Background:
Prostate cancer is the second leading cause of male cancer death in the United States. While localized disease can be cured by radiation or surgery, metastatic prostate cancer presents a clinical challenge. Metastatic prostate cancer can initially be controlled by endocrine therapies that target the androgen receptor (AR), however, these tumors will inevitably develop resistance. This stage of the disease, termed castration-resistant prostate cancer (CRPC), is responsible for practically all prostate cancer-specific deaths. Truncated AR variant (AR-V) proteins are broadly enriched in CRPC cell lines and clinical samples, and can function as ligand-independent, constitutively active transcription factors. Recent studies have indicated that AR-V expression levels are regulated by mRNA polyadenylation.

Methods:
To understand the mechanism of *AR* polyadenylation in greater detail, we conducted biochemical assays examining the roles of candidate trans-acting factors and cis-regulatory elements in regulation of *AR* alternative polyadenylation and growth of CRPC cells. We used siRNA and shRNA strategies to perform knockdown of trans-acting factors and used antisense-oligomers to disrupt cis-regulatory sequences that regulate alternative polyadenylation of *AR*.

Results:
Several well-characterized AR-Vs, such as AR-variant-7 (AR-V7) and AR variant-9 (AR-V9) arise from splicing of different cryptic exons (CEs), located within intron 3 of the *AR* gene to *AR* exon 3. We found that blocking the alternative poly(A) site in *AR* exon CE3 reduced expression of AR-V mRNAs and protein and increased expression of full-length AR mRNA and protein in 22Rv1 CRPC cells, suggesting this single alternative poly(A) site in exon CE3 is utilized to generate AR-Vs, including AR-V7 and AR-V9. We also found the CPSF complex component, CPSF1, regulated selection of this alternative poly(A) site based on the finding that knockdown of CPSF1 in 22Rv1 cells reduced expression of AR-Vs and increased expression of full-length AR. Our data has also nominated a negative regulatory region ~50 bp downstream of the poly(A) site in exon CE3, which can be repressed to induce *de novo* expression of AR-V7 in AR-V negative LNCaP cells.

Conclusions:
These results have identified a single alternative poly(A) site in exon CE3 of *AR* that regulates expression of full-length AR and AR-Vs in CRPC cells and have determined CPSF1 as a trans-acting regulator of the poly(A) site, highlighting new drug targets for CRPC treatment.