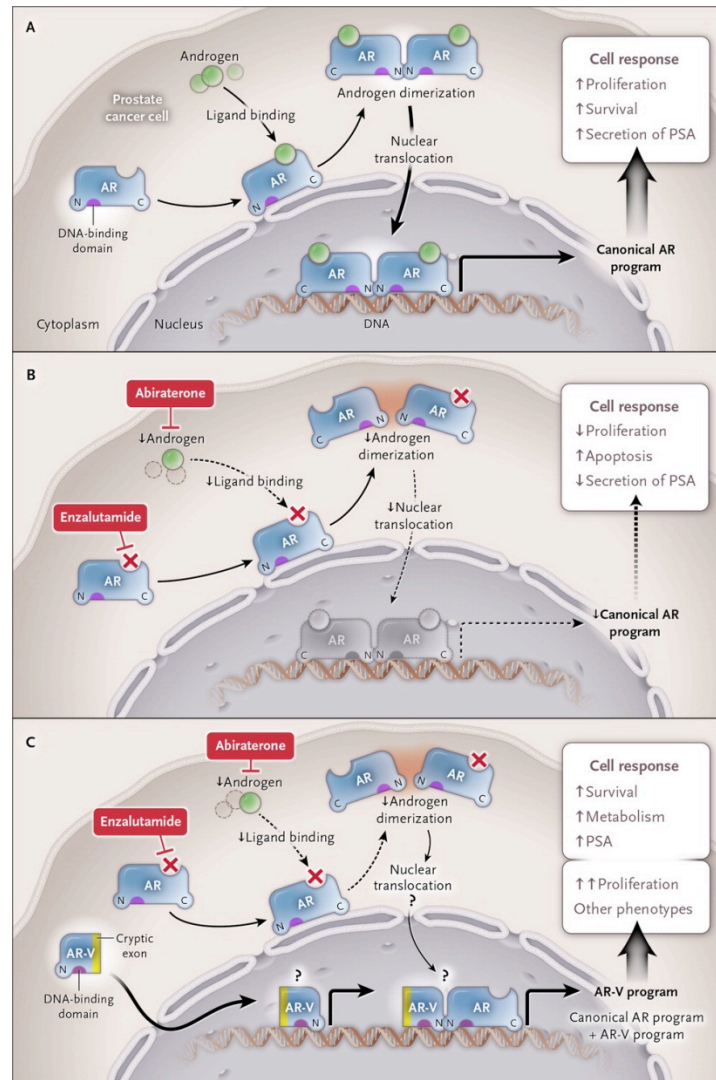


Androgen-Receptor Splice Variant–Mediated Resistance to Therapeutics Directed at the Androgen Receptor



As shown in Panel A, the androgen receptor (AR) is activated by the binding of androgen ligands, which prompts AR dimerization, translocation to the nucleus, and activation of a canonical transcriptional program that promotes cell survival, proliferation, and the secretion of prostate-specific antigen (PSA). As shown in Panel B, *Abiraterone* reduces the availability of androgens, and *Enzalutamide* inhibits androgen binding; both processes lead to the suppression of the canonical AR program and result in cell-growth arrest, apoptosis, and diminished secretion of PSA. As shown in Panel C, AR splice variants (AR-V7) resist the inhibitory effects of *Abiraterone* and *Enzalutamide* because they lack the C-terminal ligand-binding domain of full-length AR. AR-Vs, functioning independently or together with fulllength AR, exhibit constitutive activation of a transcriptional program that overlaps and extends the canonical AR program, with enhanced tumor-cell proliferation.