# Whole Transcriptome Sequencing Identifies Novel Clinically Actionable Gene Fusions Across 698,406 Solid Tumors with Comparable Outcomes to Canonical Fusion Partners

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## Background

Comprehensive RNA sequencing enables unbiased detection of clinically relevant gene fusions that may be missed by DNA- or targeted RNA-based assays. We evaluated whole-transcriptome sequencing (WTS) for detection of known and novel fusions and assessed clinical outcomes associated with novel fusion partners.

## Methods

WTS was performed on 698,406 solid tumors submitted for comprehensive molecular profiling (2019–2026). Fusion detection used STAR aligner,[1] with pathogenic/likely pathogenic (P/LP) variants classified per American College of Medical Genetics and Genomics criteria.[2] Fusions not previously reported in ClinVar[3]/CIViC[4] reference datasets were categorized as novel fusions. Diagnostic and actionable fusions were included with level 1-3 (L1-L3) evidence associations (level 1= FDA-approved, level 2 = NCCN guided therapy, level 3 = lower tier evidence based on peer-reviewed publications or in vitro pre-clinical models).[5] Overall survival (OS) was evaluated in patients with linked claims data receiving tyrosine kinase inhibitors (TKIs) or non-targeted therapies.

## Results

- WTS detected fusion transcripts in 503,460 (72.1%) of 698,406 tumors.
- Among fusion-positive tumors, 37,325 (7.4%) harbored P/LP fusions.
- Among fusion-positive tumors, 34,671 (6.9%) harbored fusions with L1–L3 therapeutic or diagnostic significance.
- Among actionable fusions identified throughout the study period, >91% were novel fusion pairs
- *ERG* and *RSPO3* were the most frequent diagnostic fusion partners.
- *ALK*, *FGFR2*, and *FGFR3* were the most common actionable fusion genes.

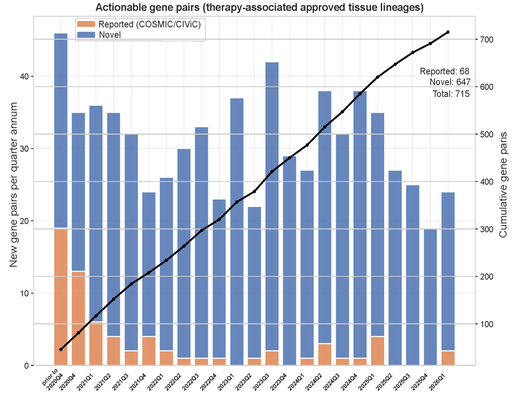



**Figure 1.** First identification of reported and novel fusions from 2020 to 2026. First bar shows fusions prior to 2020 Q4. Genes detected in tissues associated with FDA-approved targeted therapies are shown.

## Results

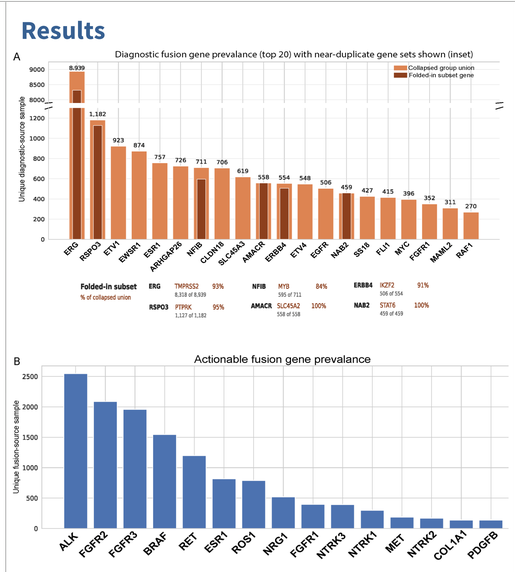



**Figure 2.** Detected fusions ranked by prevalence of clinically relevant gene partners. A) Top 20 fusions with diagnostic gene partners. B) Fusions containing genes with FDA-approved targeted therapies.

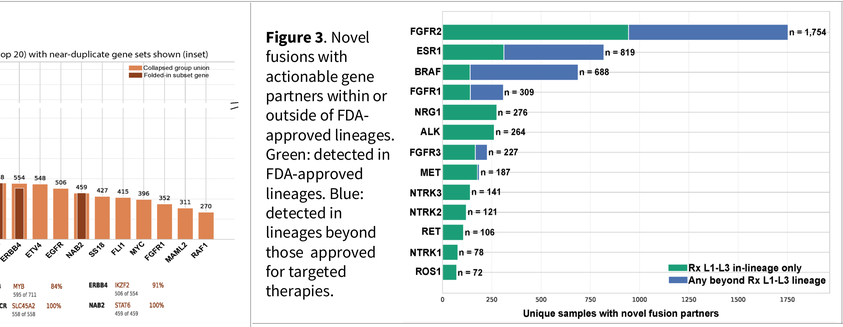



**Figure 3**. Novel fusions with actionable gene partners within or outside of FDA-approved lineages. Green: detected in FDA-approved lineages. Blue: detected in lineages beyond those approved for targeted therapies.

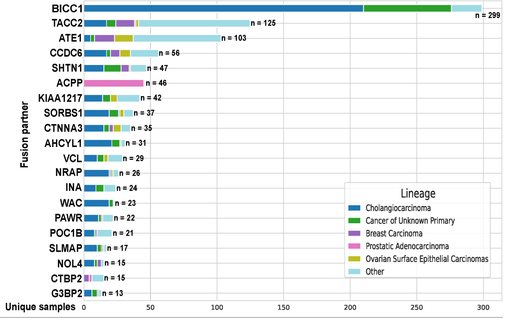



**Figure 4.** Distribution of *FGFR2* fusions across tissue lineages. Top 20 prevalent fusion partners are shown.

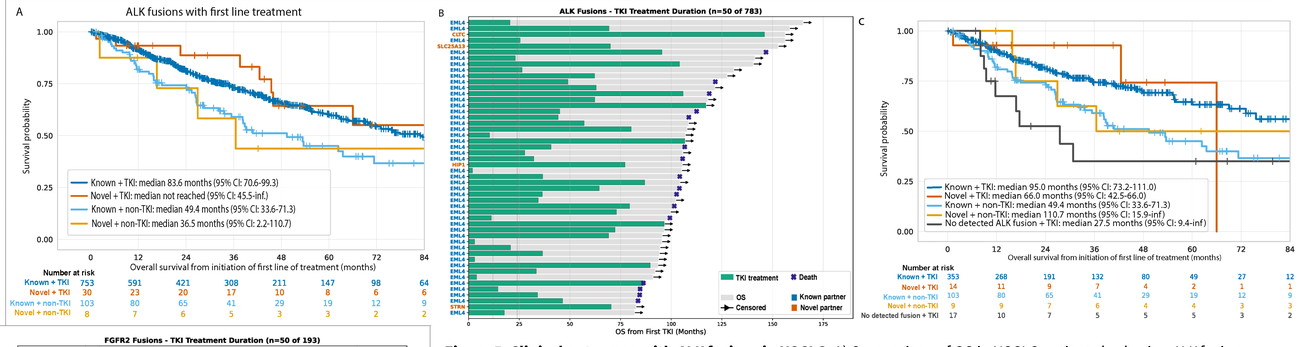



**Figure 5. Clinical outcomes with *ALK* fusions in NSCLC**. A) Comparison of OS in NSCLC patients harboring *ALK* fusions, treated with *ALK*-associated TKIs vs nontargeted therapy (immunotherapy and/or chemotherapy). B) Swimmer plots of patients with *ALK* fusions treated with TKI-targeted therapy. Top 50 responders are shown. C) Comparison of OS in NSCLC patients treated with *ALK*-associated TKIs in the presence or absence of *ALK* fusion detected by WTS.

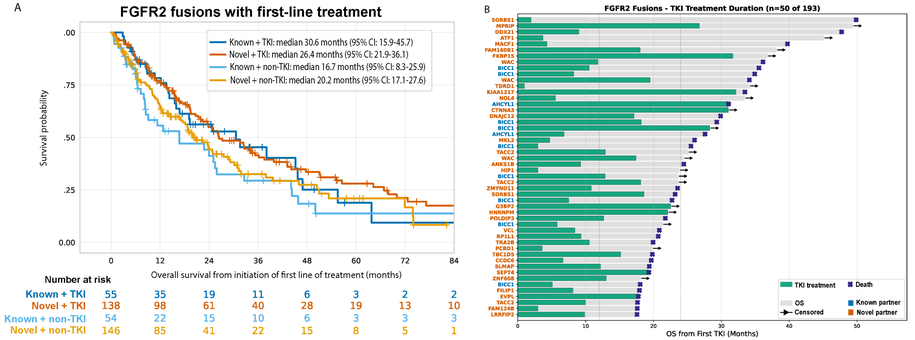



**Figure 6. Clinical outcomes with *FGFR2* fusions in cholangiocarcinoma**. A) Comparison of OS in cholangiocarcinoma patients harboring *FGFR2* fusions, treated with *FGFR2*-associated TKIs vs nontargeted therapy (immunotherapy and/or chemotherapy). B) Swimmer plots of patients with *FGFR2* fusions treated with TKI-targeted therapy. Top 50 responders are shown.

## Conclusions

- WTS identified thousands of clinically relevant fusion events, including numerous previously undescribed partners in actionable fusions.
- *ALK* and *FGFR2* fusions with novel partners demonstrated outcomes comparable to canonical fusions when treated with matched targeted therapies, supporting their clinical actionability.
- These findings highlight the value of unbiased WTS for expanding precision oncology beyond predefined fusion panels.

## References

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