

Prevalence of 9p21 (*MTAP/CDKN2A*) loss in advanced NSCLC in East and Southeast Asia using tissue- and plasma-based CGP

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INTRODUCTION

- Homozygous deletion of the 9p21 locus, frequently involving *MTAP* and *CDKN2A*, is recurrent in non-small cell lung cancer (NSCLC) and has emerging therapeutic relevance as a biomarker for *MTAP*-pathway-targeted strategies, including *PRMT5*-directed approaches.^{1,2}
- However, prevalence data from East and Southeast Asian populations remain limited.

OBJECTIVE

- To evaluate the prevalence of 9p21 loss in advanced NSCLC (aNSCLC) using real-world comprehensive genomic profiling (CGP) of tissue and plasma samples.

METHODS

- We retrospectively analyzed aNSCLC samples tested in routine clinical practice across East and Southeast Asia through July 2026 using Guardant360[®] Liquid (plasma) or Guardant360[®] Tissue. Copy number loss (CNL) was reported for 14 genes on the Liquid assay (including *MTAP* and *CDKN2A*) and 30 genes on the Tissue assay. 9p21 loss was defined as loss of *MTAP* and/or *CDKN2A*.
- CNL was classified separately by sample type:
 - Plasma:** Biallelic loss by homozygous deletion (HD) or single-copy deletion with a co-occurring loss-of-function (LoF) variant.
 - Tissue:** HD, single-copy deletion with a co-occurring LoF variant, or loss of unspecified zygosity.
- For plasma samples, an assay-reported lung molecular subtype (LUAD/LUSC/SCLC) was assigned to each sample. The dominant subtype was defined as the unique subtype with the highest score (ties excluded). Molecular subtype was considered evaluable only at tumor fraction (TF) $\geq 0.1\%$.
- Prevalence was reported per sample with Wilson 95% confidence intervals (CIs). Differences by histology and molecular subtype were assessed using exact tests. The association between 9p21-loss prevalence and ordered plasma TF categories (<10%, 10%–<20%, and $\geq 20\%$) was assessed using the Cochran–Armitage test for trend.
- The prevalence of 9p21 and *MTAP* loss was descriptively compared with that reported in published external NSCLC cohorts using tissue- and plasma-based testing.

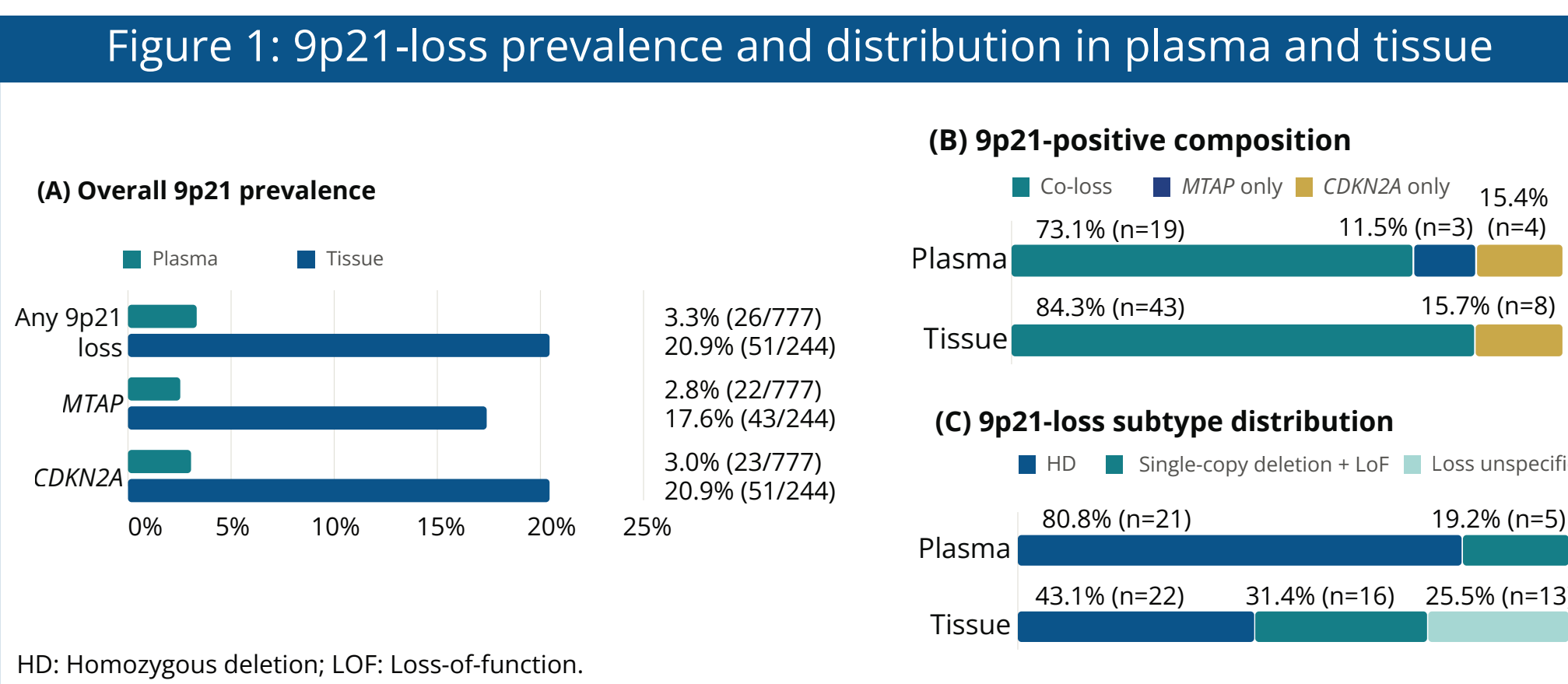
RESULTS

Cohort characteristics and 9p21-loss prevalence			
	Plasma	Tissue	
	777 samples 738 patients	244 samples 240 patients	

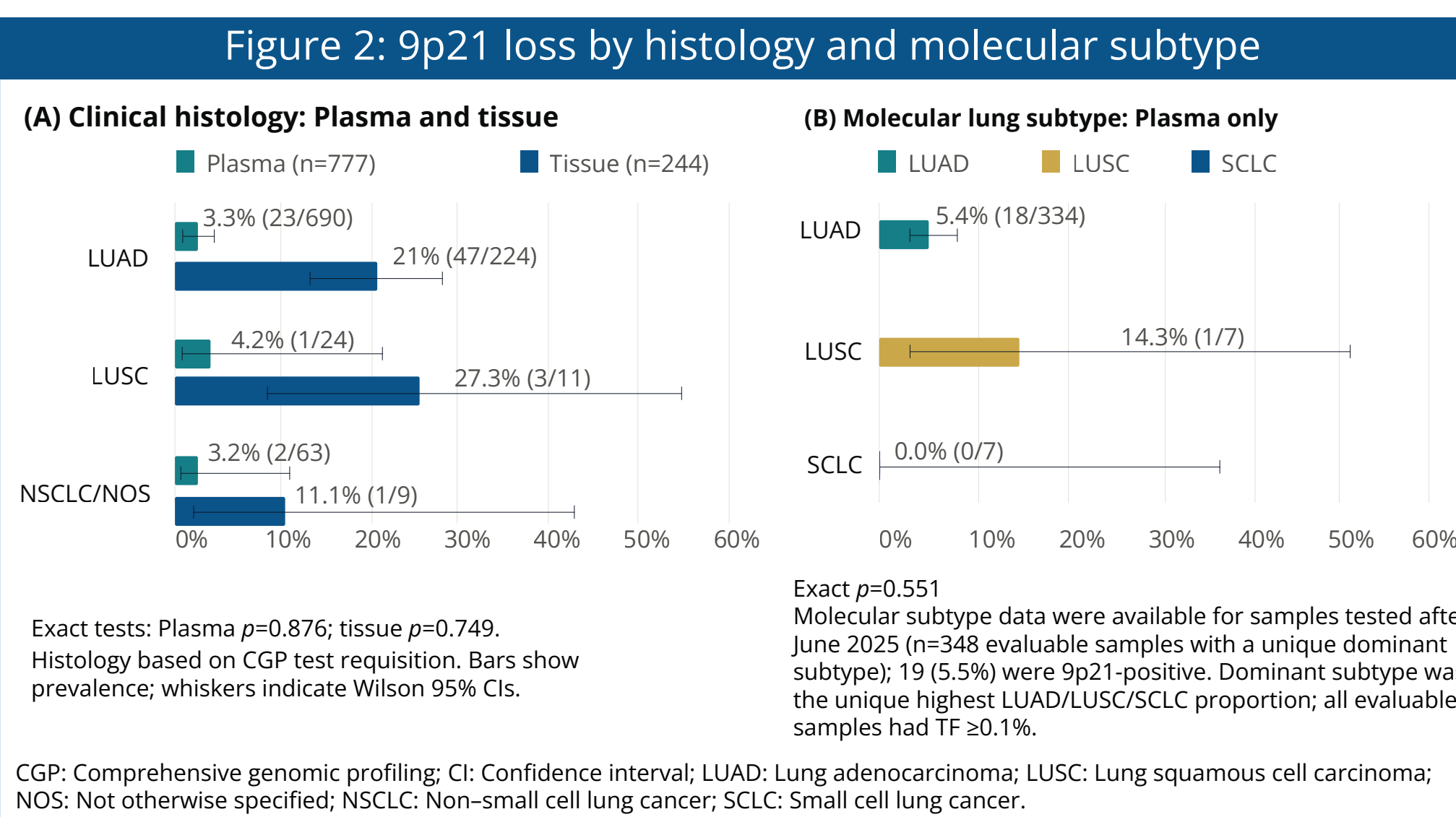
Selected cohort characteristics (all cohorts vs 9p21-loss-positive subset)				
Characteristic	Plasma All (n=777)	Plasma 9p21+ (n=26)	Tissue All (n=244)	Tissue 9p21+ (n=51)
Age, median (IQR), years	66.0 (57.0–73.0)	66.5 (59.5–73.0)	65.0 (57.5–72.0)	65.0 (55.5–73.0)
Female, n (%)	425 (54.7%)	10 (38.5%)	123 (50.4%)	23 (45.1%)
Adenocarcinoma, n (%)	690 (88.8%)	23 (88.5%)	224 (91.8%)	47 (92.2%)
TF, median (IQR), %	0.8 (0.1–6.6) n=736	36.6 (30.9–56.6)	30.0 (18.8–50.0)	40.0 (30.0–55.0)

IQR: Interquartile range; TF: Tumor fraction.

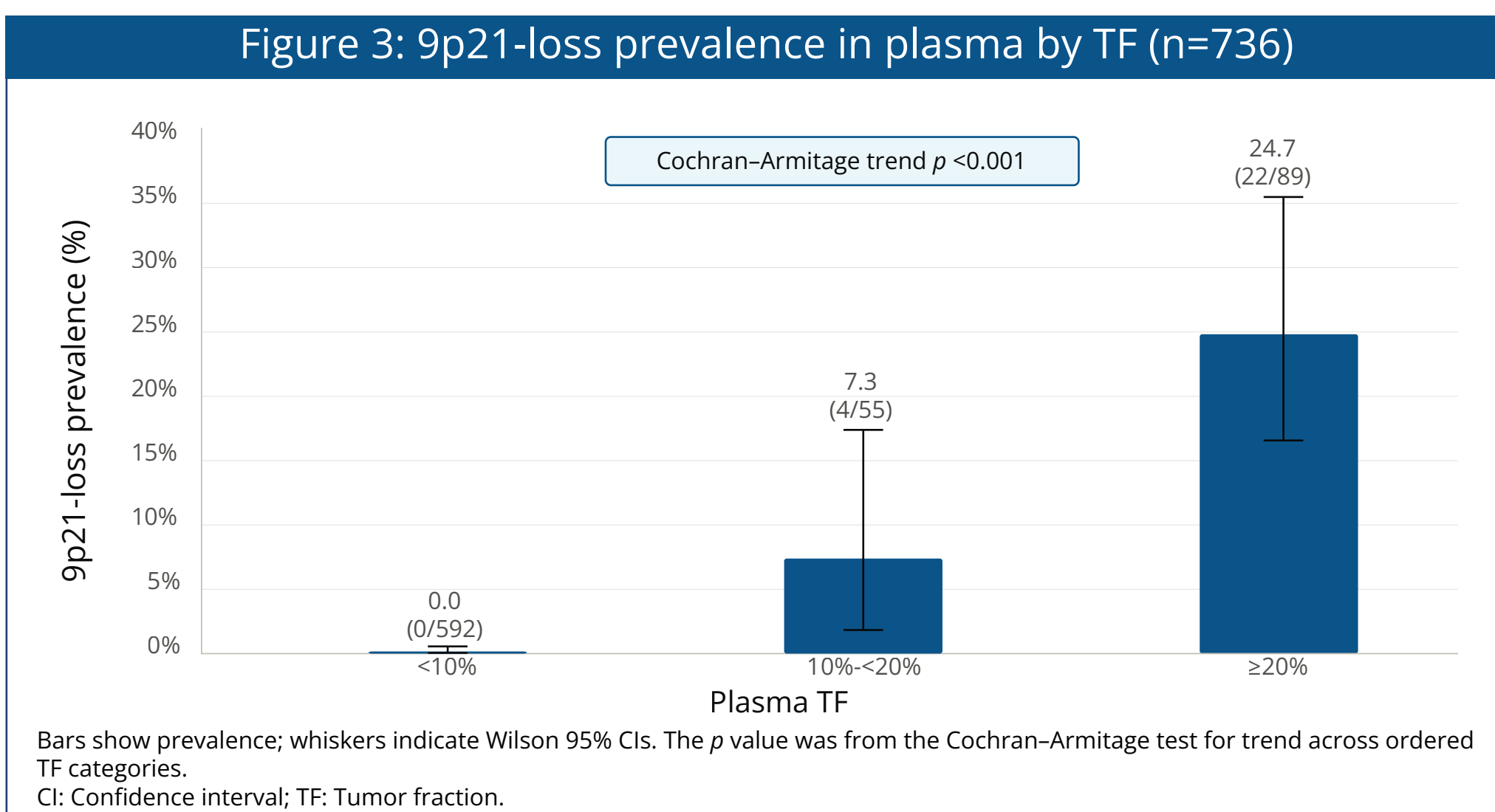
- 9p21 loss was detected in 3.3% of plasma and 20.9% of tissue samples. 9p21-positive samples had higher TF.
- Co-loss of *MTAP* and *CDKN2A* was the most common pattern among 9p21-positive samples in both plasma (73.1%) and tissue (84.3%). In plasma, most 9p21-positive cases were due to homozygous deletion (80.8%), whereas tissue samples showed a more heterogeneous distribution of loss subtypes (Figure 1A–C).



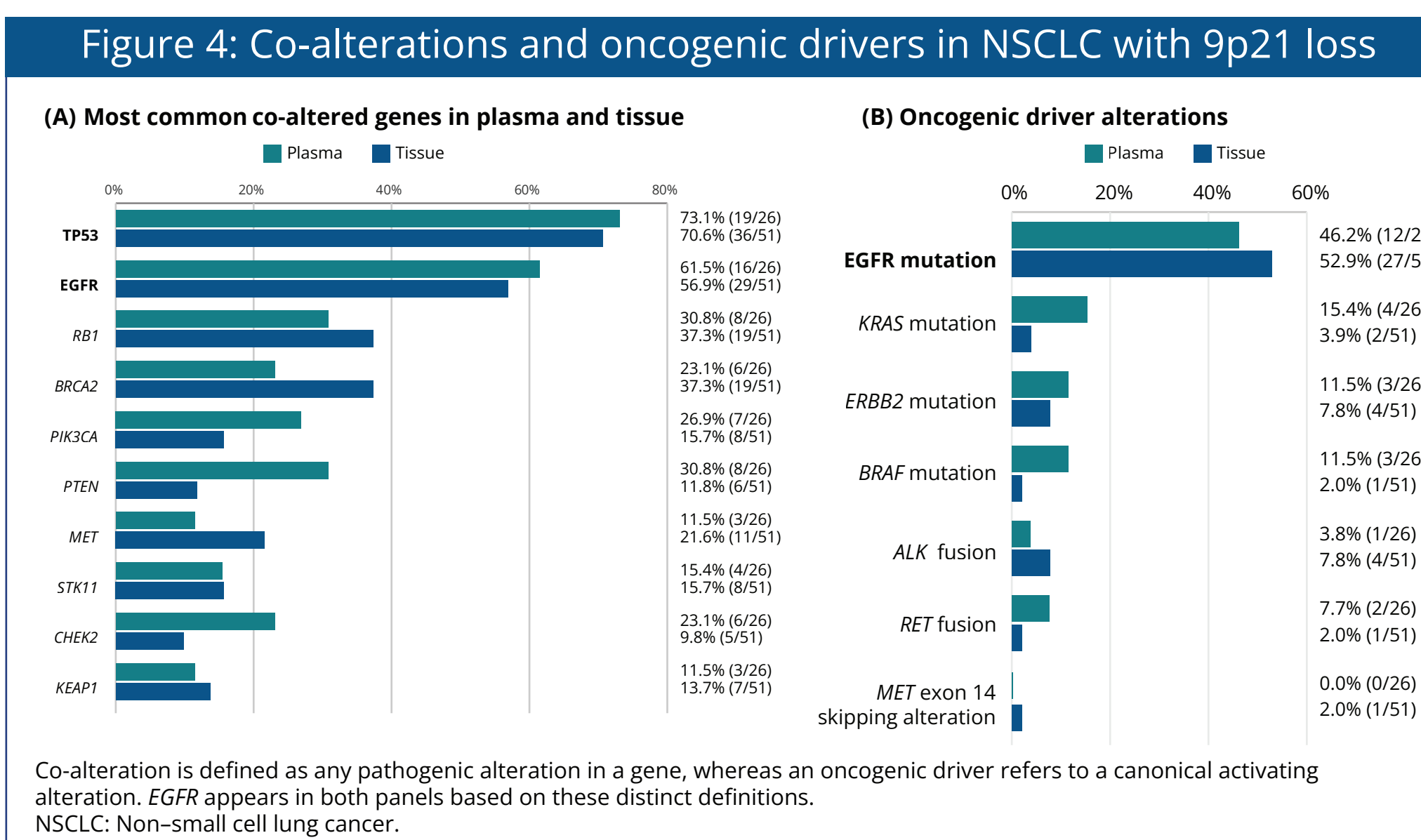
- 9p21-loss prevalence did not differ significantly by clinical histology in plasma ($p=0.876$) or tissue ($p=0.749$), or by plasma molecular subtype ($p=0.551$); estimates for non-LUAD groups were limited by small sample sizes (Figure 2).



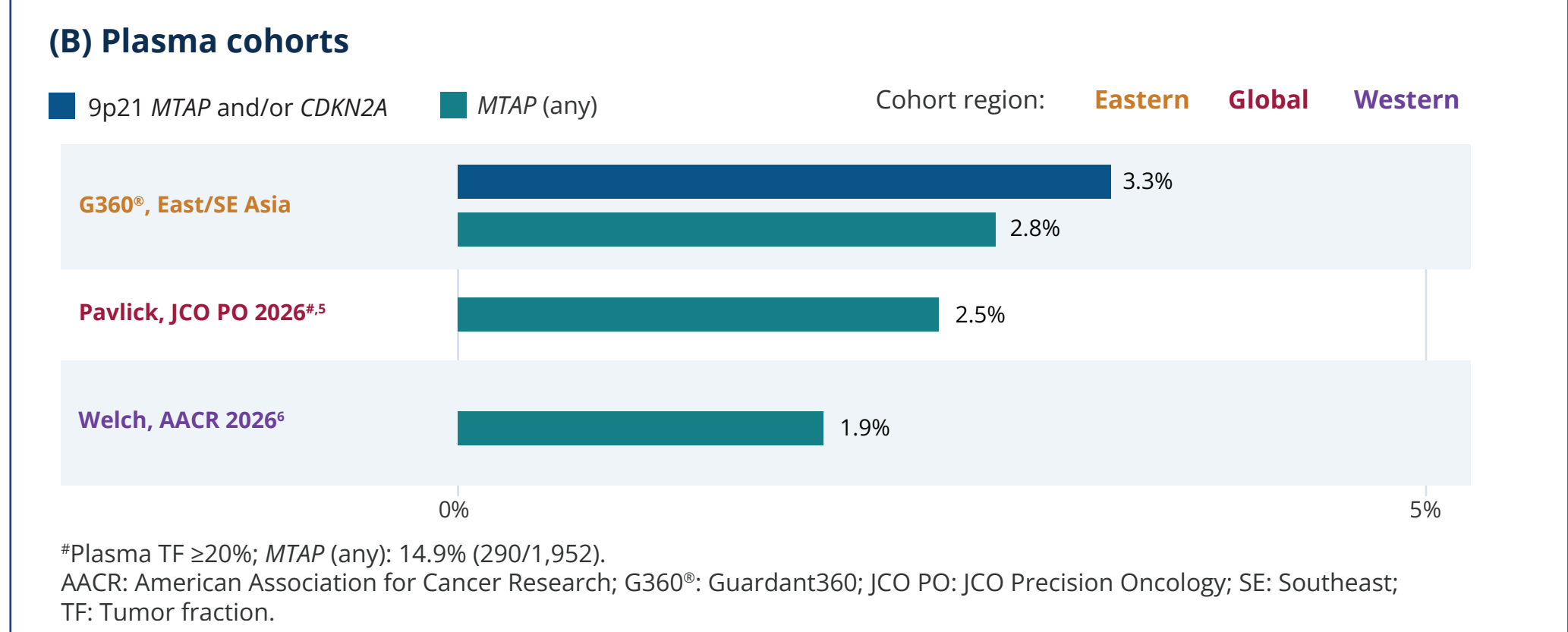
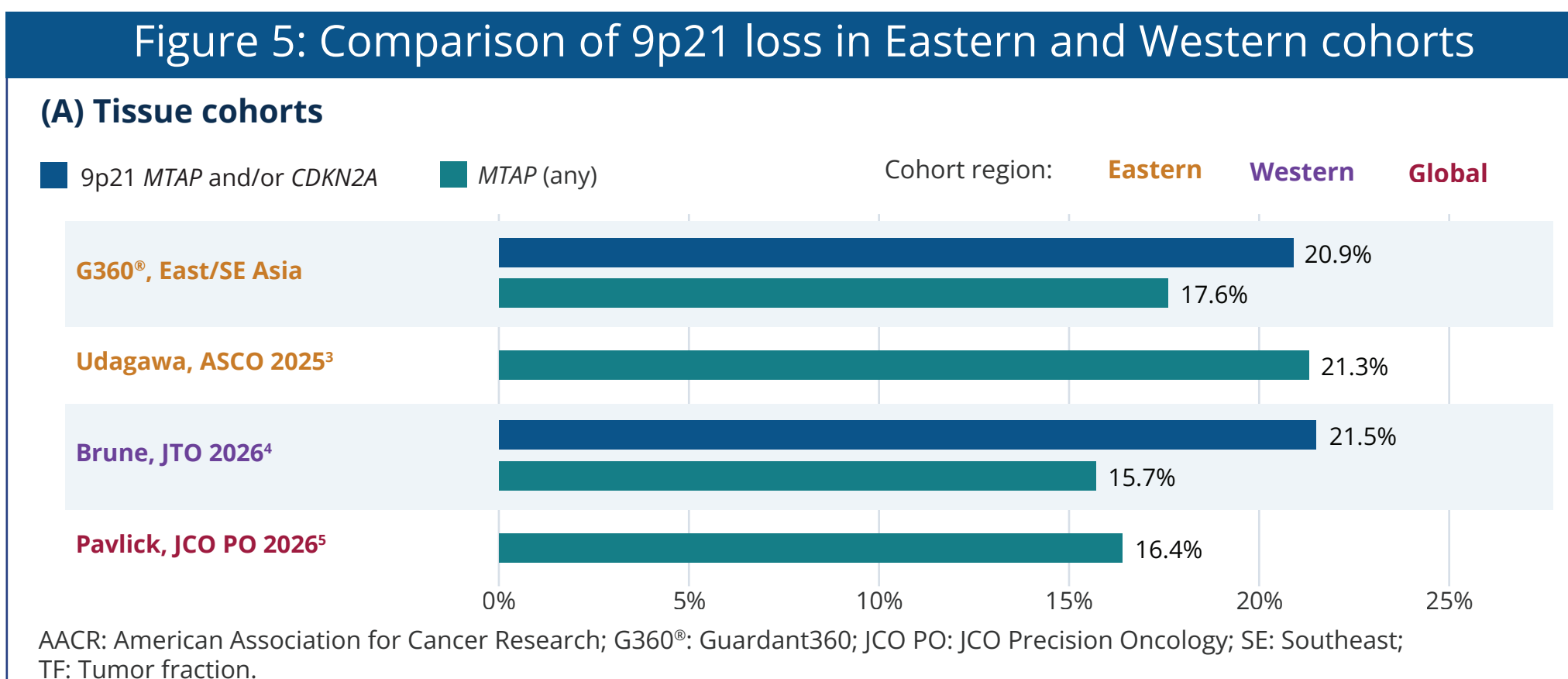
- Plasma 9p21-loss detection rose monotonically with increasing TF (0% at TF <10% to 24.7% at TF $\geq 20\%$; Cochran–Armitage trend $p<0.001$), indicating a dose-dependent relationship in which TF is a key determinant of analytic sensitivity (Figure 3).



- TP53* (plasma, 73.1%; tissue, 70.6%) and *EGFR* (61.5%; 56.9%) were the most common co-alterations in both cohorts (Figure 4A).
- EGFR* mutations were the most frequent oncogenic drivers (46.2% and 52.9%, respectively), while driver fusions were uncommon (Figure 4B).



- Guardant360[®] Tissue assay showed 9p21 loss (20.9%) and *MTAP* loss (17.6%), consistent with published tissue cohorts (15.7%–21.5%) (Figure 5A). Plasma prevalence was lower than tissue and broadly in line with prior plasma cohorts, remaining TF-dependent (Figure 5B).



CONCLUSIONS

- 9p21/*MTAP* loss is a prevalent alteration in East and Southeast Asian NSCLC, with frequencies broadly comparable to those reported in Western and global cohorts—extending eligibility for *MTAP* pathway (e.g., *PRMT5*-directed) strategies to this population.
- It is not confined by histology, molecular subtype, or driver context and commonly co-occurs with *EGFR* and *TP53* alterations.
- Detection was testing-strategy dependent: plasma sensitivity is limited by TF; therefore, a negative result in a low-TF plasma sample may not exclude 9p21 loss, and tissue testing should be considered when clinically appropriate.
- Emerging methylation-informed (epigenomic) approaches may improve detection of *MTAP* deletions at low TF, potentially narrowing the tissue–plasma detection gap.⁶

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