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Dual ctDNA and tissue sequencing improves detection of actionable variants in patients with breast cancer

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INTRODUCTION

Next-generation sequencing of circulating tumor DNA (ctDNA) and solid tissue biopsies can identify clinically actionable genomic variants that may be used for both treatment selection and disease surveillance. Due to differences in tumor biology and assay design, analysis of liquid and solid tissue next generation sequencing (NGS) results may identify unique variants. Here, we investigate a real-world dataset of breast cancer patients to determine whether clinically actionable variant detection is enhanced by dual liquid and solid tissue testing.

METHODS

We used the deidentified Tempus database to retrospectively analyze stage IV breast cancer patients. Each patient had a known hormonal subtype and dual testing—defined as clinical NGS reports from both Tempus xF (liquid) and Tempus xT (solid tumor tissue) assays. Patients were stratified according to the timing of liquid biopsy relative to solid tissue biopsy: "concurrent" was defined as samples collected ≤30 days apart and "longitudinal" was defined as liquid biopsy >30 days after solid tissue biopsy. Variants were included in analyses if they met the limit of detection criteria of both assays. Clinical actionability was defined by indication-matched OncoKB Level 1-3.

	Concurrent patients: Actionable (total)	Longitudinal patients: Actionable (total)
All (n=1,536)	407 (692)	495 (844)
Subtype		
HR+/HER2- (n=1,068)	287 (460)	376 (608)
HR+/HER2+ (n=95)	40 (44)	43 (51)
HR-/HER2+ (n=50)	20 (24)	24 (26)
HR-/HER2- (n=323)	60 (164)	52 (159)

Table 1. The number of individuals with identified actionable mutations stratified by subtype, split according to the timing between liquid and solid tissue biopsies. Figures 1, 2, and 3 display results using the "concurrent" cohort while Figure 4 displays results for the "longitudinal" cohort.

SUMMARY

- Concurrent dual testing of advanced breast cancer patients improves the identification of clinically actionable findings that may be missed by either liquid or solid tissue testing alone.
- In concurrently tested patients with actionable findings, 20% of patients had unique findings identified only in liquid that would have been missed by solid tissue testing; these findings vary across molecular subtypes and in a gene-dependent manner.
- Longitudinal dual testing identifies an enrichment in *ESR1* variants detected by liquid testing over time.

RESULTS

Concurrent dual testing identifies more patients with actionable findings than single modality testing alone

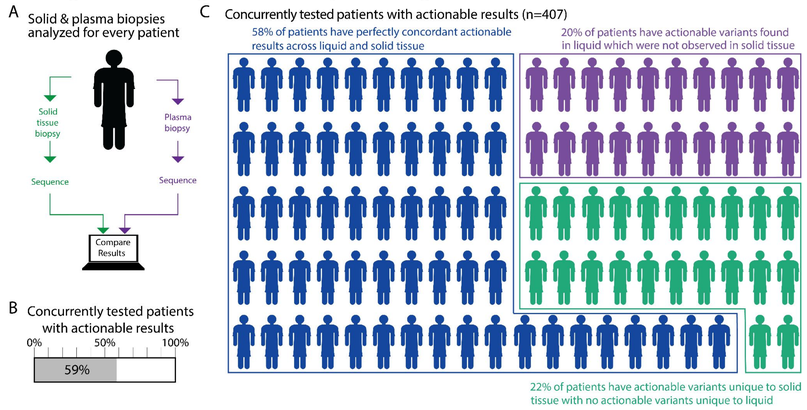

Figure 1. (A) Overview of study design. (B) All concurrently tested patients with actionable variants (n=407). (C) Breakdown of patients with actionable variants identified in either both (blue, n=236) or one assay (purple, n=82/green, n=89).

Specific genes are variably enriched in liquid versus solid tissue results across all subtypes in concurrently tested patients

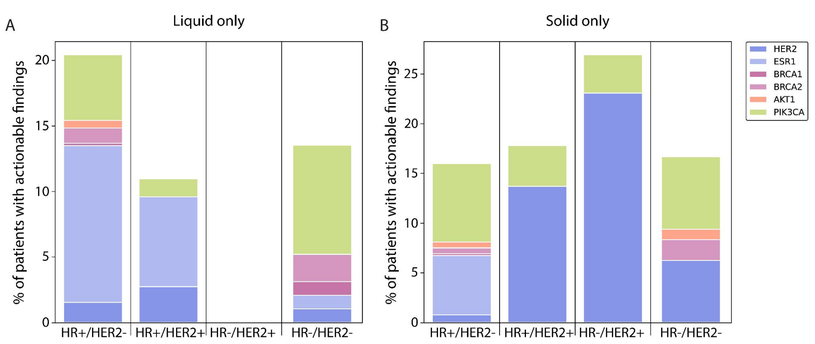

Figure 3. Of the patients with a unique actionable finding identified by liquid (A) or solid tissue testing (B), stacked bars highlight the frequency of patients with individual gene mutations for each subtype.

Patients with uniquely actionable findings identified by liquid testing varies by molecular subtype in concurrently tested patients

Figure 2. (A) The percentage of patients with an actionable finding per subtype. (B) For each subtype, the percentage of patients where solid tissue testing identified all actionable variants versus those where liquid testing identified a unique actionable variant that was not seen in solid.

In longitudinally tested patients, liquid testing identifies both enrichment and loss of actionable findings in specific genes over time

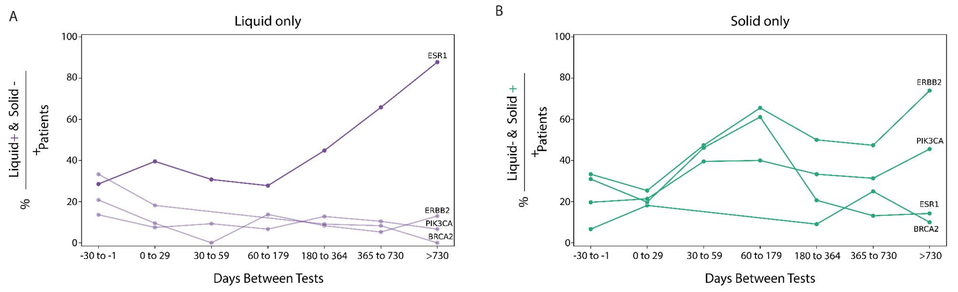

Figure 4. The percent of patients that have a unique variant found in liquid (A) or solid testing (B) at different intervals of days between liquid and solid tissue testing. Only time bins containing at least 10 samples with actionable mutations in each gene are shown.

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