Non-invasive identification of actionable biomarkers in advanced solid tumors by comprehensive genomic profiling with NEO | PanTracer LBx assay

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Abstract # PP.04

Introduction

- The clinical utility of comprehensive genomic profiling by liquid biopsy (LBx CGP) to guide therapy decisions has been demonstrated by high concordance rates with tissue CGP for guideline-recommended FDA-approved targets in patients with advanced cancers, as well as treatment response studies.
- NEO | PanTracer LBx is a 514 gene pan-solid tumor, hybrid-capture LBx CGP assay with comparable performance to both a highly-sensitive amplicon-based (InVisionFirst™-Lung) and four commercially available LBx CGP assays (**ISLB 2025 Abstract # PP.05**).
- Here we focus on the identification of actionable biomarkers to support therapeutic decisions in patients with late-stage cancer.

Methods

- Under an IRB protocol that was specifically developed in collaboration with community oncologists, advanced cancer patients (stage III-IV), representative of the intended use population, were prospectively recruited for participation in this study.
- Single-timepoint blood samples collected from 142 patients were tested with PanTracer LBx as part of the assay's clinical validation.
- A proprietary pipeline was used to generate a list of alterations across all major variant classes (SNVs/InDels, CNVs, fusions) and to estimate bTMB and MSI.
- The OncoKB database was subsequently used to evaluate variant actionability – variants were classified by the NeoGenomics Variant Science team.

Results

Patient Cohort

- Among the 142 patients included in the study cohort, 56% were males.
- Median age at diagnosis was similar between males and females and the majority of patients were white Americans (69.7%).
- Lung cancer was the most prevalent tumor type (30%) across the entire cohort, followed by prostate in males (20%) and breast cancer in females.
- The majority of patients were diagnosed with advanced stage disease (III-IV; 97.2%).
- Full patient characteristics are provided in **Table 1**.

Table 1. Patient Characteristics

Category		Male	Female	Total (%)
	N	80	62	142
Age at diagnosis (years)	*Median*	67	63	65
	Range	26-88	29-88	26-88
Race	*White*	58	41	99 (69.7%)
	African American	21	19	40 (28.2%)
	Asian	1	2	3 (2.1%)
Cancer Types (Top 5)	*Lung*	25	18	43 (30%)
	Prostate	20	0	20 (14%)
	Breast	0	18	18 (13%)
	Colorectal	8	6	14 (10%)
	Head and Neck	6	2	8 (6%)
UICC Stage (8th edition)	*I*	1	0	1 (0.7%)
	II	1	2	3 (2.1%)
	III	15	12	27 (19.1%)
	IV	62	48	110 (78.1%)

Stage missing for 1 male patient

Cancer Type Distribution

Detailed breakdown of cancer type distribution across males, females and the entire cohort is provided in **Figure 1A-C**.

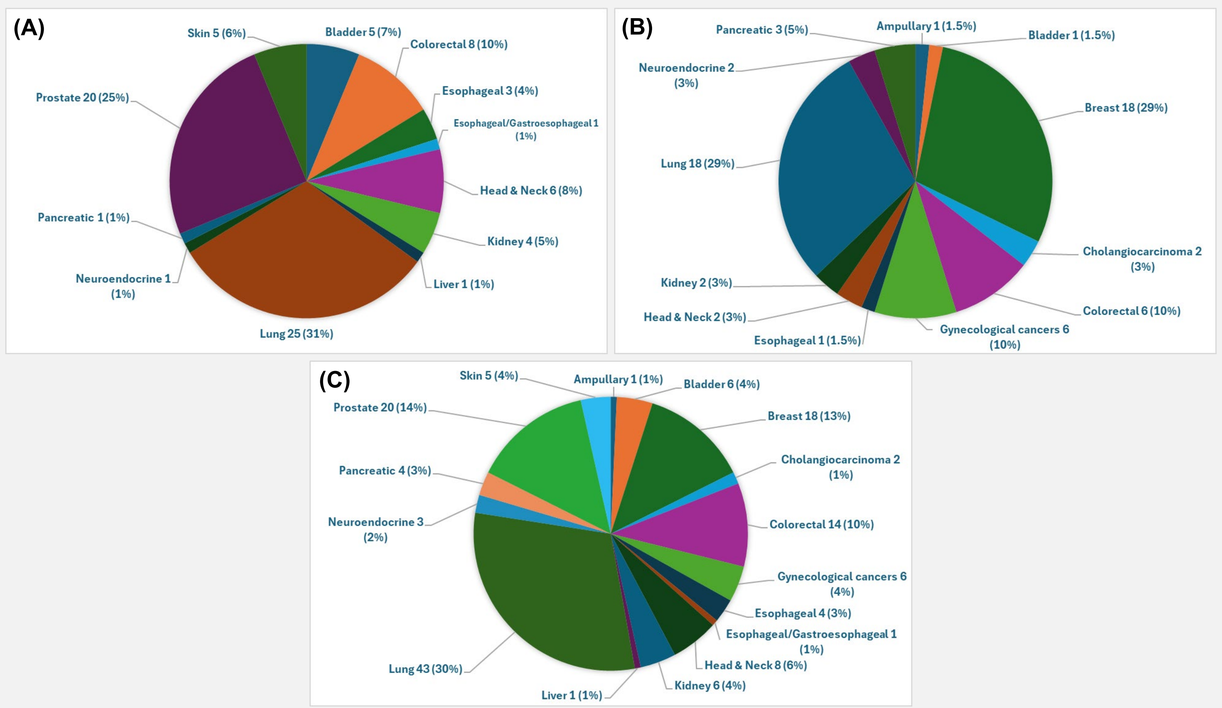

Figure 1. Cancer type distribution across (**A**) males, (**B**) females, and (**C**) the entire patient cohort. Number next to cancer type indicates total number of observed cases. Gynecological cancers: ovarian, *N*=3; endometrial, *N*=3.

PanTracer LBx Variant Detection Workflow

- A total of 801 variants were detected in 83.8% of patients (119/142; **Figure 2**):
  - 774 small variants (SNVs/InDels) across 118 patients
  - 23 amplifications in 14 patients – SNVs/Indels and fusions were also detected in 13/14 and 2/14 patients, respectively.
  - 4 fusions, in 4 patients – All patients had SNVs/InDels.

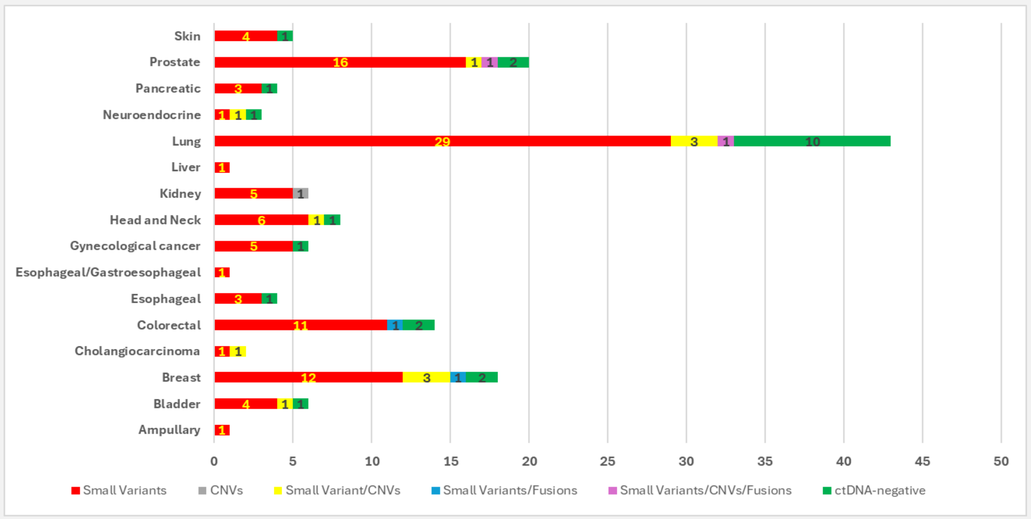

Figure 2. PanTracer LBx variant detection. Number of different classes of somatic variants detected per cancer type.

Variant Curation & Filtration

- Across the 801 detected variants, variants of unknown clinical significance accounted for 54% (*n*=430) followed by pathogenic and likely pathogenic variants at 40% (*n*=321) (**Figure 3**).
- After exclusion of 104 putative clonal hematopoiesis of indeterminate potential (CHIP) variants detected across 61 patients (**Table 2**), 697 variants (median per patient: 4; range: 1-28) remained in 114/119 patients (**Figure 4**):
  - 670 SNVs/InDels
  - 23 CNVs, and
  - 4 fusions

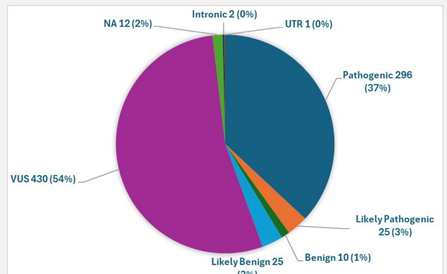

Figure 3. Classification of detected variants based on their clinical significance. NA, not available; UTR, untranslated region; VUS, variants of unknown significance.

Table 2. Number of excluded putative CHIP variants detected per gene and number of affected patients.

Gene	Total Variants	Affected Patients
ASXL1	5	5
DNMT3A	55	36
PPM1D	9	8
TET2	35	26

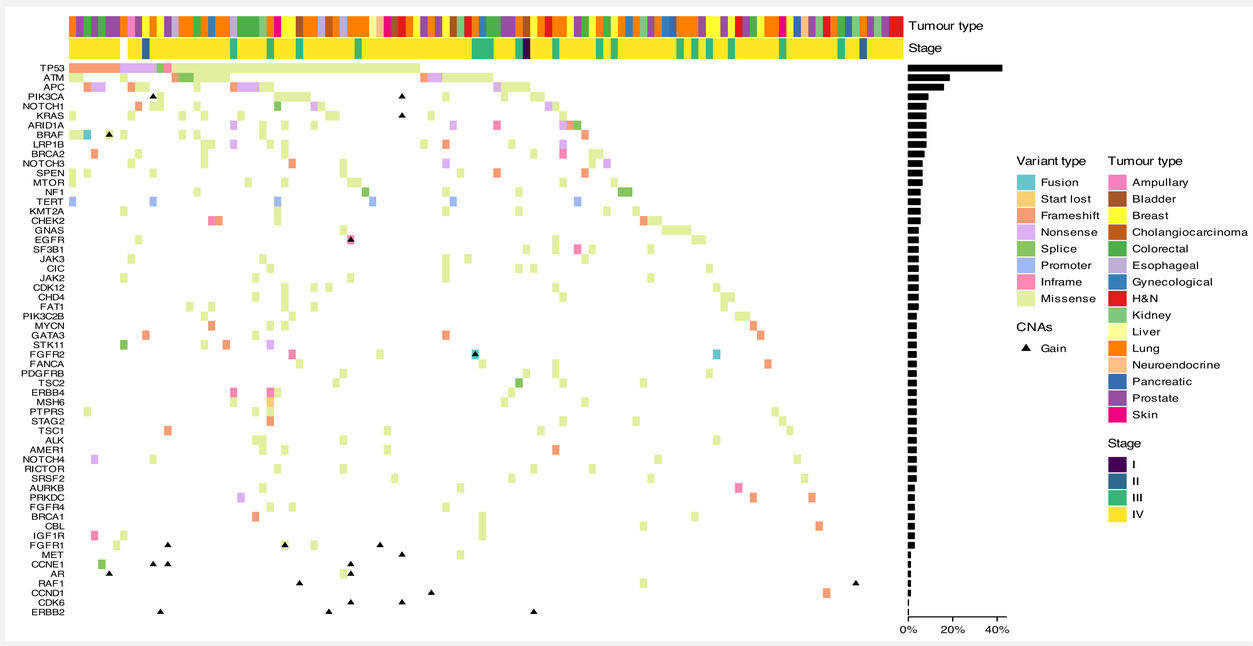

Figure 4. Top 60 most frequently mutated genes across the 697 variants remaining in 114 patients after CHIP filtration. The bar plot on the right y-axis shows the frequency of observed somatic alterations per gene.

Evaluation of Actionability

- Following CHIP filtration, 239/697 pathogenic/likely pathogenic variants (34.3%) were still present in 87/114 patients (SNVs/InDels, *n*=214; CNVs, *n*=23; Fusions, *n*=2) – median per patient: 2 variants (range: 1-7).
- The most frequently mutated gene was *TP53* (*n*=54 variants), followed by *PIK3CA* (*n*=11), *KRAS*, *ATM*, *APC* (each *n*=10), *TERT*, *SF3B1* and *NOTCH1* (each *n*=6).
- Of these, 63 variants (26.4%, **Figure 5A**) in 53% of patients (46/87) were classified as actionable based on evidence in the OncoKB database. These included:
  - 54 SNVs/InDels in 43 patients
  - 8 amplifications in 7 patients – Actionable SNVs/InDels were present in 5 patients
  - 1 fusion in 1 patient with no other actionable alterations.
  - **Figure 5B** shows the distribution of these 63 actionable variants across these 46 patients

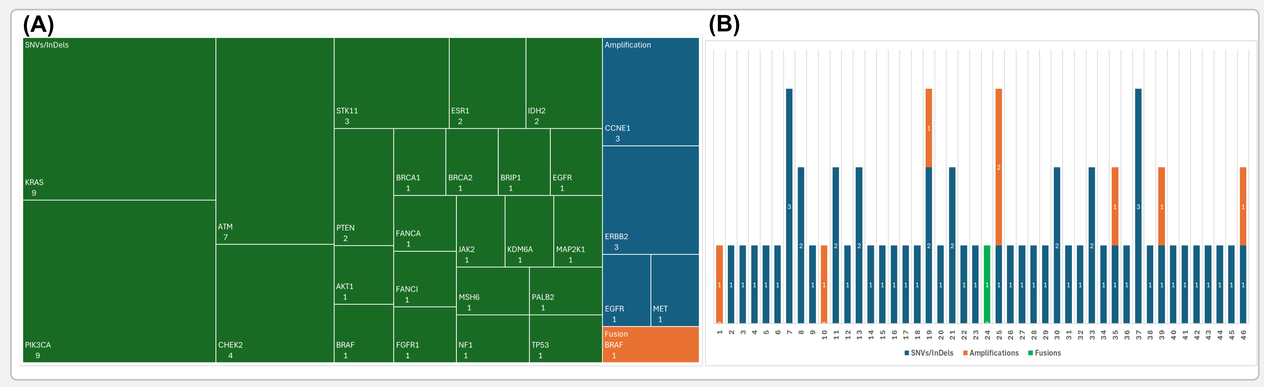

Figure 5. Detection of actionable variants. (A) Distribution per variant class. Majority of observed actionable variants were SNVs/InDels and were most frequently seen in *KRAS*, *PIK3CA* and ATM. Amplifications were limited to *CCNE1*, *ERBB2*, *EGFR* and *MET*, while one fusion (CNTNAP2-BRAF) was detected in a colorectal cancer patient . (**B**) Distribution of actionable variants per patient showing also the co-occurrence of different variant classes.

MSI and bTMB

- **MSI-H** was found in 2 patients:
  - One prostate cancer patient with no actionable variants, and
  - One colorectal patient (#29, **Figure 5B**) with an actionable BRAF SNV.
- **bTMB** (at tumor fractions ≥1%) was observed at a median score of 19.3 muts/Mb (range: 11.2-66 muts/Mb) in 35 patients:
  - 20 patients had at least 1 actionable variant,
  - 15 patients had no actionable variants - 1 patient was MSI-H
  - 25 patients had a bTMB score of ≥16 muts/Mb – 7 of them had no other actionable variants or MSI-H status
- Taken together, actionable changes that could be amended by either genomically-driven targeted therapies or immunotherapy were seen in 47/114 patients with detected variants (41%; **Figure 6**).
- This number can potentially increase when bTMB score has been fully validated thought large prospective studies

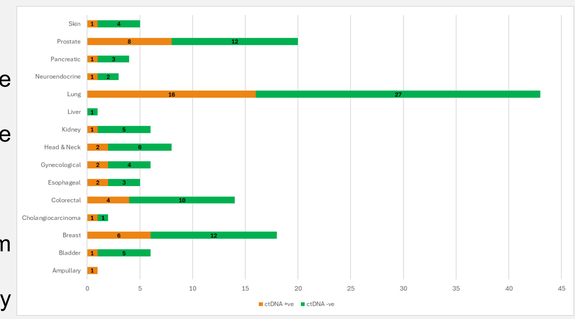

Figure 6. Distribution of actionable alterations per cancer type. ctDNA+ve, detection of actionable variants and/or MSI-H; ctDNA –ve, absence of actionable alterations

Conclusions

- Comprehensive genomic profiling (CGP) via liquid biopsy (LBx) has emerged as a powerful tool for treatment selection in advanced solid tumors.
- Further investigations on variant actionability utilizing additional sources, such as the ESMO ESCAT system are ongoing.
- Findings from this study support the use of PanTracer LBx as a tool for timely guiding patients with advanced malignancies to appropriate, guideline-recommended therapies for improved disease outcomes.

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7TH ANNUAL CONGRESS Liquid Biopsy
November 1 - 3, 2025 | Orlando, USA

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