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Together, We Beat Cancer

Mapping Genomically Classified Molecular Clusters to Therapeutic Outcomes in a Pan-Indian Lung Cohort: A Strategy for Smarter Clinical Trial Randomization

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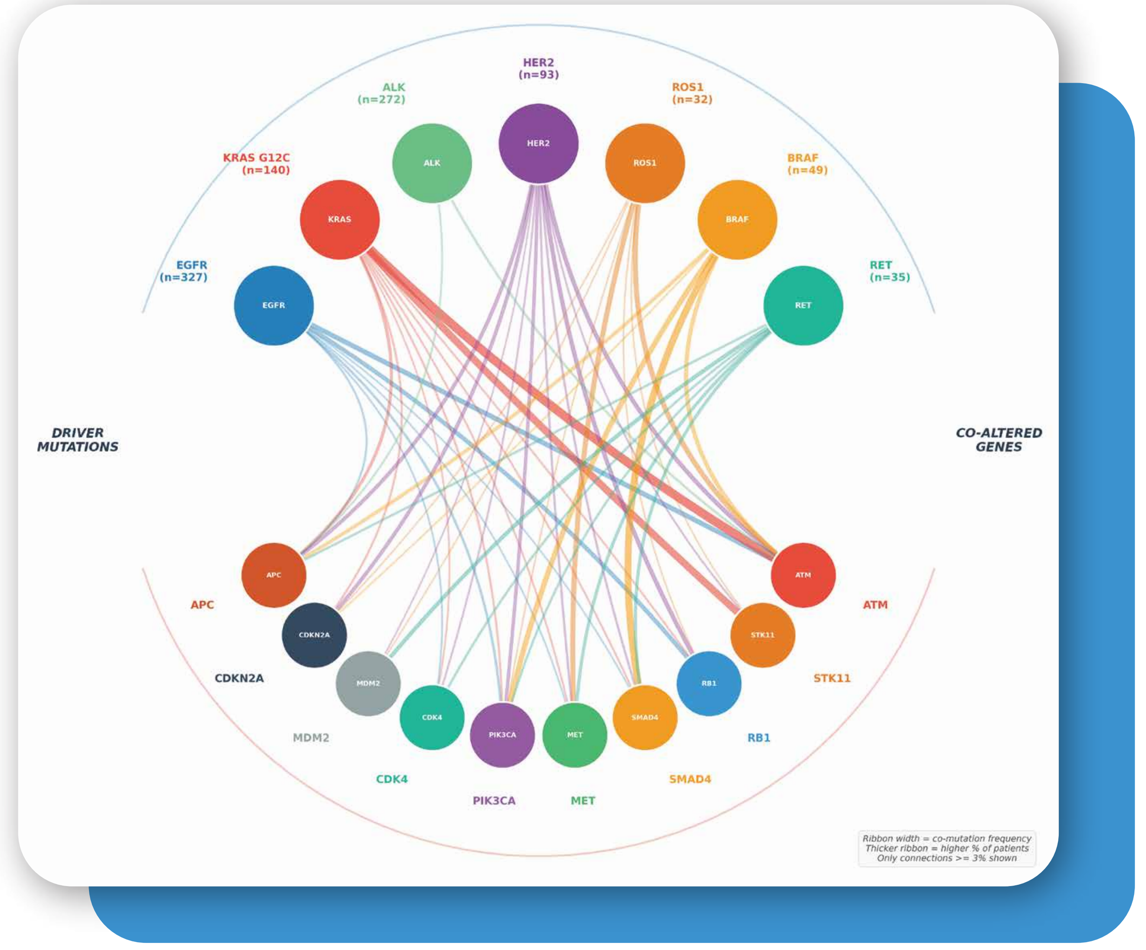
INTRODUCTION

Lung cancer exhibits substantial genomic heterogeneity. Current clinical classification based on histology or single-driver alterations (EGFR, ALK, KRAS) often overlooks co-occurring molecular events that influence treatment response. Advances in next-generation sequencing (NGS) enable comprehensive characterization of co-mutations and pathway-level dysregulation, revealing biologically distinct tumor subgroups beyond traditional frameworks. Here, we present one of the largest real-world genomic datasets of Indian lung cancer patients (n=4,852), integrating driver alterations, co-mutations, and pathway signatures to evaluate their role in improving patient stratification and precision oncology trial design.

METHODS & MATERIALS

A total of 4,852 NSCLC patients were profiled using TARGT First, comprehensive NGS 72 gene panel SNV/Iindels (87), CNVs (72) and Gene fusions (11).

Tumors were stratified by major drivers (EGFR, ALK, KRAS, MET, RET, BRAF, ERBB2, driver-negative) and further characterized by co-mutations, Tumor suppressor loss (TP53, RB1, CDKN2A/B), DDR and cell-cycle alterations, and Pathway activation (PI3K-AKT-mTOR, RAS-MAPK). Unsupervised clustering and network analysis were used to identify co-alteration patterns and mechanistic subgroups. Statistical analyses included chi-square/binomial tests with Benjamini–Hochberg FDR correction (<0.05).



Key Finding: Cross driver co alteration network, ribbon width reflects co mutation frequency and co altered groups

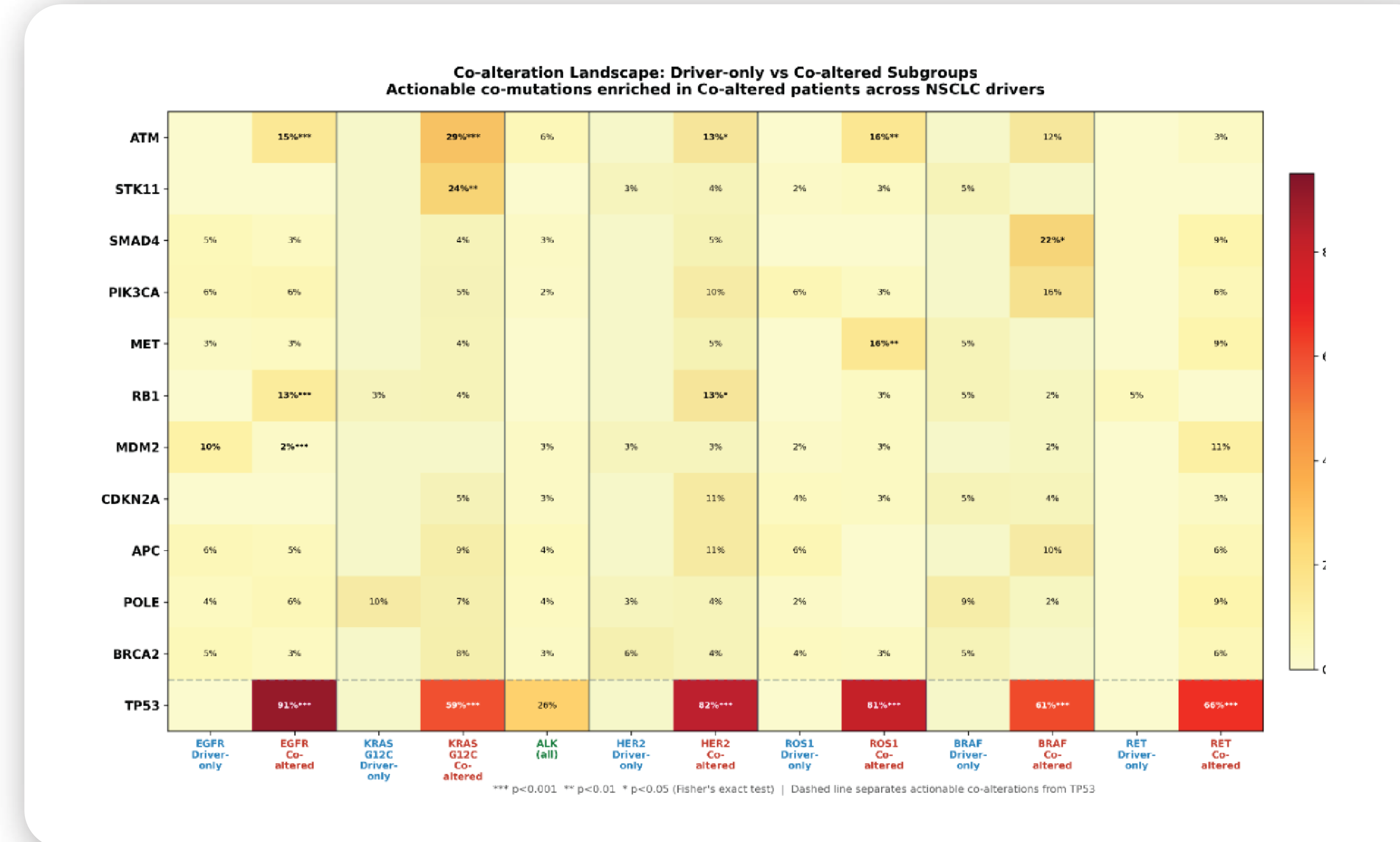


Figure 3: TP53 stratification reveals distinct co-mutation landscapes across driver-defined NSCLC subgroups

RESULTS | A total of 4,852 NSCLC patients with 17,462 variants were analyzed.

Co-alterations were highly prevalent across driver-defined subgroups, with the majority of tumors harboring additional genomic events beyond the primary driver.

1. **Co-alterations are highly prevalent across NSCLC drivers (Figure 1):**
   a. **KRAS G12C** showing the highest co-mutation burden (83%)
   b. **HER2** (75%), **BRAF** (69%), **EGFR** (65%), and **RET** (61%)
   c. **ROS1** demonstrated a lower co-altered fraction (40%) with a relatively higher proportion of driver-only tumors.
   d. **ALK-positive**: homogeneous (no clear subgroups identified)
2. **Distinct and statistically significant co-mutation patterns were observed within each driver subgroup (Figure 2):**
   a. **KRAS G12C** tumors were enriched for **ATM** (29%) and **STK11** (24%) alterations, indicating a highly complex genomic landscape.
   b. **EGFR**-driven tumors showed enrichment of **ATM** (15%), **RB1** (13%), & **MDM2** (~10%).
   c. **HER2** tumors demonstrated co-alterations in **ATM** (13%) and **RB1** (13%).
   d. **ROS1**-positive tumors, **MET** (16%) and **ATM** (16%) alterations were enriched.
   e. **BRAF** tumors were characterized by **SMAD4** enrichment (22%), suggesting distinct driver-specific biology.

TP53 emerged as the most frequent co-mutation across all driver groups (59–91%); however, due to its ubiquitous presence, it was excluded from enrichment analyses to enable identification of independent co-alteration patterns (Figure 3).

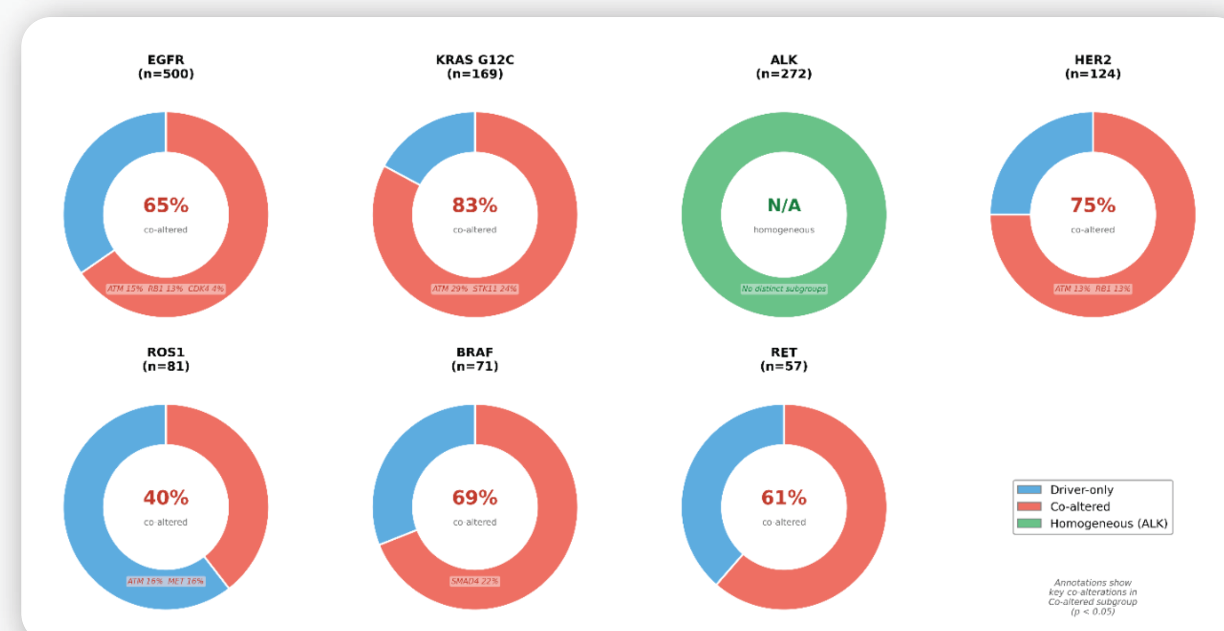


Figure 1: Distinct co-mutation signatures define biologically unique NSCLC subgroups

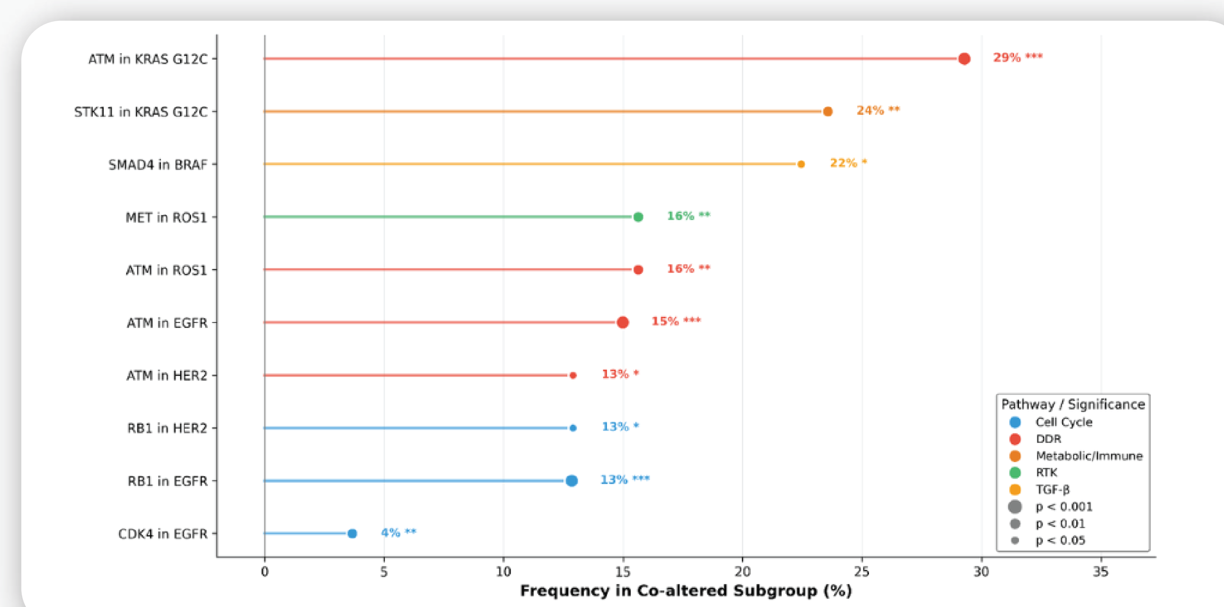


Figure 2: Co-mutation-driven clustering reveals actionable subgroups beyond single-driver NSCLC

These findings support moving beyond a "ONE DRIVER–ONE DRUG" approach

Co-alterations are prevalent across NSCLC drivers, with most tumors harboring additional genomic events beyond the primary driver. Higher co-alteration burden in KRAS G12C, HER2, EGFR, and BRAF reflects increased molecular complexity, while relative homogeneity in ALK and higher driver-only proportion in ROS1 may explain more consistent therapeutic responses. Recurrent alterations in DDR and cell-cycle pathways across multiple drivers indicate shared biological vulnerabilities, while driver-specific events (e.g., STK11 in KRAS G12C, SMAD4 in BRAF) highlight the need for tailored strategies.

Collectively, these findings challenge the conventional "one driver–one drug" paradigm and support a shift toward integrated genomic profiling that incorporates both primary drivers and co-alteration landscapes. Such an approach has the potential to refine patient stratification, inform rational combination therapies, and improve the design of precision oncology clinical trials.

KEY TAKEAWAY

Distinct co-mutation patterns define biologically separable subgroups in NSCLC. Multi-dimensional genomic stratification captures intra-driver heterogeneity and can redefine NSCLC trial design and precision oncology.

Work in progress: 20 genes show frequency shifts vs TCGA/MSK datasets which highlights the importance of population-specific genomic profiling

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