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Commentary

Comment on: Intratumor heterogeneity and clonal evolution revealed in castration-resistant prostate cancer by longitudinal genomic analysis by Jing Li et al.

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Prostate cancer is uniquely characterized both by its heterogeneous development *in situ* and protracted rate of progression to metastasis and treatment resistance; patients diagnosed today with high-risk localized hormone-sensitive prostate cancer (HSPC) may wait more than a decade until the development of metastatic castration-resistant prostate cancer (CRPC) with currently available treatment modalities [1]. To understand the range and contribution of genomic alterations that contribute to the eventual lethality of metastatic CRPC, numerous analyses have been performed that assess both somatic point mutations and copy number alterations across the entire disease spectrum. To date, thousands of tumors have been profiled in sizeable cohorts, consisting largely of either localized HPSC, which include The Cancer Genome Atlas (TCGA) and the Canadian Prostate Cancer Genome Network (CPC-GENE), or metastatic CRPC, which include the East and West Coast Stand Up To Cancer-Prostate Cancer Foundation (SU2C-PCF) cohorts [2]. Although these efforts have produced immense volumes of genomic data with statistically robust identification of tumor drivers, attempts to compare metastatic CRPC to localized HSPC reflect the juxtaposition of two fundamentally different diseases without distinguishing the biologically complex processes of metastasis from treatment resistance.

Different experimental approaches can be used to assess the genomic differences between treatment-naïve and treatment-resistant prostate cancer. Certainly, prostate cancer cell lines *in vitro* and xenografts *in vivo* can identify phenotypes and pathways contributing to drug resistance, but these efforts invariably rely upon immortalized models that do not reflect the genomic complexity of real-world disease [3]. By contrast, studies of treatment resistance in human tissue samples must be performed within a clinical context to introduce hormonal therapies, including androgen receptor- (AR-) targeted agents, guided by a framework that is conducive to patient care. Until recently, this has remained a challenge because hormonal therapies in prostate cancer have historically been limited to those patients with metastatic disease at diagnosis, or suspicion of occult micrometastases due to rising serum prostate specific antigen (PSA) levels after initial definitive local therapy (*i.e.* surgery or radiation). However, compelling data from the STAMPEDE and PROSPER trials, among others, have demonstrated the efficacy of AR-targeted therapies against metastatic HPSC and nonmetastatic CPRC, respectively, in reducing the incidence of distant metastases and improving overall survival [4]. Thus, although androgen deprivation therapy (ADT) has been the mainstay of treating metastatic HSPC for decades, the earlier introduction of AR-targeted therapies suggests that targetable alterations may be present earlier in the treatment history of the tumor.

For considering alterations in localized prostate cancers that have the potential to become castration-resistant, a series of correlative studies around recent clinical trials of neoadjuvant (*i.e.* before surgery) ADT have allowed the direct comparison of human tissues on a matched pre- vs. post-treatment analysis. In a study of patients with high-risk localized prostate cancer receiving six months of neoadjuvant ADT plus the AR inhibitor enzalutamide, Wilkinson et al. [5] reported that in a patient with a nonresponding tumor, mutations to *TP53* and *PTEN* were subclonal in pre-treatment biopsies and had greater clonal

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prevalence in post-treatment radical prostatectomy tissues. While *TP53* and *PTEN* are canonical drivers of ADT resistance, their direct role in facilitating metastasis remains unclear. However, Cmero et al. [6] found that somatic losses to *SNAI2*, a purported driver of metastasis via its expression of the Slug transcription factor facilitating the epithelial-to-mesenchymal transition (EMT), occurred only in responding patients in a trial of neoadjuvant ADT plus the CYP17A1 inhibitor abiraterone. This finding may suggest that ADT resistance may not be completely independent from the biology of metastasis, especially since both hormone independence and EMT rely on a terminally differentiated tumor cell to regain at least partial lineage plasticity [7]. In both of these studies, treatment response was determined by the presence of residual tumor in the prostate, which effectively disconnects any occurrence of metastasis from the biological phenotypes of treatment resistance, whereby all residual tumor in these contexts is castration-resistant, in patients that did not harbor any metastases at the time of treatment.

In contrast to these prior studies, Zhang et al. [8] now reports on the direct comparison of pre- and post-treatment prostate tumor tissues, in tissues taken from only from the prostate, from patients who also harbored metastatic disease. This key difference in study design is the ability to identify potentially novel genomic drivers of *bona fide* metastasis while simultaneously controlling for treatment resistance. In this analysis of 14 samples from five patients, 1–3 prostate tumor biopsies per patient were acquired either prior to or shortly after the initiation of ADT, and then one biopsy per patient was acquired again after the onset of resistance to ADT. The multi-sampling strategy enabled authors to distinguish between clonal and subclonal mutations in *de novo* tumors and track clonal prevalence of mutations in post-treatment samples.

In all five patients, the mutational frequencies in the pre-treatment tumors, along with reconstruction of tumor phylogenies, suggest a population bottlenecking phenomenon had occurred in response to therapy [9]. Although incomplete sampling of the post-treatment tumor can also explain this result, the most common result was the detection of fewer mutations by whole-exome sequencing in the CRPC specimens relative to the matched HSPC specimen, consistent with extinction of treatment-sensitive subclones. In patient L, the pre-treatment specimen harbored a subclonal mutation to *SPOP*, which is prognostic for ADT sensitivity [10]. Indeed, that subclone was not observed in the post-treatment specimen, indicating that a heterogeneous tumor prior to treatment exhibited diverse responses to therapy. In addition, and also consistent with prior findings, was a strong correlation between mutations found at baseline with their post-treatment counterparts. These include alterations to *TP53* in patients Y and N, which identify tumor clones with potential for ADT resistance. A limited number of studies have identified genomic drivers at baseline that remain targetable in CRPC [11], and loss of cell cycle checkpoint control via mutations *TP53* continues to emerge as a robust genotype.

More importantly, however, are the mutations distinct to CRPC samples. On top of the *TP53* alterations, patients Y and N also harbored gains to chromosome X around the *AR* gene, which is a common somatic genotype observed in ADT-resistant tumors. However, patient N also harbored a CRPC-restricted mutation to *MMRN2*, which is involved in VEGF signaling and interacts with both FAK and integrin signaling pathways [12]. The CRPC sample from patient B harbored a mutation to *STYK1*, which is also associated with integrin-mediated cell adhesion, and the CRPC sample from patient Y harbored a mutation to *LRIG2*, which is implicated in cytokine signaling [13,14]. Although these anecdotal findings require extensive validation in larger cohorts, they collectively hint at a convergent selection for phenotypes involving increased microenvironmental interactions. Thus, the finding from Cmero et al. [6], which showed that ADT-sensitive tumors lost the ability to undergo EMT, intriguingly link ADT resistance to genes mediating cell adhesion, motility, and vascularity. If validated, the results from Zhang et al. [8] suggest that patients receiving first-line ADT for metastatic HSPC could also benefit from the addition of angiogenesis and nonreceptor tyrosine kinase inhibitors that specifically target the drivers of metastasis.

CRediT authorship contribution statement

Scott Wilkinson: Writing – original draft, Writing – review & editing. **Adam G. Sowalsky:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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