

#1795

Real-World Genomic, Treatment and Outcomes of Pure and Mixed-Histology Lung Adenocarcinoma Stratified by MLSP-Derived LUAD Proportion

Jinesh Gheeya, MD, PhD¹, Fawzi Abu-Rous, MD², Sheila Solomon, MS³, Jayati Saha, PhD, MPH³, Christine Lovly, MD, PhD⁴
1. The Ohio State University, Columbus, OH; 2. Henry Ford Health, Detroit, MI; 3. Guardant Health, Palo Alto, CA; 4. City of Hope, Pasadena, CA



Background

- Non-small cell lung cancer (NSCLC) includes histologic subtypes, most commonly adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), and small cell lung cancer (SCLC).
- Limited diagnostic tissue sampling can complicate histologic classification, leading to uncertainty in optimal treatment.
- Plasma-based epigenomic Molecular Lung Subtype Predictor (MLSP) was developed using circulating tumor DNA (ctDNA) from the Guardant360 Infinity assay to quantify LUAD, LUSC, and SCLC contributions (Figures 1. and 2.).
- We applied MLSP to assess histologic variations, genomic profiles, treatment patterns, and real-world (rw) outcomes among patients (pts) with pure LUAD and mixed-histology LUAD.

Methods

- InfinityAI™, a longitudinal claims-based database links de-identified genomic/epigenomic results from Guardant360 to claims data including diagnostic and procedure codes.
- Patients with first-line (1L) systemic therapy after a Guardant360 test with MLSP were included. Tumors were defined as pure LUAD when ≥90% of MLSP signal was LUAD and mixed-histology LUAD–LUSC or LUAD–SCLC when 60–80% LUAD with 20-30% LUSC or SCLC, respectively.
- Cohorts were stratified by MLSP/test requisition form concordance and 1L therapy of chemotherapy, immunotherapy (IO), or other.
- Rw time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) were estimated via Kaplan–Meier and compared by log-rank test.

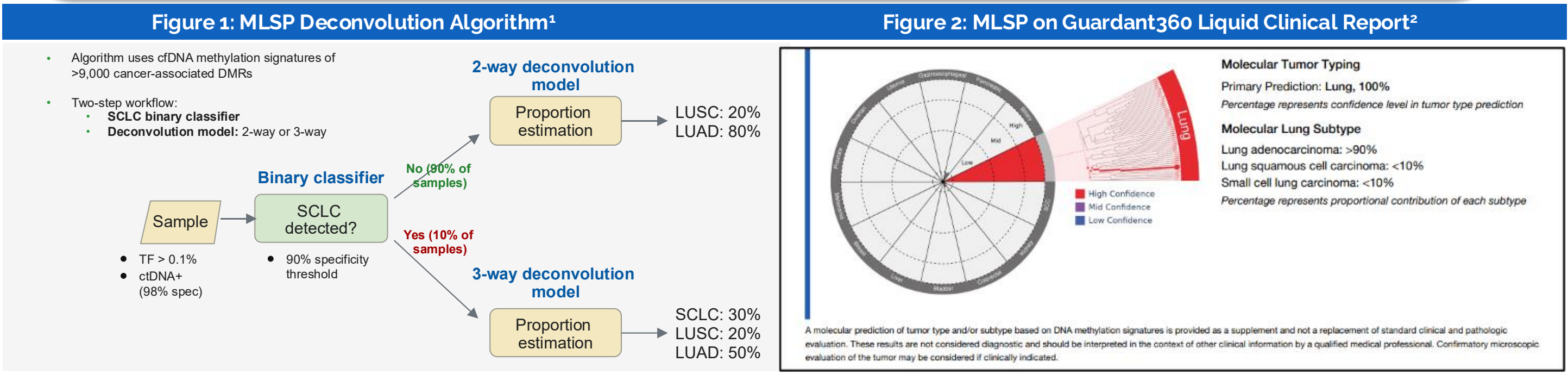


Table 1. Patient Demographics

Characteristics	Pure LUAD		LUAD–LUSC		LUAD–SCLC	
	N	%/SD	N	%/SD	N	%/SD
Total N with treatment data	1868		98		26	
Age (years)						
<50	84	4%	4	4%	0	0%
50-65	512	27%	13	13%	8	31%
>65	1269	68%	81	83%	18	69%
Mean	68.8	10.5	71.8	9.3	68.2	8.5
Median (Range)	70	(21-85)	72	(44-84)	67.5	(53-85)
Gender						
Male	853	46%	58	59%	9	35%
Female	995	53%	39	40%	16	62%
Unknown/Missing	20	1%	1	1%	1	4%
Smoking History						
Ever-Smoker	823	44%	53	54%	15	58%
Race						
Caucasian	1167	62%	70	71%	16	62%
African American	193	10%	13	13%	3	12%
Asian	124	7%	4	4%	3	12%
Other	202	11%	6	6%	1	4%
Unknown/Missing	182	10%	5	5%	3	12%

Results

PURE LUAD BY MLSP

n = 5,940

pure adenocarcinoma

treatment data available n = 1,868

LUAD–LUSC BY MLSP

n = 365

mixed with squamous component

treatment data available n = 98

LUAD–SCLC BY MLSP

n = 119

mixed with small-cell component

treatment data available n = 26

COHORT & GENOMICS

- MLSP classified 5,940 pts as pure LUAD, 365 with LUAD-LUSC and 119 with LUAD-SCLC, of which 1868 (32%), 98 (7.8%) and 26 (2.1%) had available treatment data, respectively.
- Ever-smokers (Table 1) were more common in mixed histology (54.1% LUAD–LUSC; 57.7% LUAD–SCLC) vs pure LUAD (44.1%).
- Oncogenic drivers (Table 2) were enriched in pure LUAD vs LUAD-LUSC or LUAD-SCLC.
- TP53 mutations were higher in mixed LUAD cohorts (81.6% LUAD–LUSC, 73.1% LUAD–SCLC) vs 64.1% in pure LUAD.
- RB1 mutations were present in LUAD-SCLC (11.5% vs. 3.0% pure LUAD).
- Concurrent TP53/RB1 mutations were ~2x and ~3.6x more common in LUAD-LUSC and LUAD-SCLC cohorts, respectively, than in pure LUAD cohort.

TREATMENT & OUTCOMES

- Chemo-IO therapy predominated mixed histologies (LUAD–LUSC (48.0%) and LUAD–SCLC (38%), while targeted therapy was more commonly used in pure-LUAD (29.5%).
- Patients with mixed histology trended toward shorter rwTTNT and rwTTD compared to patients with pure LUAD.
- Rw outcomes in pure LUAD varied across therapy types (chemo, chemo/IO, targeted).
- Median rwTTNT was not reached, particularly in the IO cohort.
- Overall, median TTD was shortest with chemo-treated cohort and longest with IO.

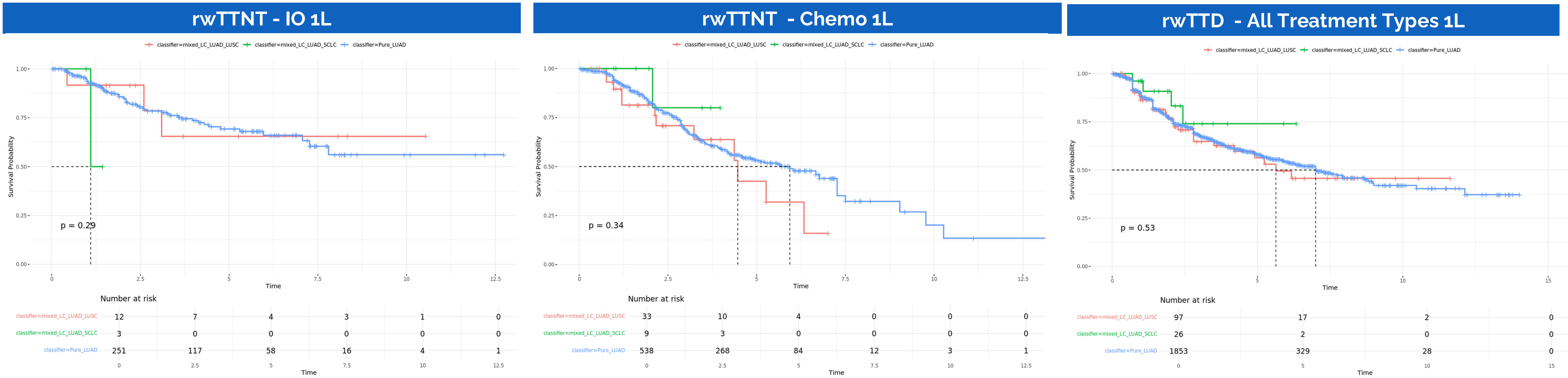


Table 2. Key Genomic Differences by MLSP-Defined Histology

Mutation	Pure LUAD	LUAD–LUSC	LUAD–SCLC
TP53	64.1%	81.6%	73.1%
KRAS	27.7%	14.3%	19.2%
EGFR	25.3%	13.3%	15.4%
RB1	3.0%	4.1%	11.5%
Concurrent TP53/RB1	2.1%	4.1%	7.7%

Conclusions

- This hypothesis generating study demonstrates that pure-LUAD and mixed-histology LUAD have distinct clinical and genomic features.
- Methylation-based plasma MLSP quantification of histologic admixture may serve as a clinically relevant biomarker informing clinical management of NSCLC with mixed subtypes.
- Small sample size and short follow-up may limit the interpretation of rwTTNT in this study.

References:
1. Valouev (Eltoukhy), AACR 2025; 2. Guardant Health, Palo Alto, CA