

Real-world performance of plasma ctDNA epigenomic subtyping of lung cancer in Asia and the Middle East

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BACKGROUND

- Lung cancer is histologically heterogeneous, with mixed histologic patterns and histologic transformation that can emerge over the treatment course.
- Tissue-based subtyping may be limited by specimen adequacy, sampling bias, and interobserver variability, underscoring the need for noninvasive approaches to complement standard pathologic assessment.
- Plasma circulating tumor DNA (ctDNA) assays incorporating epigenomic signals may enable lung cancer subtyping¹; however, real-world data from Asia and the Middle East (AME) remain limited.

OBJECTIVE

- To evaluate the real-world performance of plasma ctDNA-based epigenomic subtyping of lung cancer in routine clinical practice among patients from AME.

METHODS

- This retrospective analysis included Guardant360[®] liquid biopsy samples obtained from patients with advanced lung cancer as part of routine clinical practice across AME through July 2026.
- The assay evaluates genomic biomarkers across as many as 746 genes and around 20,000 cancer-associated differentially methylated regions.
- In samples with tumor fraction (TF) $\geq 0.1\%$, a validated epigenomic classifier reported proportions of lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung cancer (SCLC).² Other uncommon subtypes were not evaluated. The dominant subtype was defined as the subtype with the highest relative proportion. Concordance was assessed as positive percent agreement (PPA) between the dominant molecular subtype and the clinical diagnosis listed on the test report.
- In a separate subset analysis, histopathology reports were available for 173 patients, and concordance with the histopathology-confirmed diagnosis was evaluated for patients with confirmed LUAD, LUSC, or SCLC.
- Descriptive statistics were used to summarize concordance. Group comparisons used two-sided Fisher's exact tests; when multiple biomarkers or alterations were compared, p-values were adjusted for multiplicity using the Benjamini-Hochberg false discovery rate (FDR). Individual biomarker-level tests were exploratory and reported as nominal p-values.

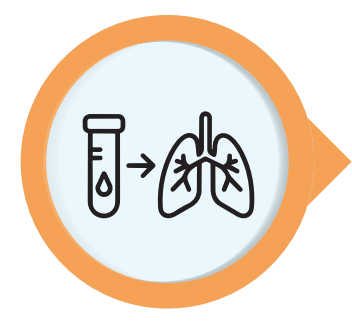
CONCLUSIONS



In this real-world AME cohort, plasma ctDNA epigenomic profiling enabled molecular subtyping in most lung cancer samples with sufficient ctDNA and showed high concordance with available reference diagnoses.



Enrichment of guideline-relevant actionable alterations in LUAD-only calls, together with *RB1/TP53* co-alteration tracking the SCLC methylation signal, supports the biological relevance of the assay output.



Together, these findings support plasma epigenomic profiling as a noninvasive complement to tissue—adding lineage-level information beyond mutation profiling from a single blood draw—with potential relevance where tissue is limited or histologic transformation is a concern.

LIMITATIONS

- The retrospective, real-world study design relied on reference diagnoses from test requisitions and available histopathology rather than central pathology review, introducing the potential for misclassification.
- Subtyping required a tumor fraction $\geq 0.1\%$; therefore, low-shedding tumors were not evaluable, and findings may be most applicable to ctDNA-detectable disease.
- LUSC and SCLC sample sizes were small, resulting in wide confidence intervals. The classifier reported only LUAD, LUSC, and SCLC; uncommon histologies were not assessed.

References

- Baca SC, Seo JH, Davidsohn MP, et al. Liquid biopsy epigenomic profiling for cancer subtyping. *Nat Med*. 2023;29(11):2737-2741.
- Valouev A, Tian W, Singh K, et al. Non-invasive cell free DNA (cfDNA) methylation profiling for accurate proportional quantification of lung cancer subtypes [abstract]. *Cancer Res*. 2025;85(8_Suppl_1):Abstract 1142.

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RESULTS

- Among 1,071 patients, the median age was 65 years, and the median TF was 0.85% (range, 0.05%–90.0%). The classifier returned a molecular subtype in 746/1,071 unique patients (69.7%; 89.3% of the 835 with TF $\geq 0.1\%$) (Figure 1).

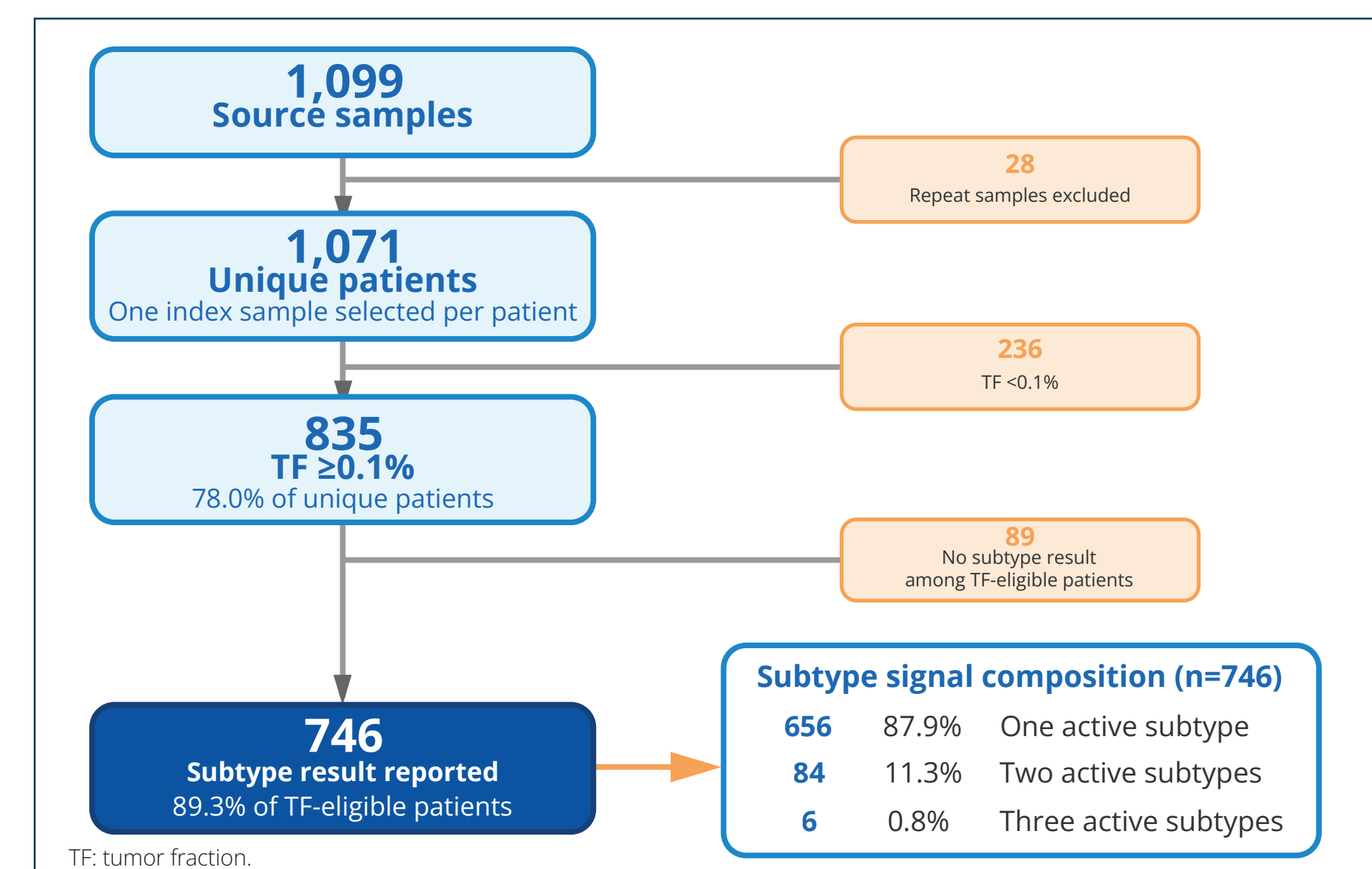


Figure 1. Consort flow

- Dominant-subtype PPA with the requisition diagnosis was 97.7% for LUAD (593/607), 70.0% for LUSC (14/20), and 44.4% for SCLC (4/9). The 96.1% overall value (611/636) reflects the adenocarcinoma-predominant case mix (Figure 2).

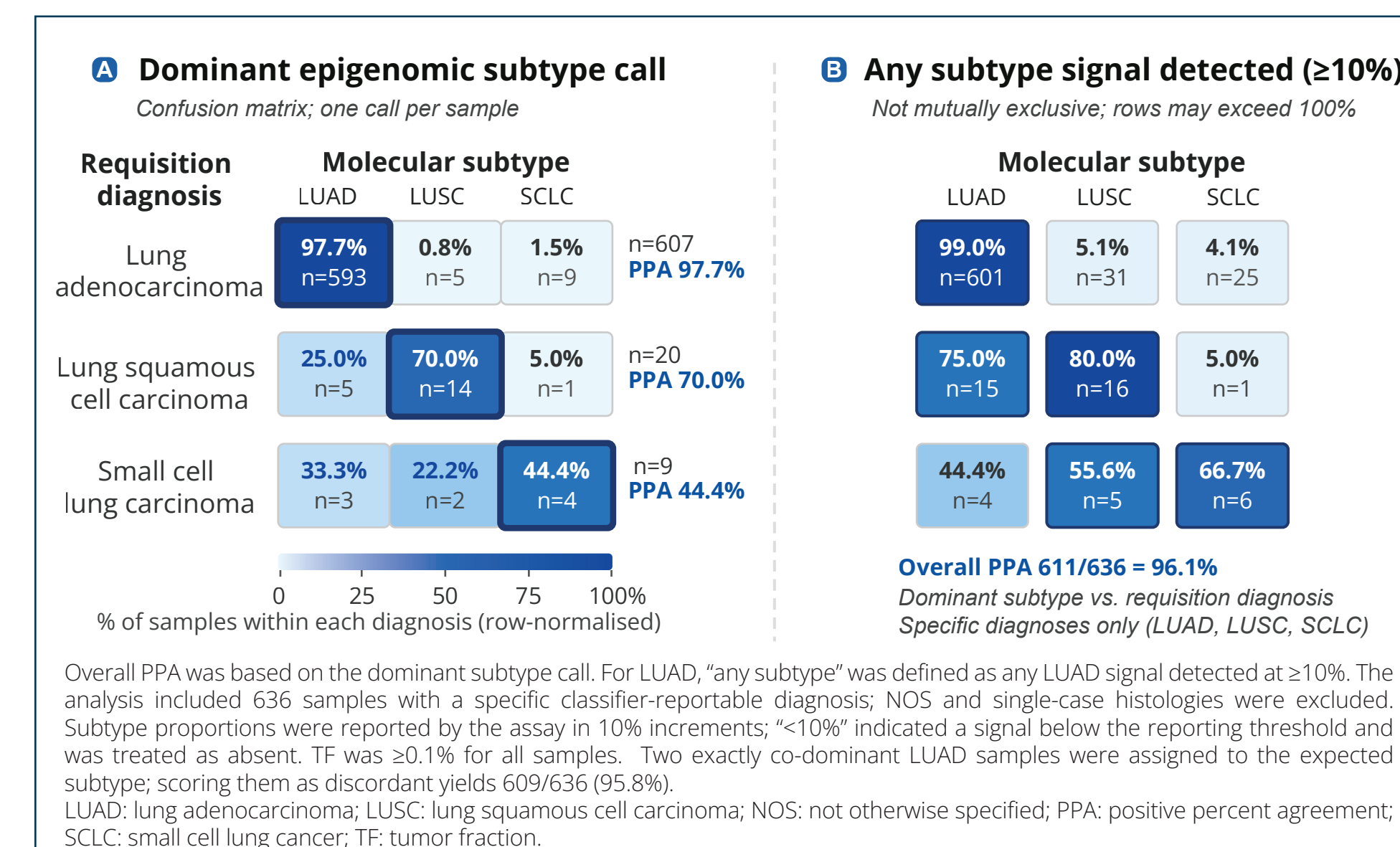


Figure 2. PPA and confusion matrix plot

- Among discordant dominant subtype calls, 48.0% (12/25) still had the expected subtype signal detected, but it was not dominant (Table 1).

Table 1. Discordant subtype calls

Requisition diagnosis	Discordant by dominant subtype calls	Expected subtype detected, but not dominant	Expected subtype not detected
LUAD	14	8	6
LUSC	6	2	4
SCLC	5	2	3
Overall	25	12	13

LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; SCLC: small cell lung cancer.

- LUAD-only calls were enriched for actionable drivers (84.0% vs. 50.7%, significant after FDR correction). Additional methylation subtype signals flag a distinct LUAD subset with fewer targetable alterations, indicating that the epigenomic subtype calls may carry biological information beyond genotome alone (Figure 3).

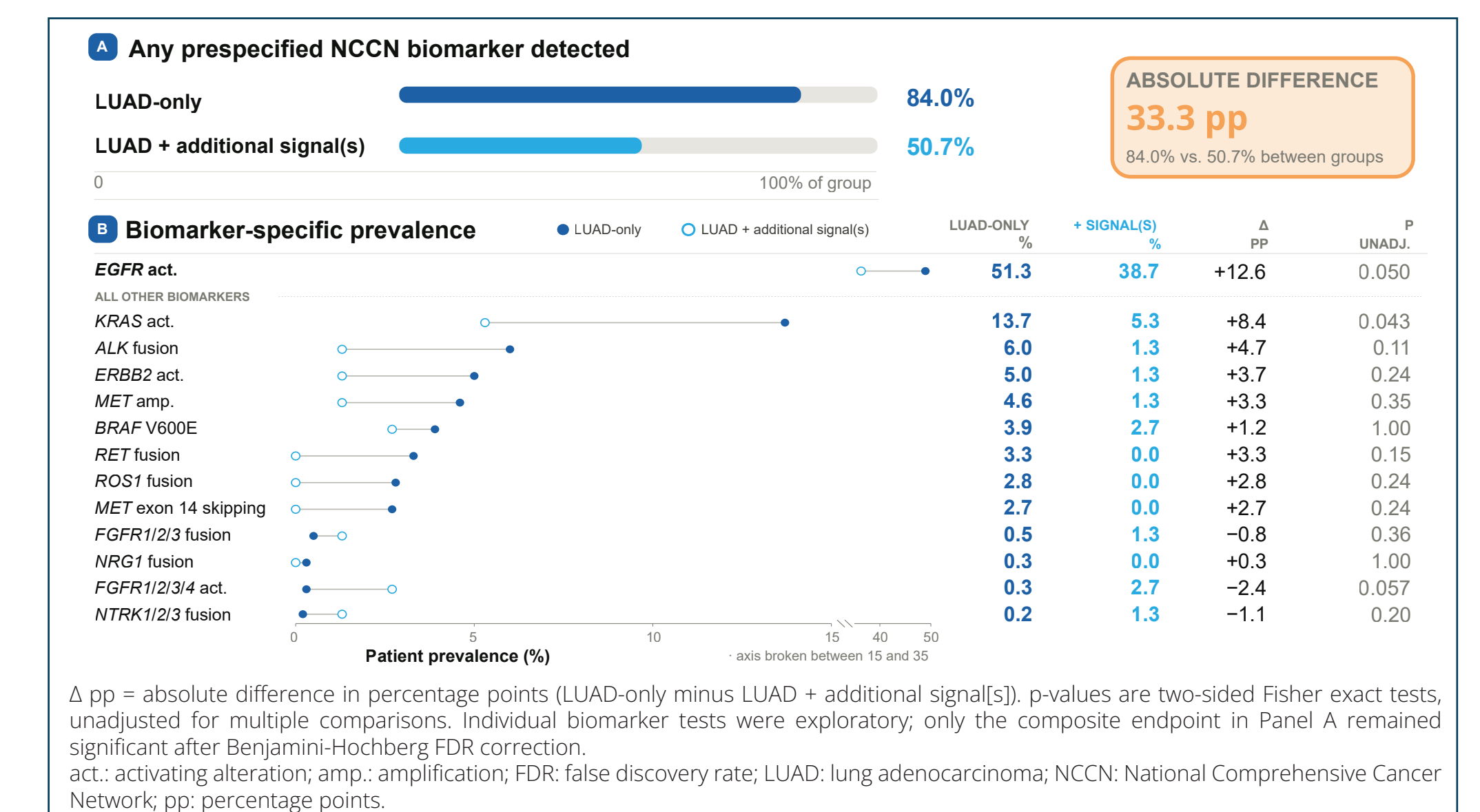


Figure 3. LUAD-only vs. LUAD with additional methylation subtype signal(s)

- An SCLC methylation signal $\geq 10\%$ was detected in 5.4% (40/746) of subtype-informed patients. Samples with an SCLC methylation signal had a higher prevalence of concurrent *RB1* + *TP53* alterations than the remainder of the cohort (57.5% vs. 7.5%; significant after FDR correction), supporting biological concordance with SCLC (Figure 4).

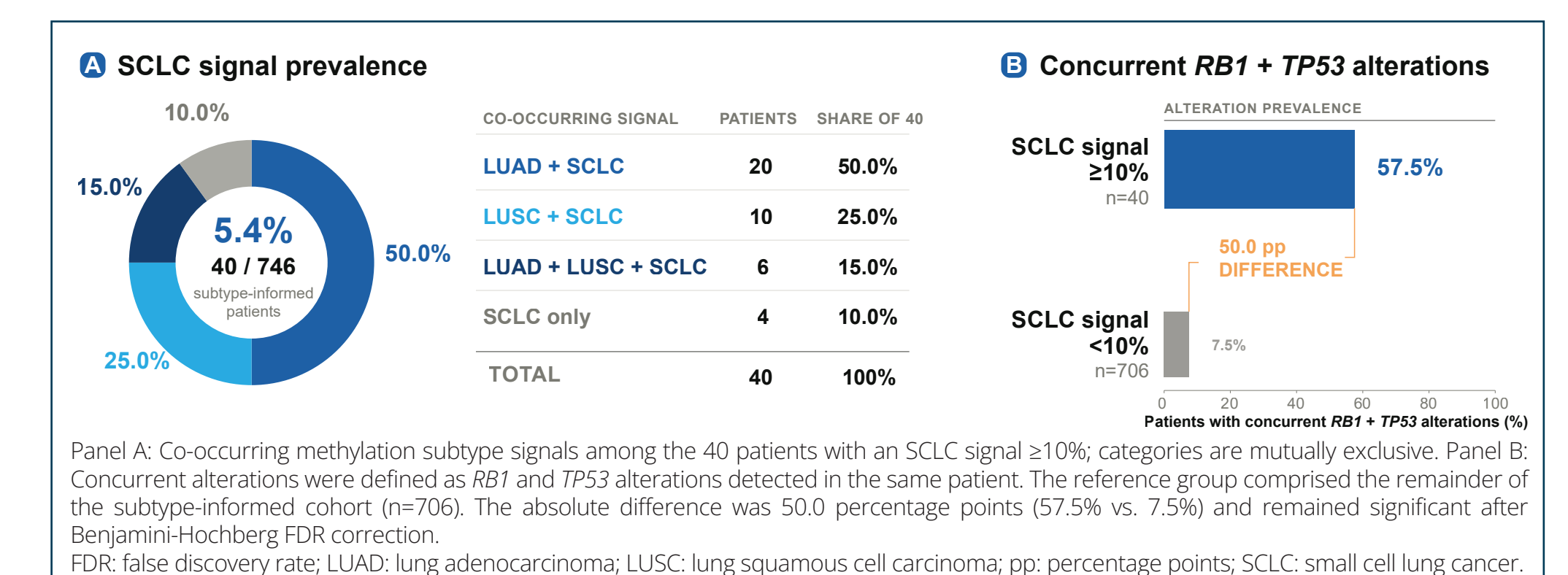


Figure 4. Concurrent *RB1* and *TP53* alterations are associated with the SCLC methylation signal

- Against histopathology (n=132), dominant-subtype PPA was 97.7% and any-subtype PPA was 98.5% (Figure 5).

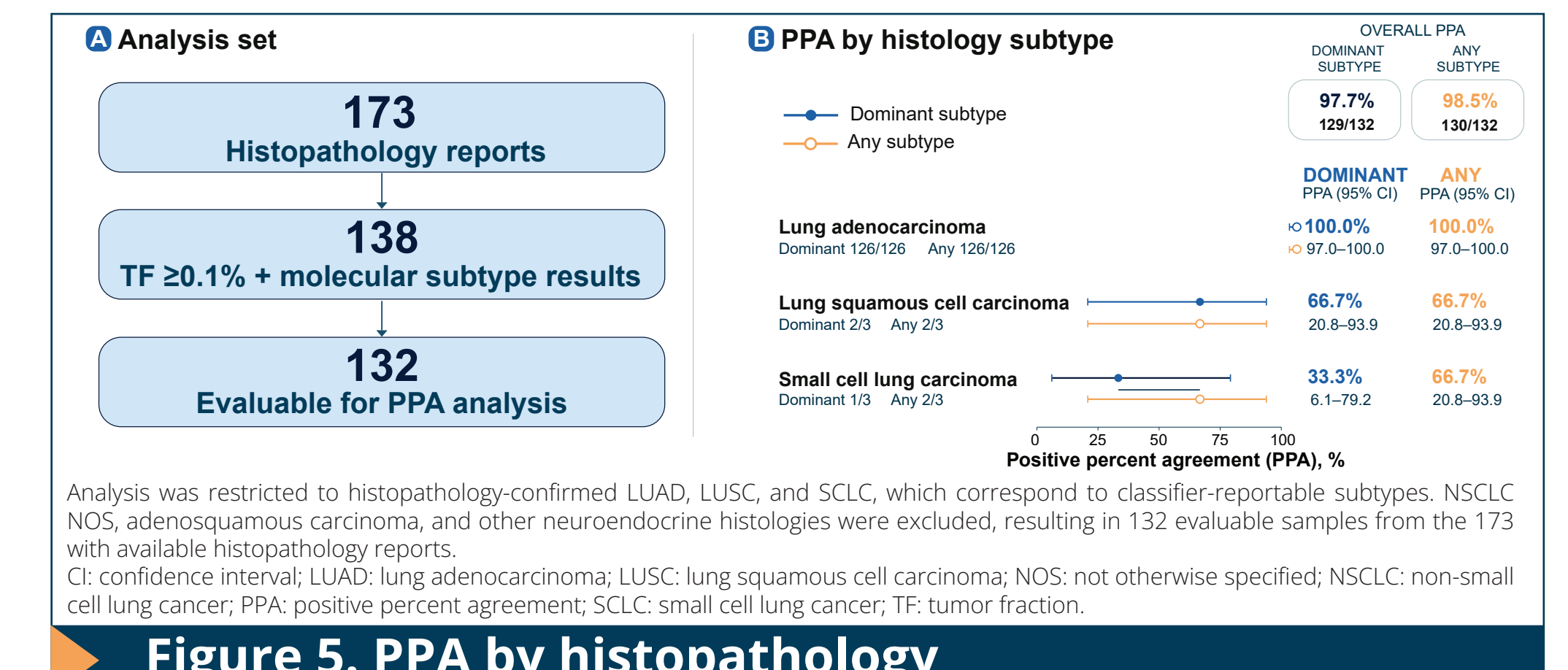


Figure 5. PPA by histopathology