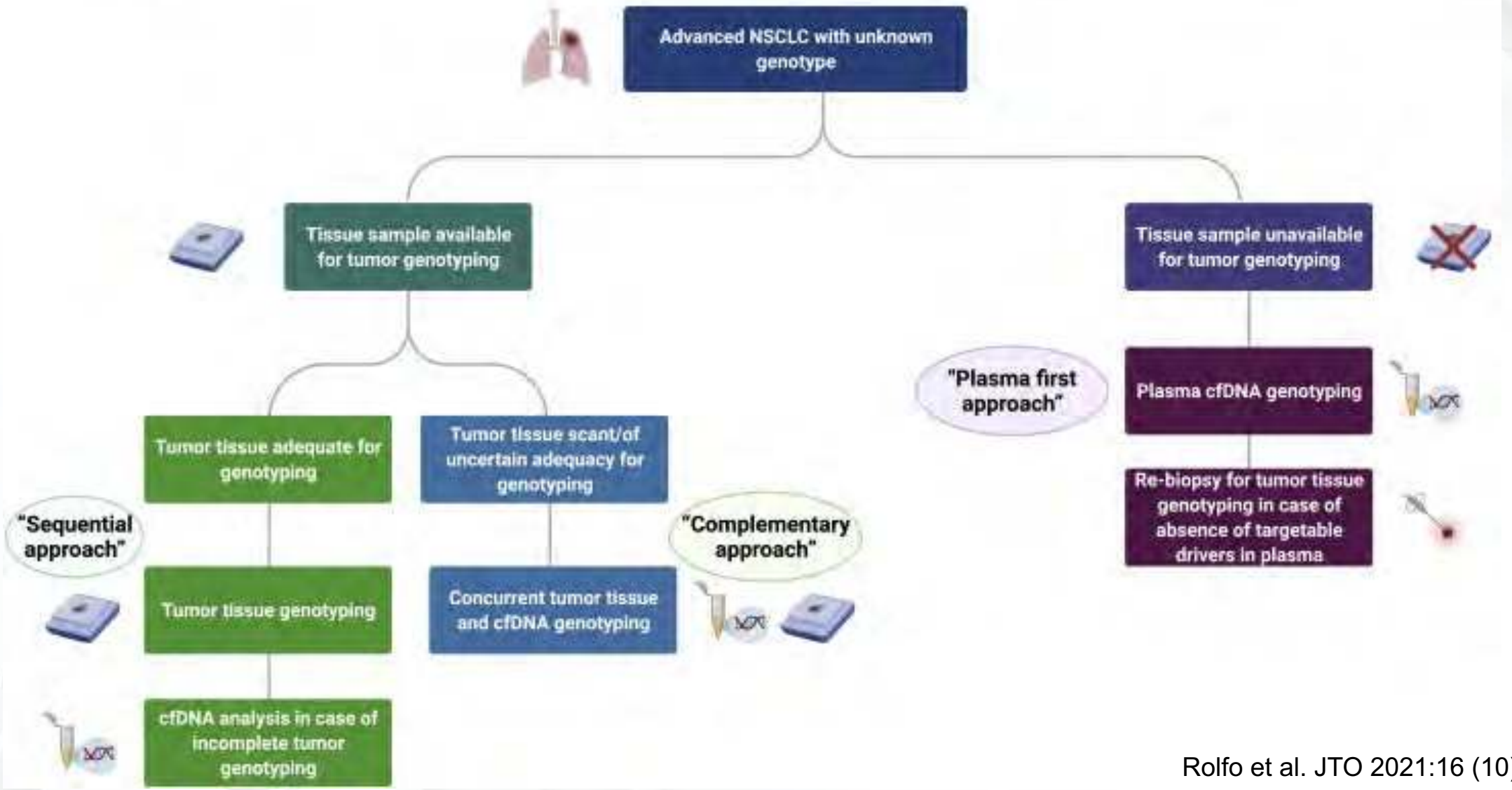
I have no conflicts of interest to disclose.

Not for debate:

- Patients with advanced non-squamous NSCLC **REQUIRE** molecular testing at diagnosis.

- Rather than piecemeal mutation testing, all patients should get comprehensive **Next Generation Sequencing (NGS)**
  - Rapid pace of FDA approvals in NSCLC
  - Clinical trial options
  - Efficient use of precious tissue samples
  - Lower limit of detection
  - Detects all variants in analyzed gene region, not just hot spot probes

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



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

Tissue NGS

Advantages:

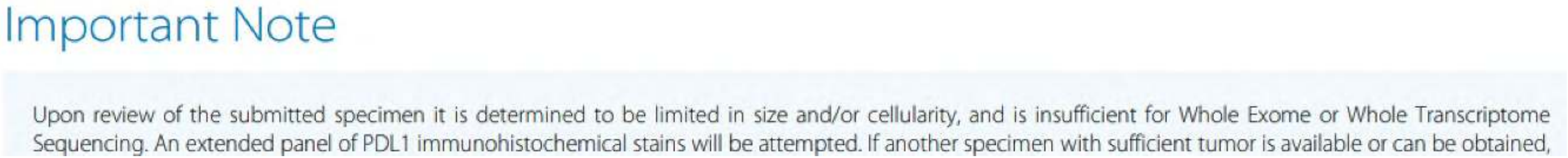
- Need pathologic tissue diagnosis
- PD-L1 assessment
- At progression can assess for histologic transformation

Disadvantages:

- Unfavorable biopsy site – CNS, Bone, multiple small pulmonary nodules
- Risks of invasive procedure – 5% complication rate in CT guided lung biopsies
- Time for scheduling procedure / time for processing and results reporting
- Cost

Pitfall of tissue NGS

3 weeks later you get the result:



Important Note

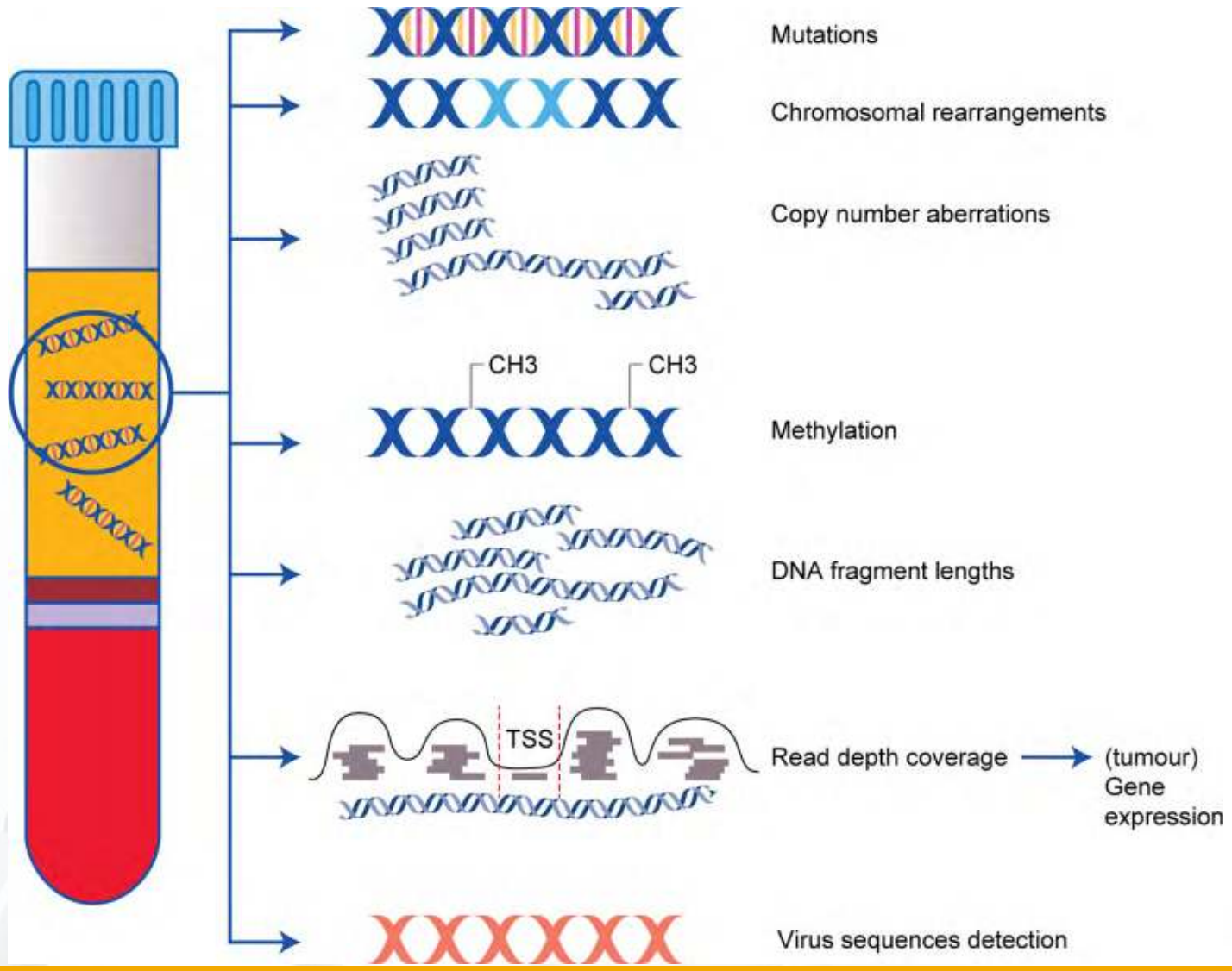
Upon review of the submitted specimen it is determined to be limited in size and/or cellularity, and is insufficient for Whole Exome or Whole Transcriptome Sequencing. An extended panel of PDL1 immunohistochemical stains will be attempted. If another specimen with sufficient tumor is available or can be obtained,

QNS- quantity not sufficient

With just a few drops of blood…

Just kidding!

Circulating Tumor DNA



2-3 tubes of whole blood (10-16 cc)

Tumor mutation burden

Microsatellite stability status

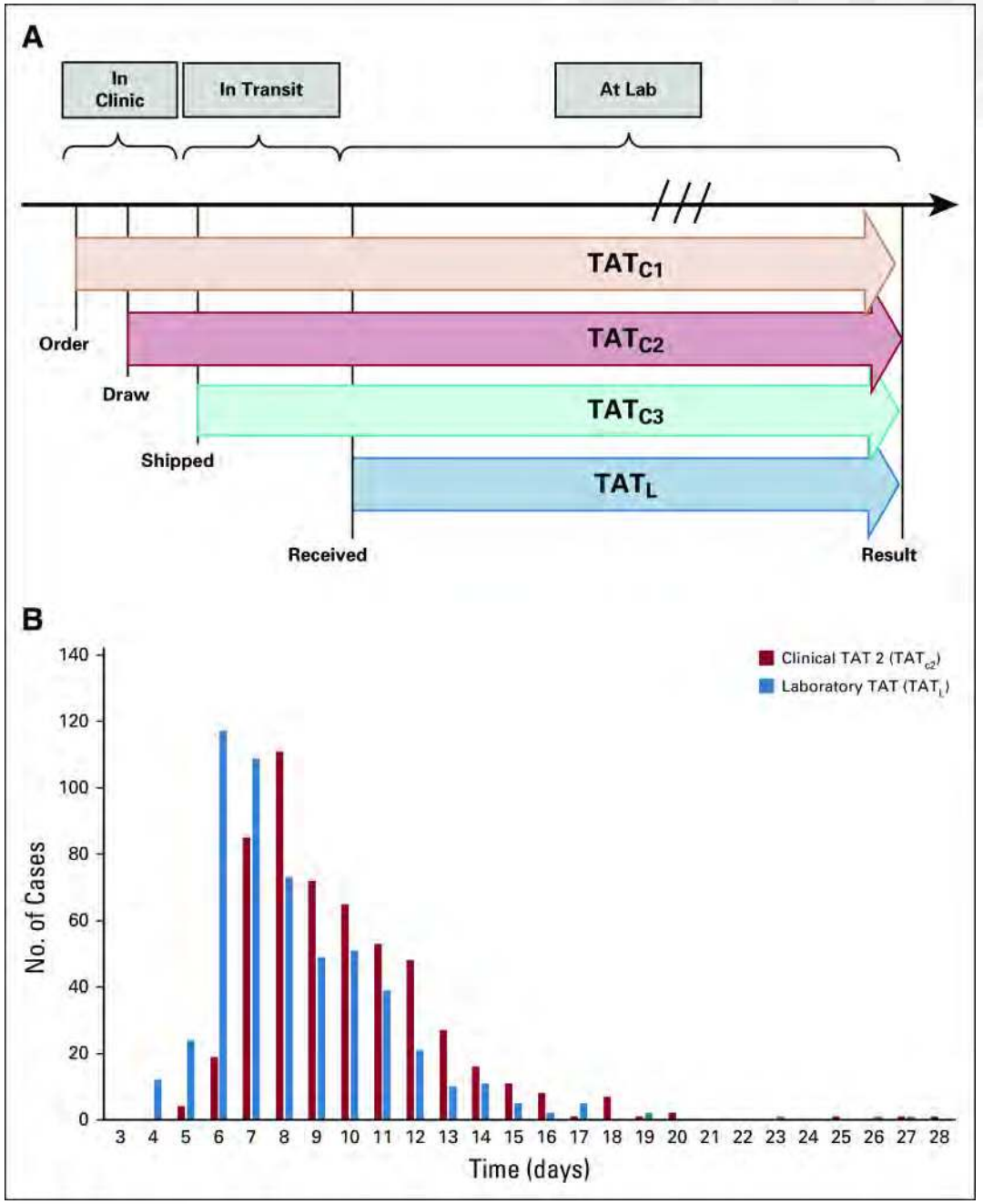
Tumor heterogeneity

Germline mutations – variant allele frequency ~50% for heterozygous mutations
- confirm with formal genetic testing

Keller et al. British J Cancer 2021:124;345–358

Workflow of PLASMA NGS

- Most commercial partners have turn around time of 7-10 days
- Start time can vary from date of blood draw to the date of receipt of specimen
- Billing typically handled by the company, with patient assistance programs that will minimize out of pocket costs to the patient



Lee et al. JCO Precis Oncol. 2020; 4: PO.20.00121.

Pitfalls of PLASMA NGS

- **False Negatives: "non-shedders"**

  Many variables impact amount of ctDNA:

  -total tumor burden
  -location and extent of metastases
  -proliferation rate
  -apoptotic potential
  -genome instability
  -gene amplification and loss (proportion of mutant alleles)

a

Histological subtype			TNM Stage I	II	III	Total
LUAD	ctDNA detected	Yes	5	2	4	11
		No	34	7	6	47
LUSC	ctDNA detected	Yes	16	12	2	30
		No	1	0	0	1
Other	ctDNA detected	Yes	1	2	2	5
		No	2	0	0	2

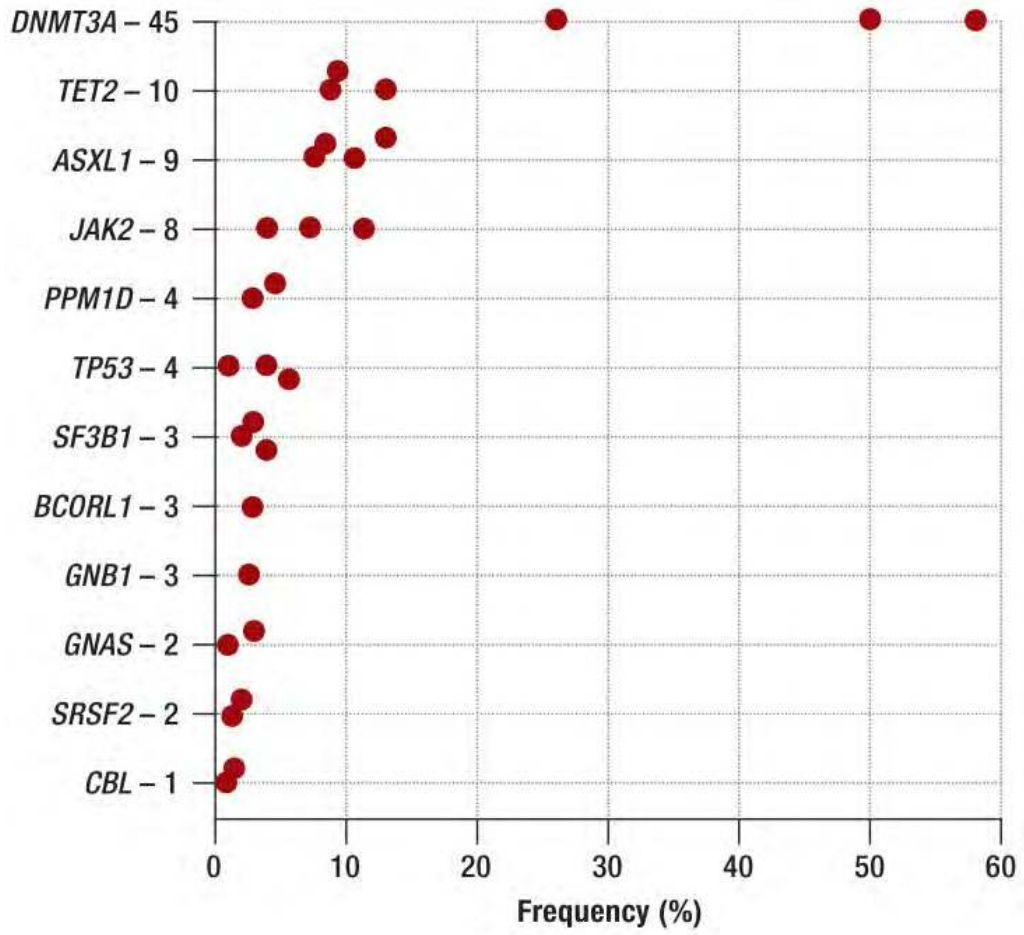
Abbosh C.et al. Nature. 2017; 545: 446-45

Pitfalls of PLASMA NGS

- **Confusion re: non-tumor mutations**

Clonal hematopoiesis of indeterminate potential

- somatic mutations found in immune cells
- no other criteria for hematologic neoplasia
- prevalence rises with age and is roughly 10% among persons aged 70 to 80

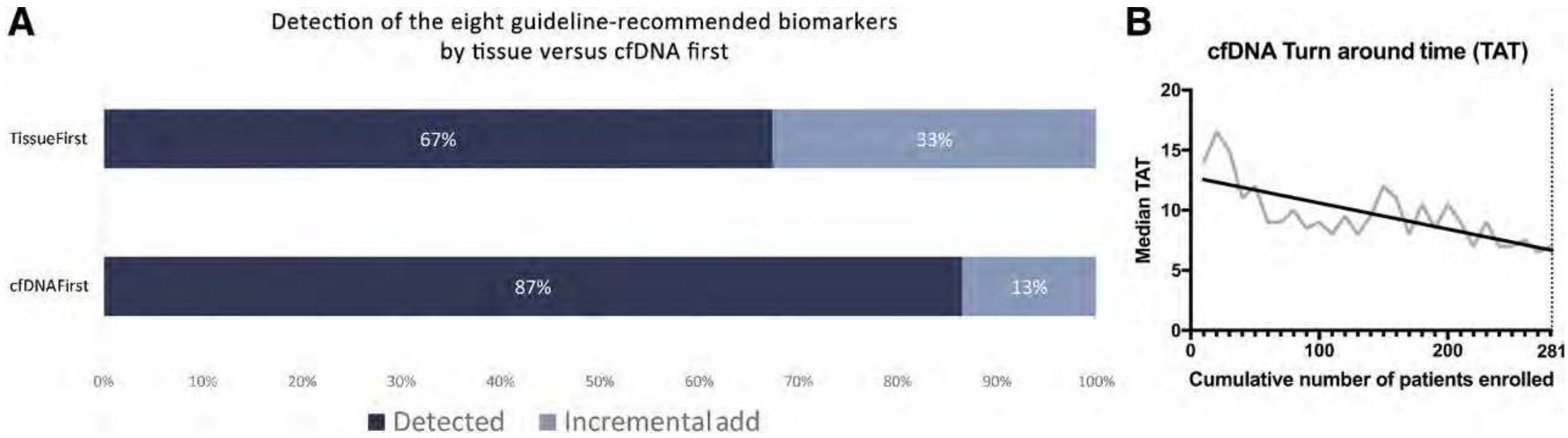


Hueser et al. Dtsch Arztebl Int. 2016; 113(18): 317–322

Concurrent Tissue and Plasma Testing

NILE study (Non-invasive versus Invasive Lung Evaluation; NCT03615443)

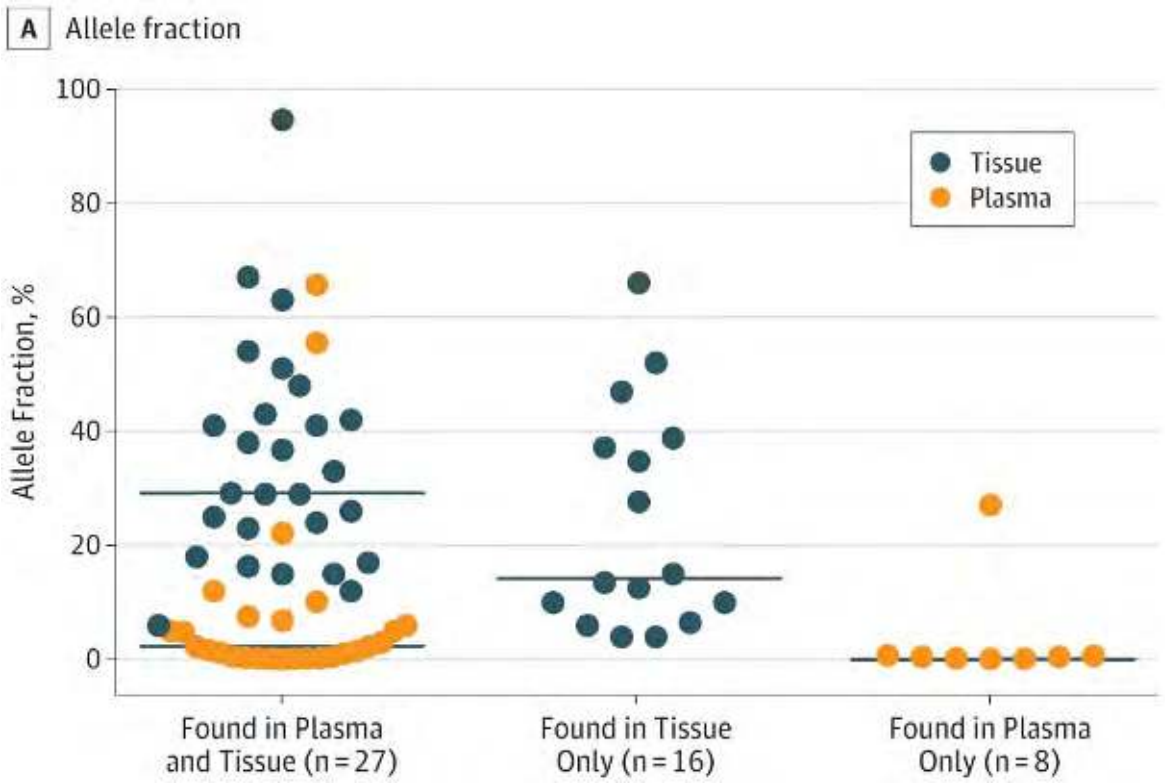
enrolled 307 patients with biopsy proven, previously untreated, nonsquamous mNSCLC (stage IIIB/IV) undergoing physician discretion SOC tissue genotyping at one of 28 North American centers

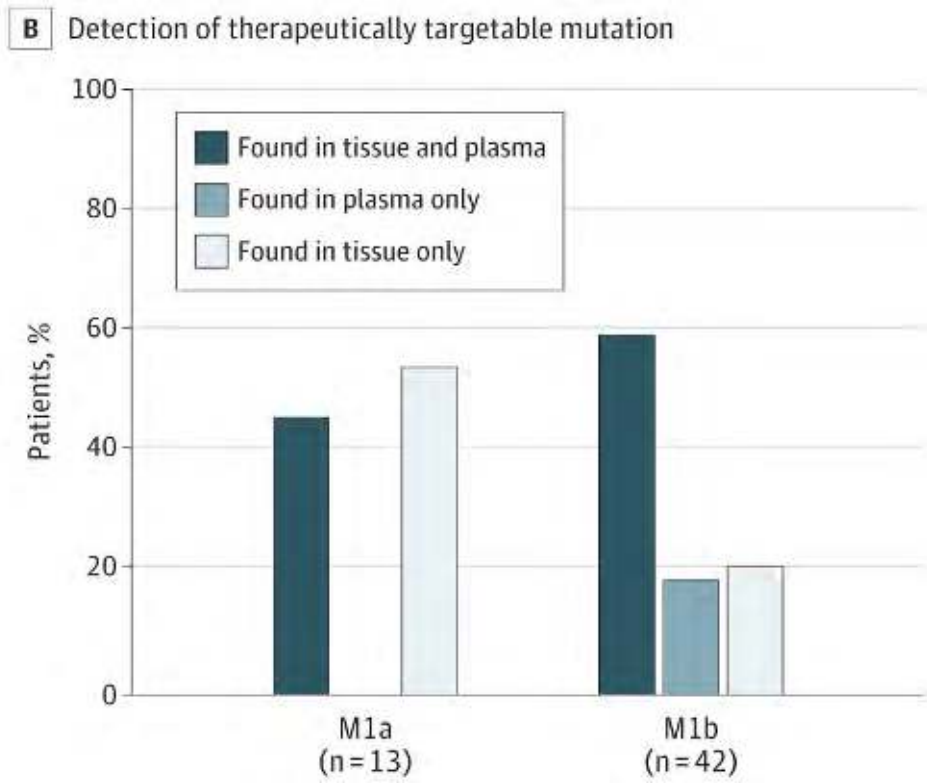


Leighl et al. Clin Cancer Res. 2019;25(15):4691-4700.

Concurrent Tissue and Plasma Testing

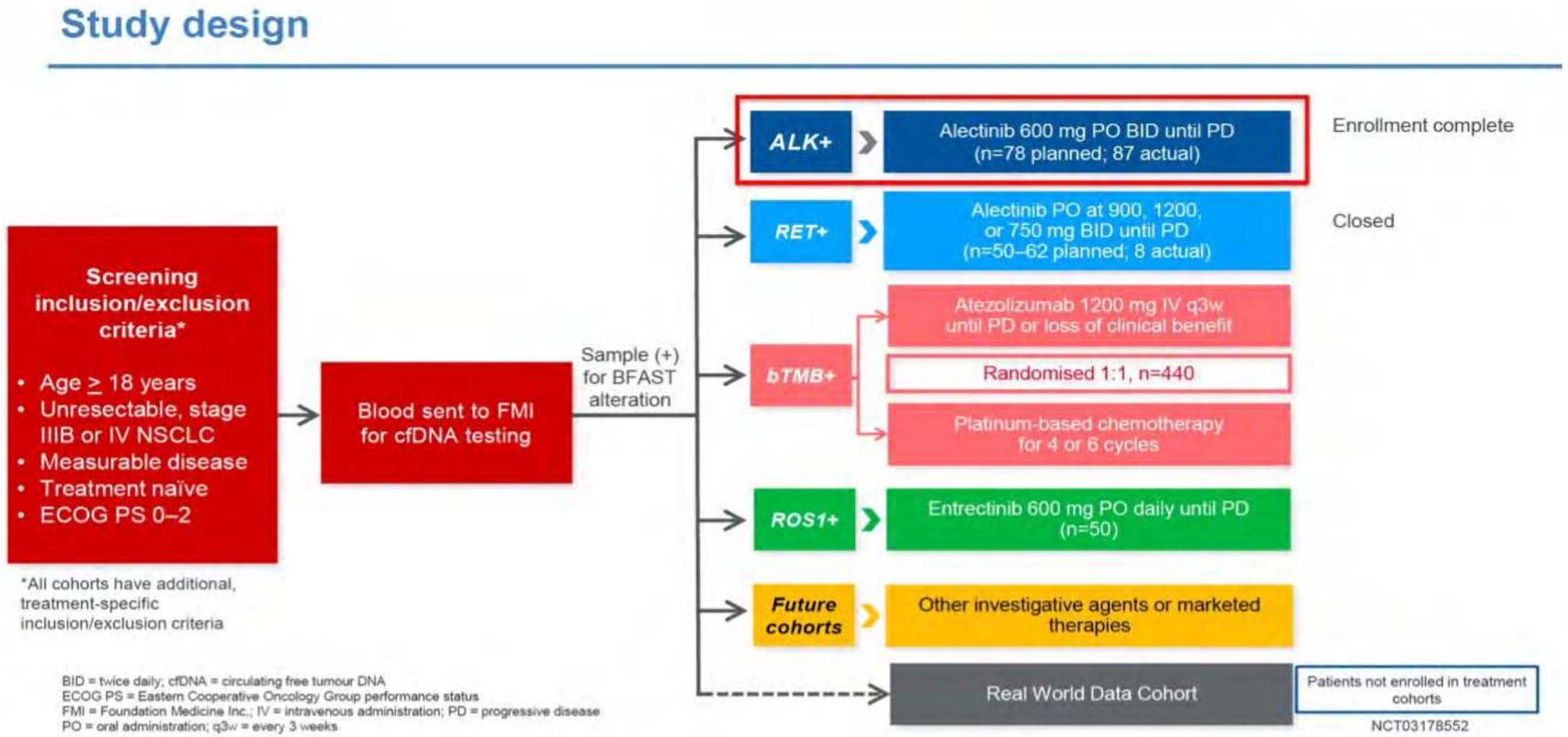
Prospective single institution study of 323 patients with metastatic NSCLC
Tissue alone detected targetable mutations for 47 patients (20.5%)
Adding plasma sequencing increased targetable mutation detection to 82 (35.8%)





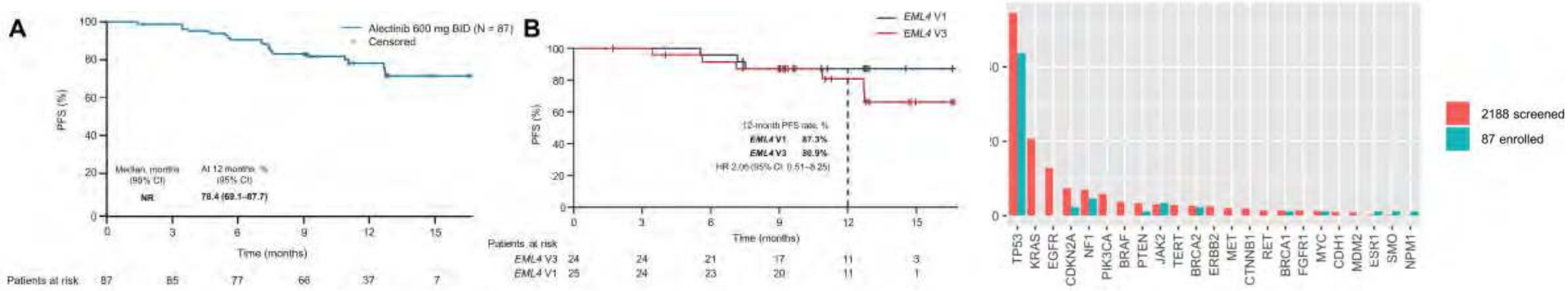
Aggarwal et al. JAMA Oncol. 2019;5(2):173-180.

Blood First Assay Screening Trial (BFAST)



Gadgeel et al. Annals of Oncology (2019) 30 (suppl_5): v851-v934.

BFAST: Treatment-Naive Advanced or Metastatic NSCLC: Initial Results of the Phase 2 *ALK*-Positive Cohort

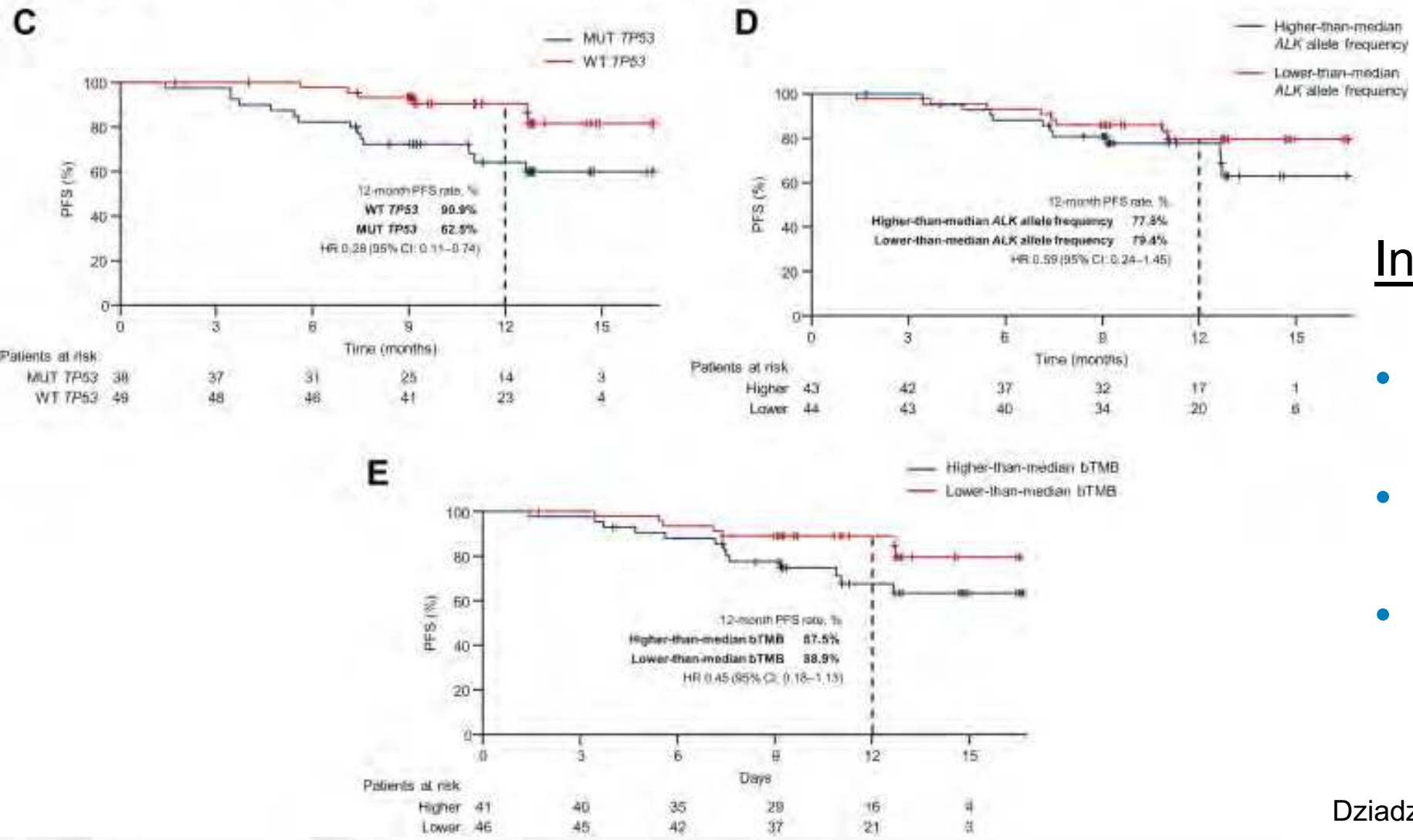


Primary endpoint of the *ALK*+ cohort: investigator-confirmed ORR of 87.4% (central review 92.0%)
Key secondary endpoints: 6-month DoR 90.4%, 12-month PFS 78.38%

Clinical utility of blood-based NGS as a method to inform clinical decision-making in *ALK*+ NSCLC

Dziadziuszko et al. JTO 2021:16(12): 2040-2050.

BFAST: Treatment-Naive Advanced or Metastatic NSCLC: Initial Results of the Phase 2 *ALK*-Positive Cohort

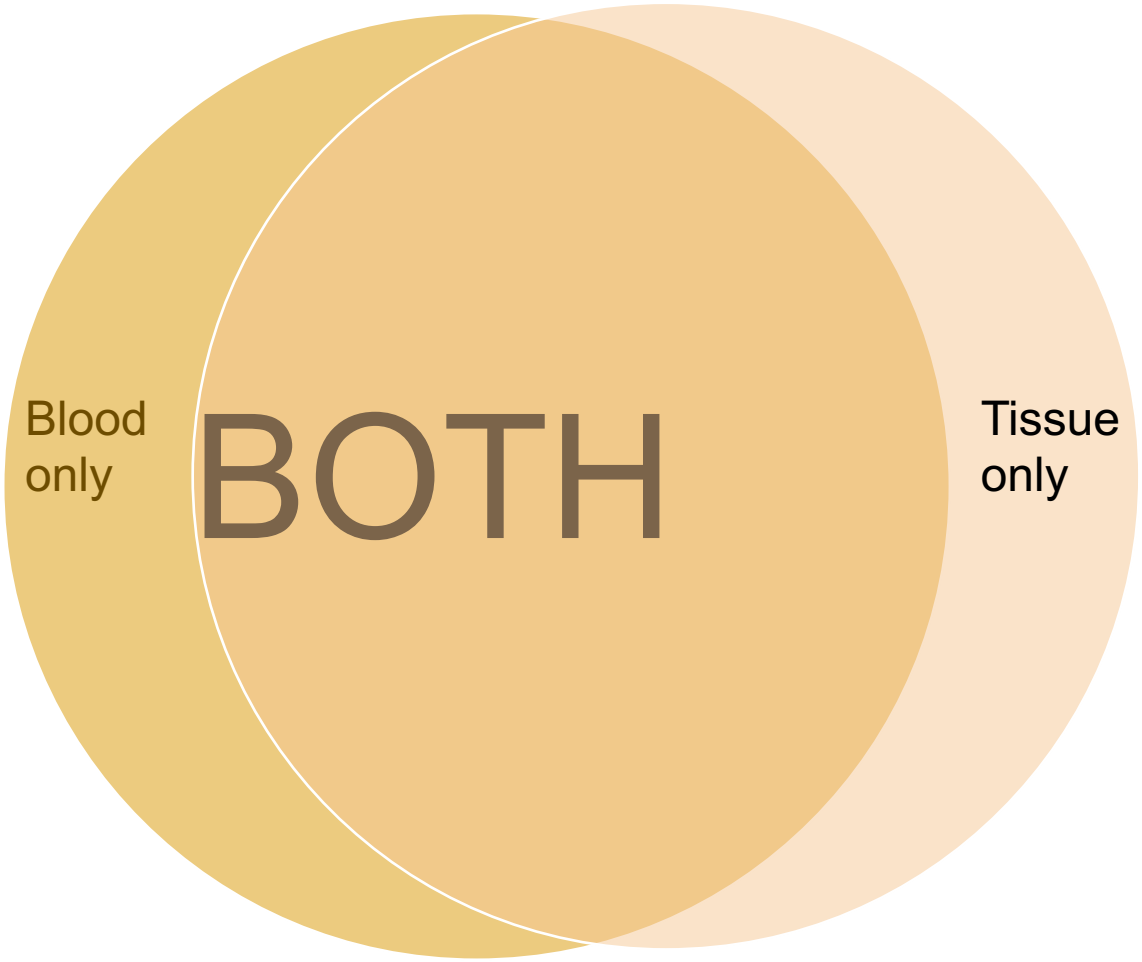


Investigation the impact of:

- Co-mutations
- Allele frequency
- TMB

Dziadziuszko et al. JTO 2021:16(12): 2040-2050.

In my practice:



Blood draw today, results in 7 days

I call the patient with actionable results from clinic the next week

Otherwise wait on tissue testing for mutations and PD-L1 score

Conclusion: add plasma NGS testing at Diagnosis of advanced NSCLC

Concurrent tissue & plasma NGS	Sequential tissue → plasma NGS
Identifies more targetable mutations	Saves (some) cost
Saves time / start targeted therapy sooner	
Additional research opportunities	
Ease of use may increase uptake of comprehensive NGS?	