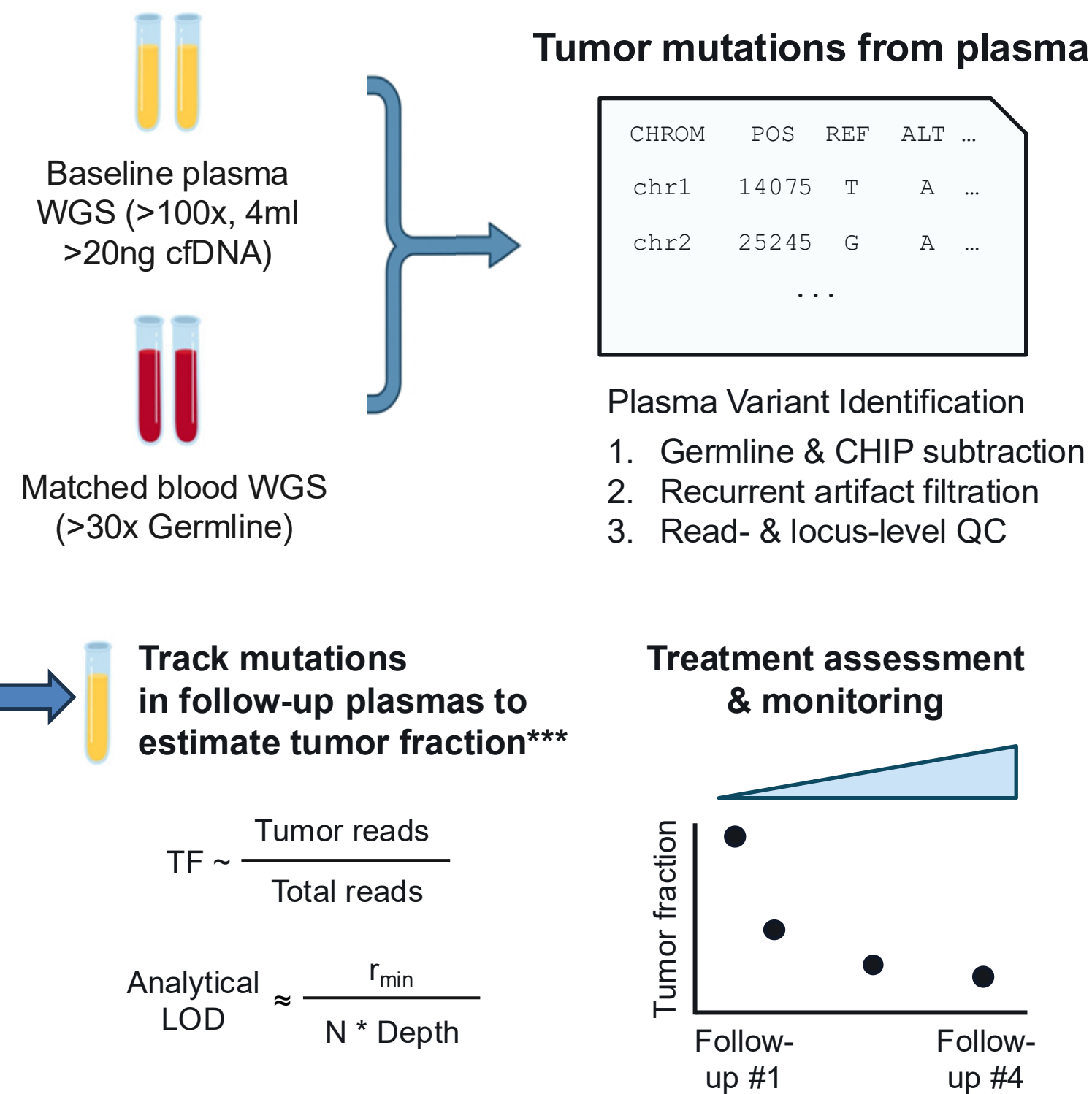


Motivation

Minimal residual disease (MRD) testing has rapidly emerged as an important clinical tool for assessing treatment response and longitudinal monitoring in patients with lung cancer. When matched tumor tissue is available, tumor-informed assays that combine whole-genome tumor profiling with cell-free DNA (cfDNA) sequencing, such as MRDVision™, can achieve ultra-high sensitivity, with a limit of detection as low as 1 part per million (ppm). However, many patients with advanced lung cancer lack the required baseline tumor tissue, since surgical resection or biopsy are not part of standard care*. This leaves tumor-naïve assays, which generally have lower sensitivity (>300 ppm), as the fallback option. To enable sensitive, tissue-free MRD monitoring, we developed the plasma tumor-informed MRD assay (pTIMA). pTIMA uses high-fidelity Ultima Genomics paired plus-minus sequencing (ppmSeq) to identify somatic mutations in baseline plasma cfDNA from samples with sufficient tumor fraction (TF). These mutations are unique to each patient and provide the targets for MRD monitoring in follow-up plasma.

Proposed Method**



Dataset

Cohort. Feasibility of pTIMA was assessed retrospectively on 153 plasma samples with ppmSeq whole-genome sequencing (median depth 75x), available at Inocras.

Reference measurement. Tumor fraction was determined independently by MRDVision™. Plasma-derived variants were called *de novo*, without using tumor tissue.

Data composition

- Healthy controls (n = 52)
- Cancer patients (n = 101)
 - TF > 1%: (n = 31)
 - TF 0.1–1%: (n = 21)
 - TF 0.01–0.1%: (n = 24)
 - TF < 0.01%: (n = 25)

Cancer types — ovarian, lung, breast, pancreatic and others, including advanced lung cancer cohorts from Seoul National University Hospital (n = 10) and Severance Hospital (n = 9).

Plasma-derived variants are tumor-specific and scale with tumor fraction

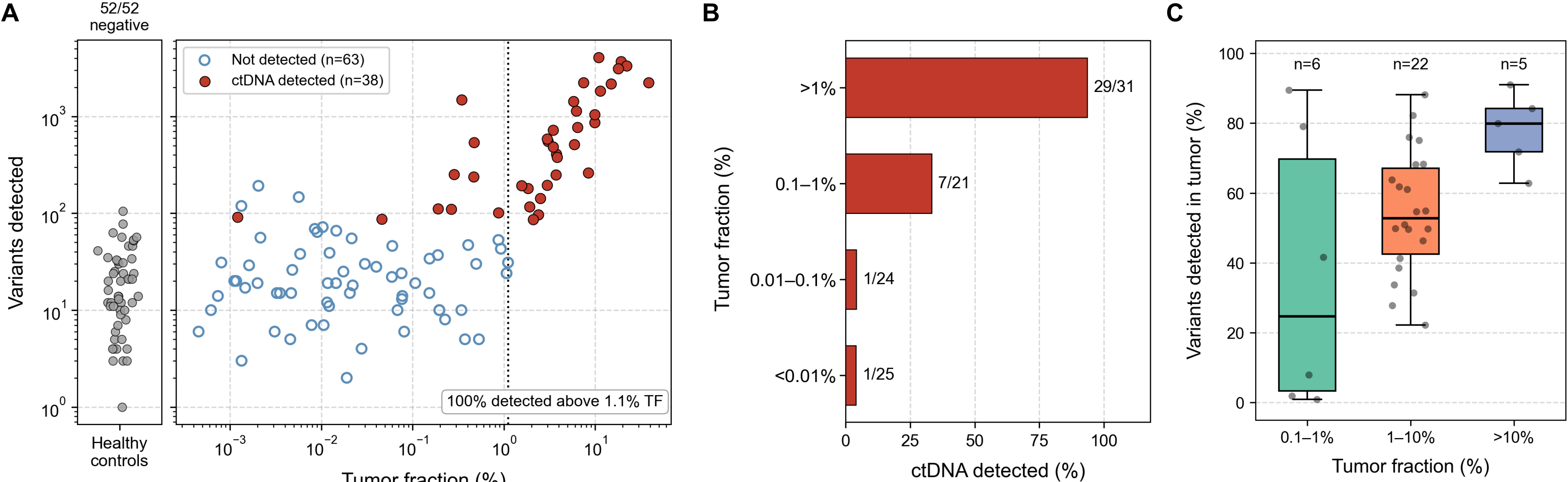


Figure 1. ctDNA detection and variant precision across tumor fractions. (A) Plasma-derived variant counts vs tumor fraction (MRDVision™). Samples were called ctDNA-positive (filled) when counts exceeded the 99.5th percentile of a depth-matched negative binomial model fitted to healthy controls (p < 0.005). Controls (grey) are shown separately. Dotted line: lowest tumor fraction with 100% detection. (B) Detection rate by tumor fraction band. (C) Proportion of plasma-derived variants confirmed somatic in matched tumor tissue, among detected samples.

Baseline plasma mutations enable MRD tracking

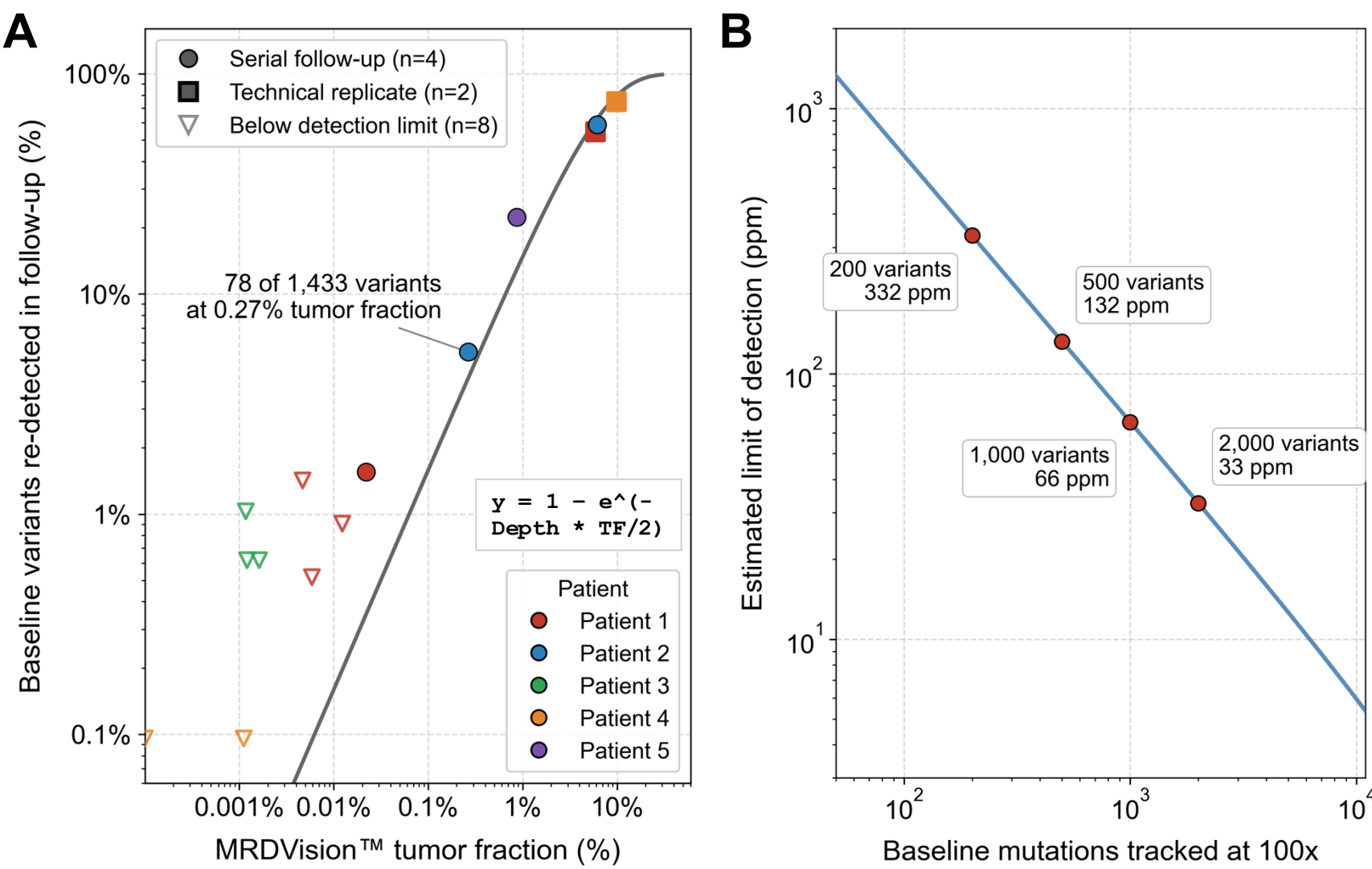


Figure 2. MRD tracking using baseline plasma. (A) Baseline mutations (486–1,433 variants, 5 patients) tracked in 14 follow-up samples. Grey line: re-detection expected from cfDNA molecule sampling at median follow-up depth (65x). (B) Projected LOD95 versus baseline variants tracked, at 100x depth. Binomial model, residual error 3.5×10^{-7} .

High TMB improves variant recovery in advanced lung cancer

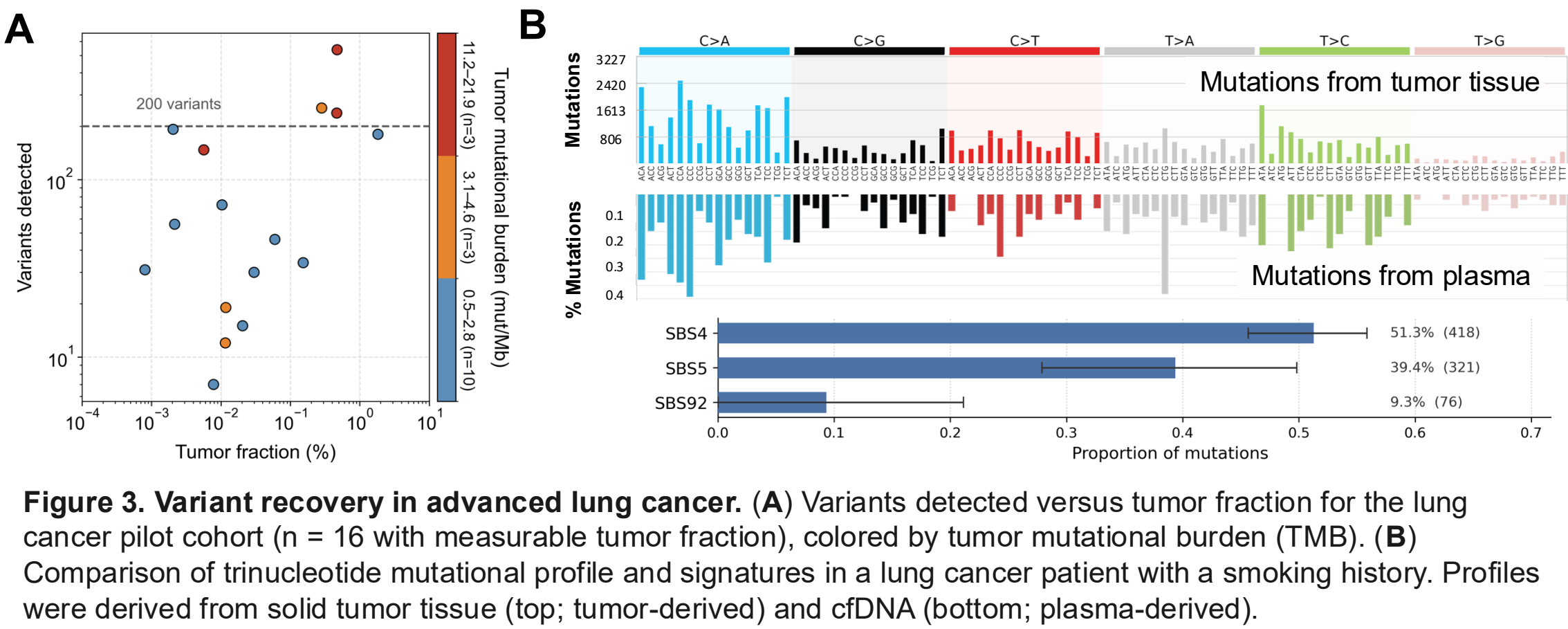


Figure 3. Variant recovery in advanced lung cancer. (A) Variants detected versus tumor fraction for the lung cancer pilot cohort (n = 16 with measurable tumor fraction), colored by tumor mutational burden (TMB). (B) Comparison of trinucleotide mutational profile and signatures in a lung cancer patient with a smoking history. Profiles were derived from solid tumor tissue (top; tumor-derived) and cfDNA (bottom; plasma-derived).

Key Results

ctDNA-positive samples yielded a median of **494** plasma-derived variants, 55% of which were tumor-informed. High mutational burden compensated for low tumor fraction. Baseline signatures of 486–1,433 variants were re-detected in follow-up samples from 5 patients, at tumor fraction as low as 0.012%. Detection limit depends on baseline variant count and follow-up sequencing depth.

Ongoing Work

- Prospective evaluation of a cohort of ~40 lung cancer patients, in partnership with AstraZeneca.
- Establishing the experimental limit of detection and assessing clinical feasibility of pTIMA.

Conclusions

- Somatic mutations can be identified *de novo* in baseline plasma without matched tissue, with the majority confirmed in the tumor.
- Plasma variant recovery scales with tumor fraction and mutational burden; high-TMB yield baselines < 1% TF.
- Plasma-derived baselines enable tissue-free MRD tracking, projected to 132 ppm (500 mutations, 100x depth).

AI Use Disclosure

Claude was utilized as a supportive tool for text revision and figure generation. The authors maintain full responsibility for the final content and scientific accuracy of this poster.

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Footnotes

*Baseline tissue may be unavailable, insufficient, inaccessible, or biologically unrepresentative because it is old or derived from a different disease site.
**Baseline plasma for tumor mutation fingerprinting were collected from patients with metastatic lung cancer immediately before initiation of a subsequent line of systemic therapy. CHIP = Clonal Hematopoiesis of Indeterminate Potential.
***TF: fraction of reads supporting tracked mutations. LOD: smallest TF at which $r_{\min}$ supporting reads are expected across all N tracked mutations. $r_{\min}$ = minimum supporting reads required for 95% detection; N = baseline mutations tracked; Depth = usable depth per locus.

References

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