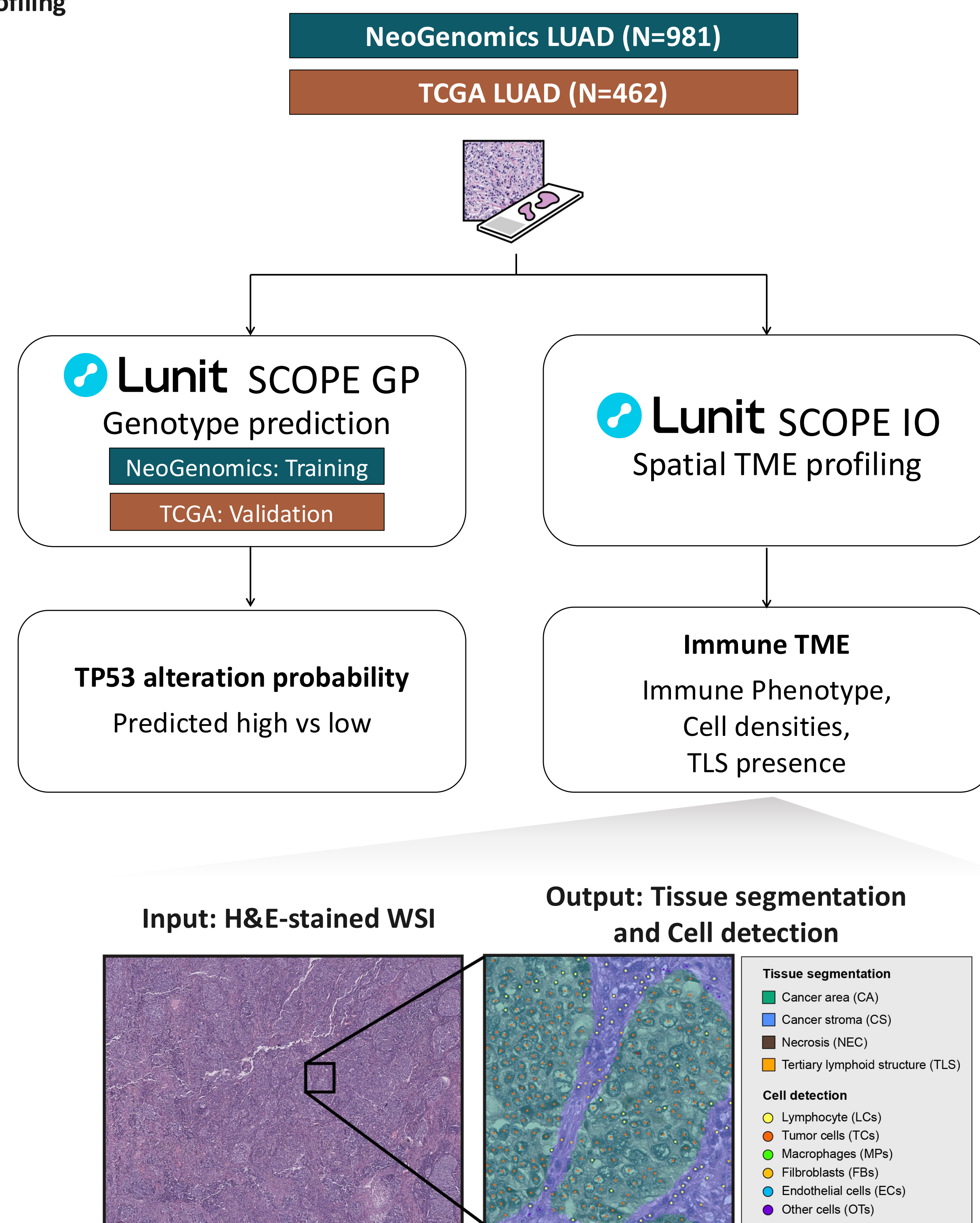


INTRODUCTION

- TP53* is the most frequently altered gene in lung adenocarcinoma (LUAD), and variant-selective agents (e.g., Y220C) have recently shown clinical promise for a historically undruggable target.
- TP53*-mutant (MT) tumors show distinct treatment outcomes - suboptimal EGFR-TKI benefit but enhanced immune-checkpoint inhibitor benefit - implying a biologically distinct tumor microenvironment (TME).
- Aim:** develop an H&E-based *TP53* genotype predictor to facilitate identification of eligible patients, and characterize the *TP53*-associated TME using a well-established AI-powered H&E analyzer.

METHODS

Figure 1. Study design: H&E-based genotype prediction and AI-powered spatial TME profiling



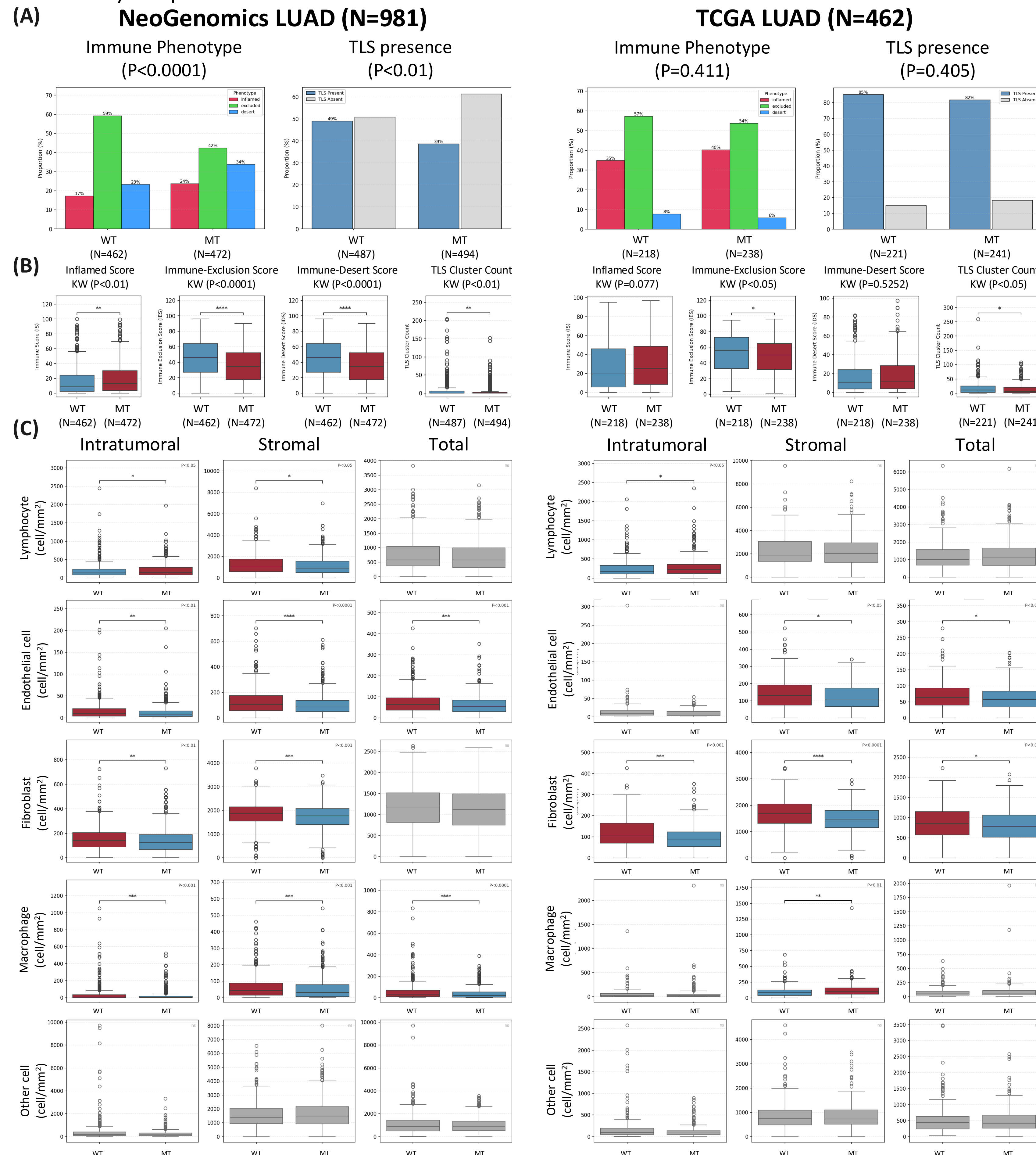
RESULTS

Table 1. H&E-based *TP53* genotype predictor performance by cohort and driver mutation

	<i>TP53</i> -MT Proportion	AUROC
Training set: NeoGenomics (N=981)	494/981 (50.4%)	0.741 (3-fold CV)
Validation set: TCGA (N=462)	241/462 (52.2%)	0.759 (Sn 82%, Sp 63%)
TCGA subgroup: <i>EGFR</i> -MT (N=60)	39/60 (65.0%)	0.623
TCGA subgroup: <i>KRAS</i> -MT (N=156)	62/156 (39.7%)	0.774
TCGA subgroup: <i>STK11</i> -MT (N=69)	25/69 (36.2%)	0.756

Figure 2. AI-powered TME profiling by *TP53* status in two independent LUAD cohorts

(A) Immune phenotype and TLS presence (B) Immune phenotype scores and TLS cluster count (C) Spatial cell densities by compartment



DISCUSSION AND CONCLUSION

- TP53* mutations can be predicted from H&E WSIs with promising accuracy (AUROC 0.759 in TCGA), which may enable enrichment for emerging clinical trials as a screening tool.
- TP53*-MT LUAD was relatively immune-inflamed with higher intratumoral lymphocyte density.
- TP53*-WT tumors displayed an immune-excluded, fibroblast- and endothelial-rich TME, reproduced across two independent cohorts and supported by transcriptomics.
- TP53* mutations can be predicted from H&E WSIs with promising accuracy, which may enable enrichment for emerging clinical trials as a screening tool. *TP53*-MT lung adenocarcinoma was relatively inflamed, whereas *TP53*-WT tumors display an immune-excluded, fibroblast and endothelial-rich TME.

REFERENCES

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- Lunit SCOPE GP:** An AI framework that infers genomic alterations from H&E morphology, providing slide-level prediction.
- Lunit SCOPE IO:** The H&E WSI analyzer segments the tissue into cancer epithelium, stroma, and background. Detected cells are classified into lymphocytes, tumor cells, endothelial cells, fibroblasts, or other cells. Cell densities are used in downstream analysis.