Clinical Impact of Matched Plasma & WBC DNA Sequencing for Variant-origin Classification of PARP Inhibitor-associated Alterations in Prostate Cancer

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Background

Plasma-based liquid biopsy is increasingly used to identify homologous recombination repair (HRR) gene alterations that guide poly ADP-ribose polymerase inhibition (PARPi) therapy in prostate cancer. NCCN guidelines include use of a plasma circulating tumor DNA (ctDNA) liquid biopsy assay when tissue biopsy cannot be feasibly performed.[1] However, clonal hematopoiesis (CH) mutations confound liquid biopsy results and potentially mislead treatment decisions. We evaluated the prevalence and clinical impact of CH-derived variants in homologous recombination repair (HRR) genes associated with PARPi sensitivity in prostate cancer.

Methods

We retrospectively evaluated 4,547 patients with prostate cancer assessed by a liquid-biopsy assay that simultaneously performs whole-exome sequencing on plasma cell-free and white blood cell (WBC) DNA to determine variant origin. Analysis focused on pathogenic/likely pathogenic (P/LP) alterations in guideline-associated PARPi-sensitivity HRR genes. Variant origin was classified as CH, tumor, or germline by comparing plasma and WBC variant frequency and read characteristics. Treatment exposure was assessed using linked insurance claims data.

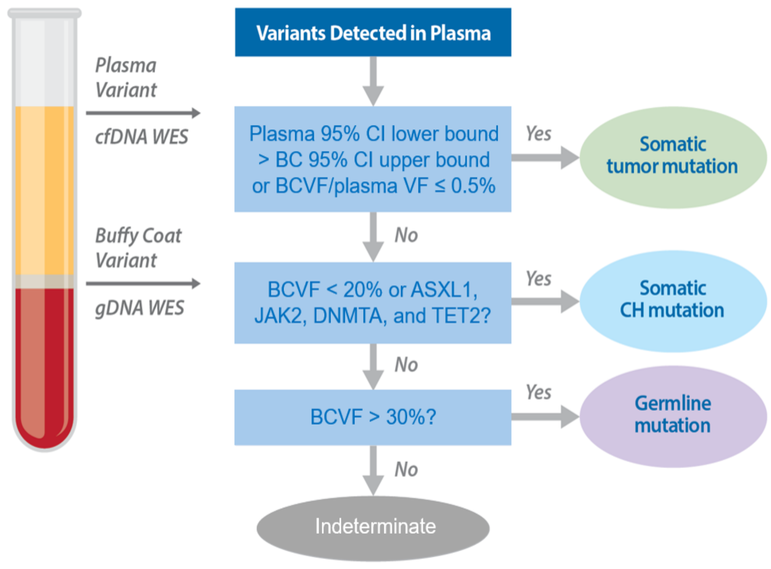


Figure 1. Liquid biopsy workflow: Whole blood is separated into plasma and buffy coat (BC) fractions, which are sequenced (WES) in parallel. Variant origin classification pipeline is shown. Variants were filtered to P/LP variants among 19 HRR/PARPi-associated genes in prostate cancer cases.[2,3]

Results

Among 4,547 patients with prostate cancer, 822 (18.1%) harbored HRR-gene DNA variants. Among these, 263 (32.0%) had CH-only variants; 335 (40.8% of these) had tumor-only variants; and 161 (19.6% of these) had germline-only variants. Concomitant HRR-gene variants in CH and tumor or germline were found in 4.3%.

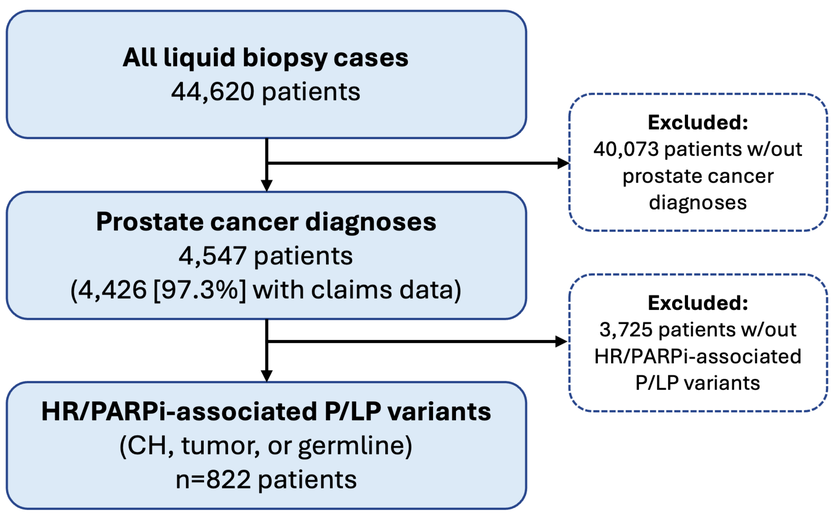


Figure 2. STROBE diagram. Among 44,620 patients subjected to liquid biopsy, 4,547 (10.2%) were diagnosed with prostate cancer. Among these patients, 822 (18.0%) harbored HRR-associated DNA variants.

Results

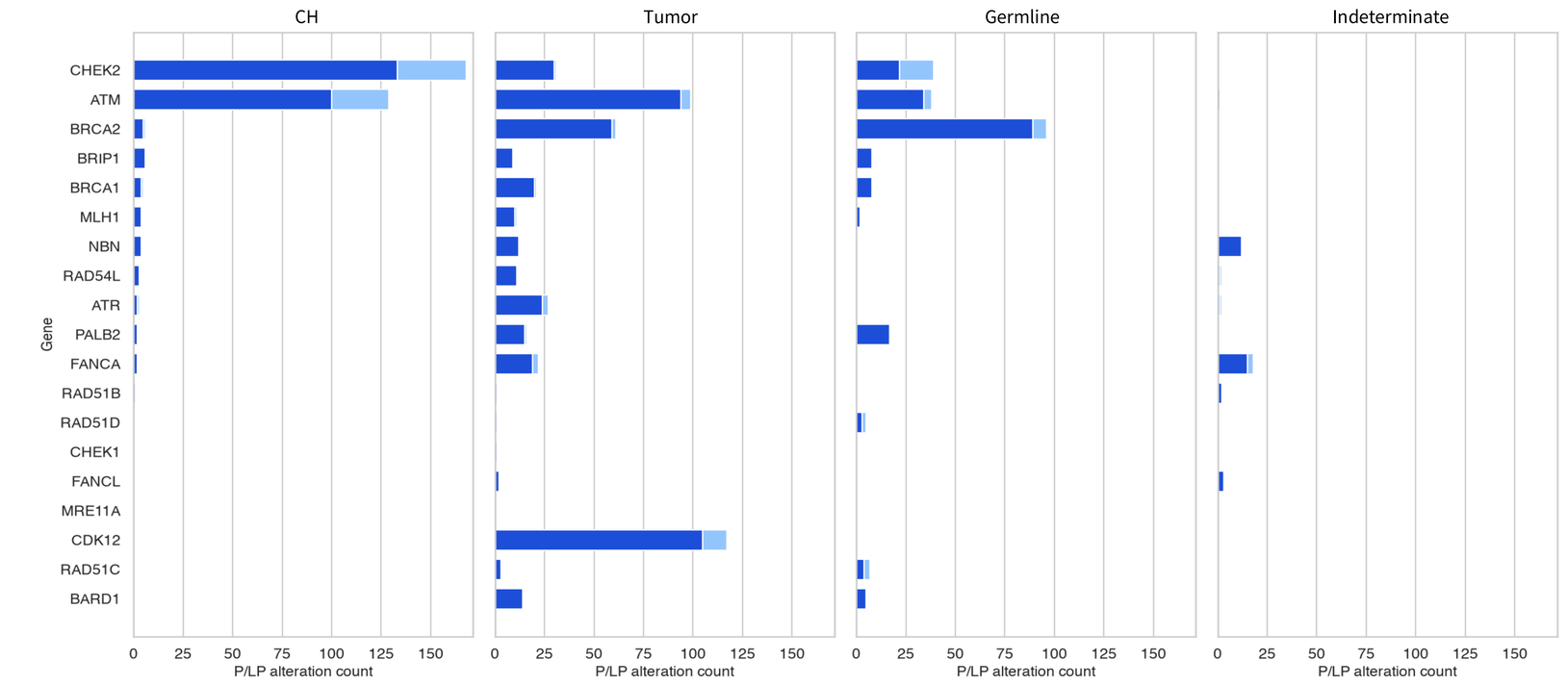


Figure 3. Distribution of PARPi-associated gene variants. CHEK2 and ATM variants overlap between CH, tumor, and germline alterations. BRCA2 and BRCA1 alterations exhibit less overlap, and more commonly annotated as tumor or germline. Overall, 70.6% of CHEK2 variants and 48.3% of ATM variants were CH-derived; comparatively, only 5.6% of BRCA1/BRCA2 alterations originated from CH. Pathogenic (P) in dark blue; likely pathogenic (LP) in light blue.

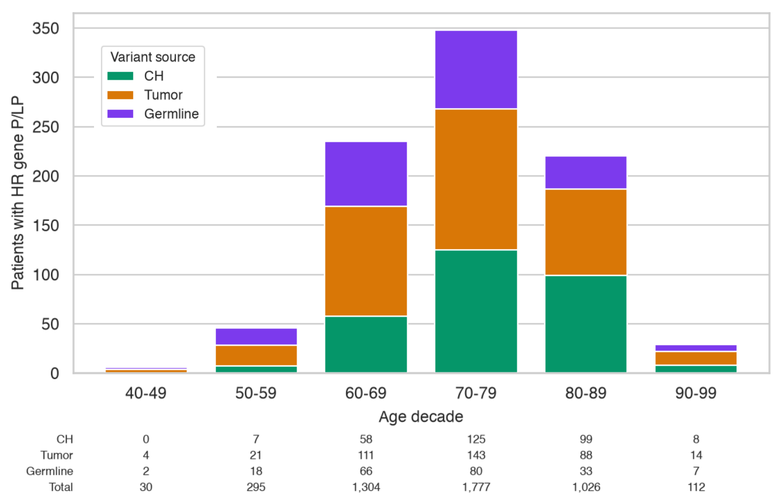


Figure 4. Prevalence of HRR/PARPi-associated genes with pathogenic/likely pathogenic variants across age groups and by origin.

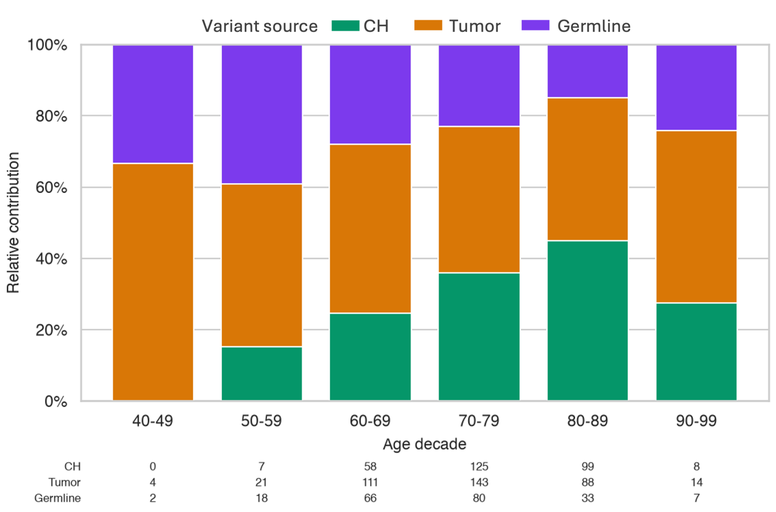


Figure 5. Relative contribution of HRR/PARPi-associated variants annotated as CH increases with age.

Demographic	Value
Age (years), median [IQR]	73 [67–80]
Age-decade, n (%)	
30-39	2 (0.0%)
40-49	30 (0.7%)
50-59	295 (6.5%)
60-69	1,304 (28.7%)
70-79	1,777 (39.1%)
80-89	1,026 (22.6%)
Male, n	4,484 (98.6%)*
Race, n (%)	
White	2,722 (59.9%)
Black	820 (18.0%)
Missing/Unknown	689 (15.2%)
Other	206 (4.5%)
Asian and Native Hawaiian or other Pacific Islander	110 (2.4%)
Ethnicity, n (%)	
Not Hispanic or Latino	3,224 (70.9%)
Missing/Unknown	833 (18.3%)
Hispanic or Latino	490 (10.8%)

Table 1. Demographic distribution of prostate cancer cohort.

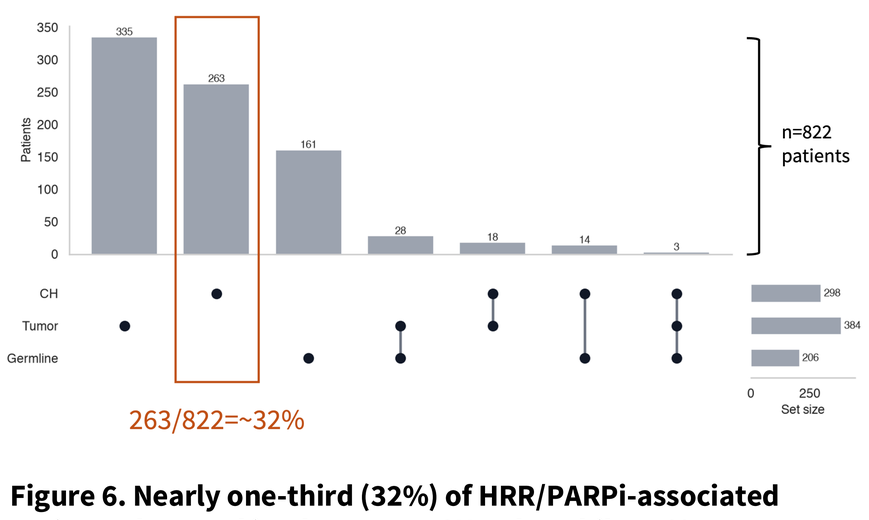


Figure 6. Nearly one-third (32%) of HRR/PARPi-associated variants detected in plasma are CH only, while 41% are annotated as tumor only.

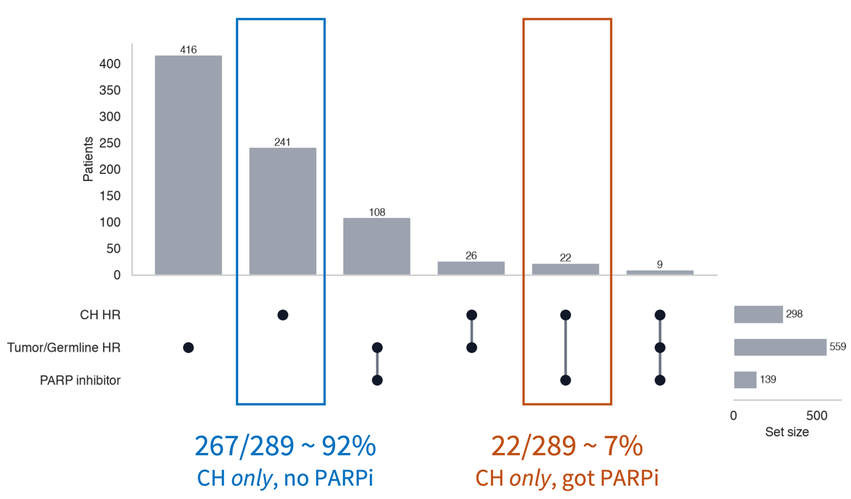


Figure 7. Patients with only CH HRR/PARPi-associated variant source were generally not exposed to PARP inhibitors, but 22 patients (7%) received PARP inhibitors without evidence of tumor or germline variants, potentially inappropriately.

Conclusions

- A significant proportion of prostate cancer patients undergoing liquid profiling have PARPi-associated HRR variants detected only as CH, especially in ATM and CHEK2.
- These findings identify a clinically meaningful risk of variant misclassification of HRR variants in prostate cancer with plasma-only testing.
- Simultaneous sequencing of matched WBC DNA distinguishes CH-derived HRR variants from actionable HRR variants, informing appropriate patient selection for PARPi therapy.

References

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2. Agarwal, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023;402(10398):291-303.
3. Agarwal, et al. PARP and Androgen-Signaling Inhibition plus ADT in Metastatic Prostate Cancer. N Engl J Med 2026;395:427-439.

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