Clinical whole transcriptome profiling improves the detection of clinically actionable fusions over DNA sequencing alone

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INTRODUCTION

Gene fusions are an important class of somatic alterations, contributing to tumorigenesis and disease progression. While targeted DNA sequencing panels can be used to detect clinically actionable fusions, technical and analytical challenges may produce false negatives. RNA-based, whole transcriptome sequencing provides a complementary method for fusion detection and may improve the identification of actionable variants. Herein, we quantify this theoretical benefit using a large, real-world clinical dataset to assess clinically actionable fusions detected from RNA in conjunction with DNA profiling.

METHODS

We retrospectively analyzed de-identified data records of 84,938 patients profiled with the Tempus xT assay (DNA-seq with fusion detection of 21 genes and RNA-seq with whole exome capture).

Fusions were detected using the Tempus bioinformatic and clinical workflow. Candidate fusions were filtered by read support thresholds, fusion annotation (i.e., breakpoints, reading frame, conserved domains), and manual review by a board-certified pathologist.

Fusions analyzed met OncoKB therapeutic level of evidence 1 or 2 in any cancer indication. Cancer-indication matched fusions are denoted as *clinically actionable fusions*.

Characteristic		%
Sex	% Female	51.0%
Race	Asian	1.9%
	Black or African American	5.5%
	American Indian or Alaska Native	0.1%
	Native Hawaiian or Other Pacific Islander	0.2%
	Other	2.1%
	White	37.0%
	Unknown	53.2%
Age	mean (95% CI)	59.3 (24.4, 82.4)

Table 1. Demographics of patient cohort (N=84,938)

SUMMARY

- We performed the **largest fusion analysis of its kind,** comprising a real-world clinical dataset of 84,938 patients, to assess the improvement in fusion detection from RNA sequencing with concomitant DNA sequencing.
- **RNA sequencing** identified **twenty-three percent** of patients with a clinically actionable fusion that would be **missed by DNA sequencing alone**. This represents a **29% increase** in the number of **patients matched to therapies** from DNA sequencing alone**.**

RESULTS

Fusion dataset encompasses wide array of cancer types and fusions

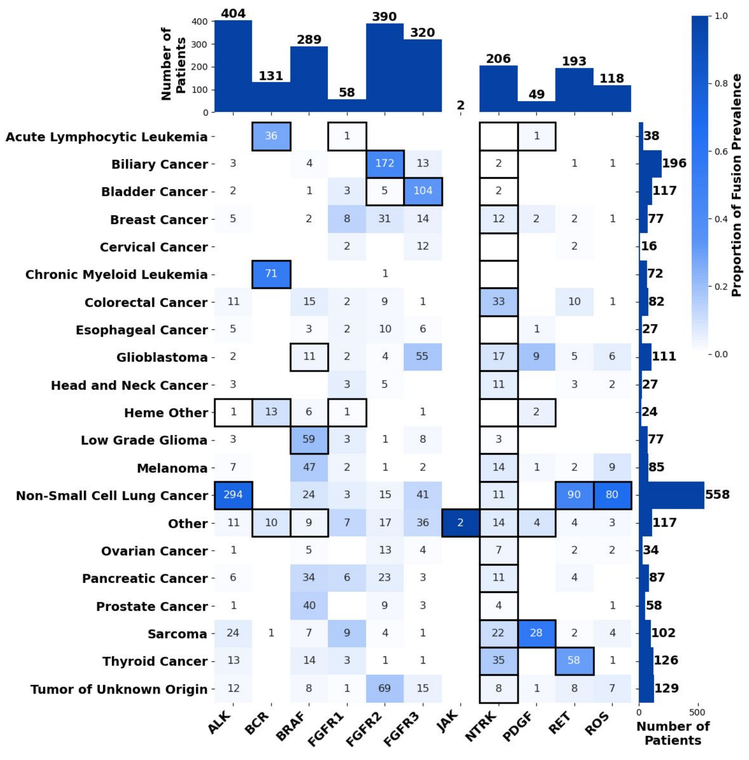

Figure 1. Fusions detected stratified by cancer type and fusion type (N=2,160 fusion events identified in 2,156 patients). Black squares designate indication-matched, clinically actionable fusions.

RNA sequencing increases the number of patients matched to targeted therapies

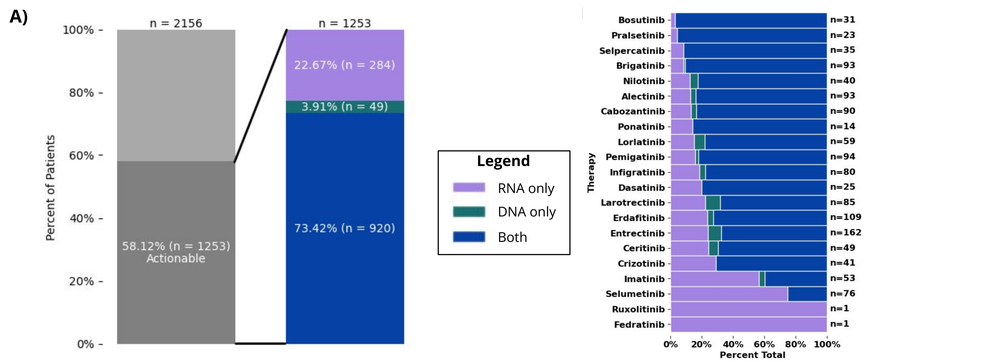

Figure 2. (A) Of patients with identified fusions, 58% of patients had at least one clinically actionable indication-matched fusions (dark grey). Of these, 23% of patients had fusions detected by RNA only (purple). This resulted in a 29% increase in the number of patients with at least one clinically actionable fusion compared to DNA sequencing alone. (B) Distribution of oncoKB recommended therapies for clinically actionable fusion events (N=1,254 fusion events), stratified by assay.

RNA sequencing improves clinically actionable fusion detection across all fusion types and cancer indications

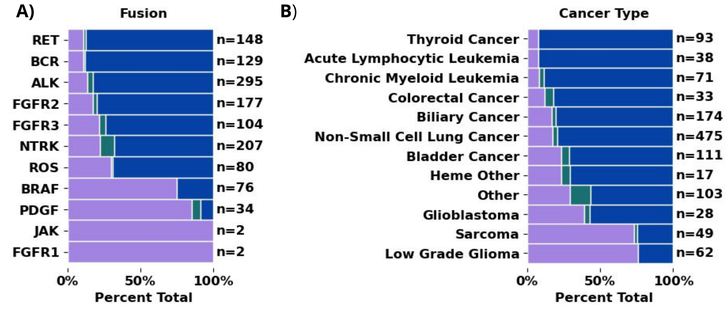

Figure 3. Percentage of clinically actionable fusions events detected by each assay stratified by (A) fusion and (B) cancer type.

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