A novel combination of tissue-informed, comprehensive genomic profiling (CGP) and non-bespoke blood-based profiling for quantifying circulating tumor DNA (ctDNA)

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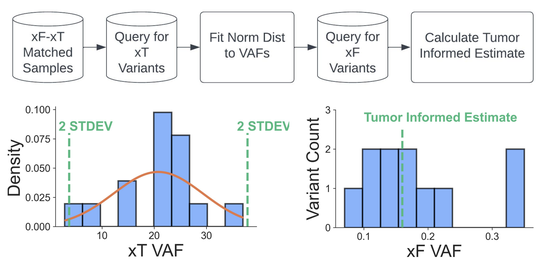
INTRODUCTION

Estimating quantitative circulating tumor fraction in liquid biopsy samples is a promising area of clinical development for monitoring therapeutic molecular response and correlates with patient outcomes. Here, we introduce a sensitive measure of estimating ctDNA tumor fraction (ctDNA TF) using a novel combination of tissue-informed CGP with a non-bespoke, blood-based liquid biopsy panel.

METHODS

Advanced pan-cancer tumor samples were sequenced with both the Tempus xF or xF+ (105 or 523 genes, liquid biopsy) and Tempus xT (648 genes, solid-tumor with matched buffy coat) NGS assays. Samples were collected within 90 days. A normal distribution was fit against the somatic variants detected in solid-tissue and somatic variants with variant allele fractions (VAF) falling within two standard deviations were used as selected biomarkers in the corresponding liquid biopsy to calculate a tumor-informed ctDNA TF for each sample.

Figure 1. Overview of the tumor-informed circulating tumor fraction estimate (TIE).



DISCUSSION

Here, we introduce a novel sensitive and specific tumor-informed, non-bespoke approach for estimating ctDNA TF. Linearity improves with increased panel size and variant number. These results suggest that a tumor-informed ctDNA TF can be utilized to improve the sensitivity of existing methods for estimating TF to help in treatment decisions using Tempus' tissue and liquid comprehensive NGS genomic profiling platform.

SUMMARY

- We introduce a novel sensitive and specific tumor-informed, non-bespoke approach for estimating ctDNA TF with linearity improving as panel size and variant number increase.
- These findings suggest that a tumor-informed ctDNA TF can be utilized to improve the sensitivity of existing methods for estimating tumor fraction to help aid treatment decisions.

RESULTS

Tumor-informed ctDNA TF correlates with liquid biopsy ctDNA TF when at least 1 tumor-informed variant is detected.

Figure 2. (A) xF tumor-informed ctDNA TF correlates with tumor-naive ctDNA TF after removing specimens with no tumor-informed variants. (B) Tumor-informed variant count in xF tumor specimens.

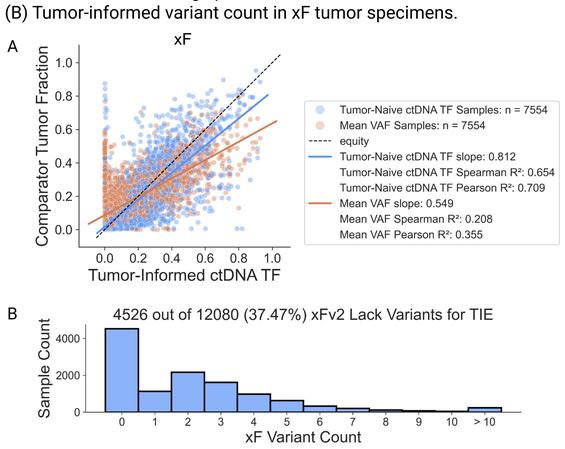
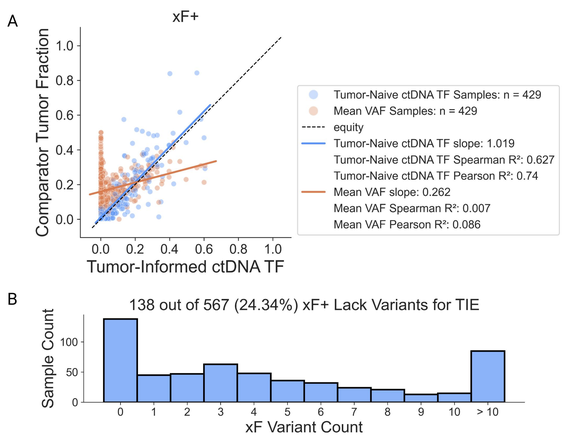


Figure 3. (A) xF+ tumor-informed ctDNA TF correlates with tumor-naive ctDNA TF after removing specimens with no tumor-informed variants. (B) Tumor-informed variant count in xF+ tumor specimens.



Variant thresholds improve tumor-informed ctDNA TF correlation with tumor-naive ctDNA TF in xF.

Figure 4. Accuracy of tumor-informed estimate in a tumor sample cohort with companion LPWGS using ichorCNA, Mean VAF, and tumor-naive ctDNA TF (xM) as the comparators.

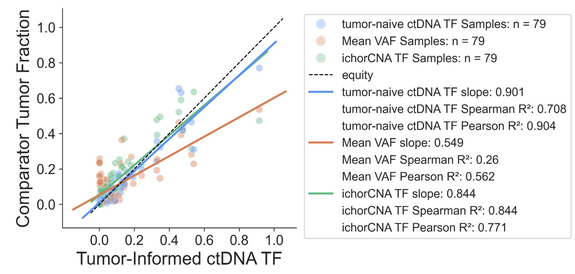
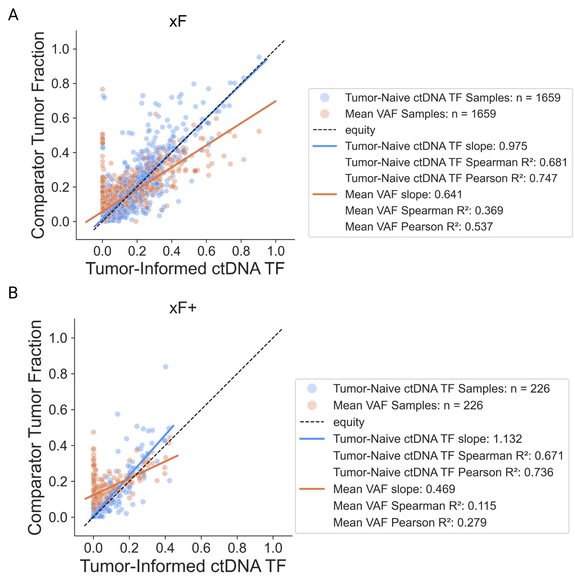


Figure 5. (A) Requiring more than 4 tumor-informed variants to calculate tumor-informed ctDNA TF for xF improves correlation with tumor-naive ctDNA TF. (B) For xF+, there is no improvement in slope and correlation with a variant threshold greater than 1.



Tumor-informed ctDNA TF achieves low LOB and LOD using presumed healthy subjects and titered controls.

Table 1. Performance metrics for tumor-informed estimate. The LOB(95) and LOB(99) were 0%. LOD hit-rate was 100% at the lowest titer evaluated in each assay.

Assay	Variant Count Threshold	LOB(95)	LOB(99)	LOD
xF	>= 5	0%	0%	<= 0.1%
xF+	>= 1	0%	0%	<= 0.25%

Figure 6. 100x bootstrapped LOB calculated from presumed healthy subjects yields a variant count distribution similar to that observed in xF and xF+ tumor specimens.

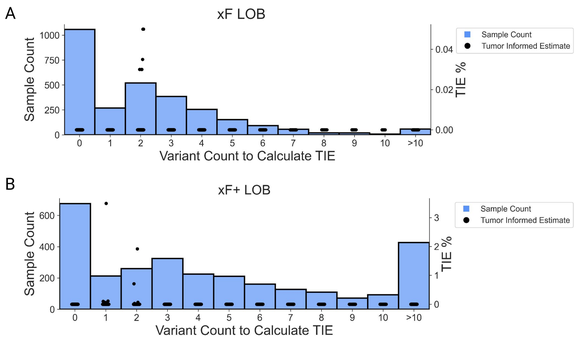
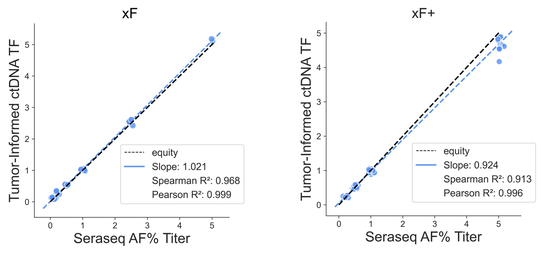


Figure 7. LOD calculated from titered Seraseq ctDNA reference material has low inter-titer variability and strong linear relationship.



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