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Cost-Savings Analysis of AR-V7 Testing in Patients With Metastatic Castration-Resistant Prostate Cancer Eligible for Treatment With Abiraterone or Enzalutamide

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Abstract

INTRODUCTION—Identification of cancer biomarkers that inform clinical decisions and reduce the use of ineffective therapies is a major goal of precision oncology. An abnormal splice variant of the androgen receptor, AR-V7, was recently found to confer resistance to novel hormonal therapies (abiraterone and enzalutamide) in men with metastatic castration-resistant prostate cancer (mCRPC), but did not negatively affect responses to taxane chemotherapies, suggesting that early use of chemotherapy may be a more effective option for AR-V7(+) patients.

METHODS—We calculated the cost savings of performing AR-V7 testing in mCRPC patients prior to starting abiraterone/enzalutamide (and avoiding these drugs in AR-V7(+) men) versus treating all mCRPC patients empirically with abiraterone/enzalutamide (without use of the biomarker).

RESULTS—We determined that AR-V7 testing would result in substantial cost savings as long as the true prevalence of AR-V7 was >5%. In our prior studies, we estimated that approximately 30% of mCRPC patients may have detectable AR-V7 in circulating tumor cells (CTCs). In this population, upfront testing of AR-V7 status (at a price of \$1,000 per test) would result in a net cost savings of \$150 Million in the United States per year.

CONCLUSIONS—AR-V7 testing in mCRPC patients would be cost-beneficial when considering the current price of treatment, and may reduce the ineffective use of abiraterone/enzalutamide, leading to a significant net cost savings to the healthcare system. Clinical-grade AR-V7 testing is currently available at our institution.

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Keywords

AR-V7 testing; CLIA-certified; cost savings; healthcare costs; prostate cancer

INTRODUCTION

The rising cost of health care in the United States is an ongoing socioeconomic challenge. The price of new oncology drugs, which continues to outpace the rate of inflation, has not correlated with clinical benefit at the societal level [1]. Efforts to contain drug costs have yet to bear fruit. An alternative approach to lowering healthcare costs is to develop diagnostic tests (i.e., biomarkers) that better inform clinical decisions. Such tests may reduce the use of ineffective treatments and may select patients more likely to have a favorable disease response.

In advanced prostate cancer, androgen deprivation therapy (ADT) has remained the backbone of therapy for decades. Recently, an abnormal mRNA splice variant of the androgen receptor, called AR-V7 [2,3], was shown to convey resistance to ADT [4,5]. In addition, in men with metastatic castration-resistant prostate cancer (mCRPC), the presence of detectable AR-V7 transcripts in circulating tumor cells (CTCs) has been associated with a high positive predictive value for non-response to novel hormonal therapies (abiraterone and enzalutamide) in several studies [6–8]. These findings suggest that treatment with either abiraterone or enzalutamide in AR-V7(+) mCRPC patients would not be expected to result in significant clinical benefits while incurring substantial costs as well as potential toxicities. Interestingly, AR-V7 status did not appear to negatively affect the response to taxane-based chemotherapy, which implies that mCRPC patients who are AR-V7(+) would be expected to benefit more from early chemotherapy use rather than abiraterone/enzalutamide in this setting [8–11].

In current practice, mCRPC patients are commonly offered treatment with abiraterone [12,13] or enzalutamide [14,15] at an estimated cost of over \$7,000 USD per 30-day supply for each medication [16,17]. In advanced prostate cancer, it is recommended that therapeutic interventions should be given for a minimum of 3 months prior to making an initial determination of disease response (i.e., PSA response, tumor response) [18]. Thus, we estimated that the cost of treatment with either abiraterone or enzalutamide would be at least \$20,000 USD (over a 3-month period) before determining futility. In a CLIA-certified laboratory at Johns Hopkins, an assay has been analytically validated to detect the presence of AR-V7 mRNA in CTCs, with an estimated cost of \$1,000 USD per clinical test. Here, we sought to determine: (i) the prevalence of AR-V7 positivity that would be theoretically required to return a net savings to the healthcare system; (ii) the net cost savings from AR-V7 testing in different mCRPC populations; and (iii) to model the net savings assuming different costs of the AR-V7 assay and the drugs.

METHODS

Assumptions

In this analysis, we assumed that the cost of either abiraterone or enzalutamide would be \$20,000 USD for a 3-month drug supply [16,17]. The cost of the AR-V7 assay was assumed to be \$1,000 USD. The true response rate to abiraterone/enzalutamide in AR-V7 (+) mCRPC patients is not known, but appears to be <5% [6–8]. We therefore assumed that the response rate would approximate zero, such that no AR-V7(+) patients would incur harm by forgoing treatment with abiraterone/enzalutamide. Accordingly, each AR-V7(+) patient treated with abiraterone or enzalutamide would be considered a \$20,000 USD loss without a corresponding clinical benefit.

Based on observations from our group and others, we have estimated the prevalence of AR-V7 to be different in several distinct mCRPC populations: (i) 10–15% prevalence in abiraterone- and enzalutamide-naïve patients; (ii) 30–35% prevalence post-abiraterone or post-enzalutamide; and (iii) 45–50% prevalence post-abiraterone and enzalutamide [6]. Finally, the number of mCRPC patients in the United States eligible for treatment with abiraterone or enzalutamide was estimated as approximately 30,000 men per year [19].

Calculations

We defined “cost neutral” or the “break-even point” as the scenario where the total cost of testing all patients eligible for abiraterone or enzalutamide for AR-V7 per year ($\$1,000 \text{ USD} \times \text{total patients}$) equals the cost of abiraterone or enzalutamide avoided in AR-V7(+) patients ($\text{total patients} \times \text{AR-V7 prevalence} \times \$20,000 \text{ USD}$). In our analysis, we calculated the prevalence of AR-V7 that would be required for testing to be cost-neutral (i.e., cost of testing = savings) by varying the cost of both the AR-V7 assay and the drugs. Using this theoretical model, we determined the net cost savings of AR-V7 testing in the above mCRPC populations using the estimated AR-V7 prevalence rates. Conversely, we also calculated how high the cost of the AR-V7 assay could go before it no longer resulted in cost savings depending on the prevalence rates of AR-V7 in different mCRPC populations.

RESULTS

We first sought to determine whether the cost of testing all mCRPC patients eligible for abiraterone or enzalutamide for AR-V7 (and treating only those with AR-V7(–) results) would result in a net cost savings compared to the current approach of treating all patients eligible for abiraterone/enzalutamide therapy. For this analysis, we assumed that mCRPC patients who were found to have AR-V7(+) CTCs would not receive either abiraterone or enzalutamide, resulting in a cost savings of \$20,000 USD per patient (we did not account for additional cost savings of clinical testing, professional fees, and drug toxicities). In our first calculation, the cost of the AR-V7 assay and the drugs were both fixed, and were estimated to be \$1,000 USD for the AR-V7 assay and \$20,000 USD for 3 months of abiraterone/enzalutamide avoided. Accordingly, the total cost of testing all mCRPC patients eligible for abiraterone or enzalutamide in the US per year would be approximately \$30 Million USD ($30,000 \text{ patients} \times \$1,000 \text{ per assay}$). To make the AR-V7 assay cost-neutral at this price,

1,500 mCRPC patients would need to have a positive AR-V7 assay (and avoid abiraterone or enzalutamide expenditures: \$20,000 USD/patient). Since 30,000 mCRPC patients are considered eligible for abiraterone or enzalutamide per year in the US, we calculate that a 5% prevalence of AR-V7 (1,500/30,000 patients) would be required in the mCRPC population to make the assay cost-beneficial.

It is increasingly understood that the prevalence of AR-V7 rises with additional exposure to second- and third-generation hormonal therapies. For example, abiraterone- and enzalutamide-naïve patients have the lowest AR-V7 prevalence (10–15%), whereas this number increases to 45–50% following treatment with both agents [6]. Focusing on the post-abiraterone or -enzalutamide mCRPC population, where the prevalence of AR-V7 is approximately 30%, we calculated the cost savings from AR-V7 testing in these patients in the US per year. We estimated that abiraterone/enzalutamide treatment would be avoided in 9,000 patients (30,000 men $\times$ 30% AR-V7 prevalence) following a positive AR-V7 assay, resulting in a cost avoidance of \$180 Million USD (9,000 AR-V7(+) patients $\times$ \$20,000 USD saved). After accounting for the total cost of the assay (\$30 Million USD spent), the net cost savings would be \$150 Million USD per year (Table I).

Although the cost of abiraterone and enzalutamide are already established, we modeled the prevalence of AR-V7 that would be required to “break even” by varying the cost of the drugs and fixing the cost of the assay (Fig. 1A). At the current cost of the drugs of \$20,000 USD (for a 3-month supply), the estimated prevalence of AR-V7 in each mCRPC population is shown in Figure 1A. Of note, testing abiraterone- and enzalutamide-naïve patients, which harbor the lowest prevalence of AR-V7 (10%), would still result in a modest net cost savings of \$30 Million USD. Assuming a 10% AR-V7 prevalence in this population, AR-V7 testing would remain cost-beneficial until the price of drug dropped below \$10,000 USD/3-month supply, which would represent a 50% reduction of its current cost. The cost savings of AR-V7 testing in the postabiraterone or -enzalutamide population (30% AR-V7 prevalence) is maintained at drug prices as low as \$3,500 USD/3-month supply. The AR-V7 prevalence in the post-abiraterone and -enzalutamide population is shown for reference, but is not applicable to this analysis since no additional hormonal therapies are currently FDA-approved for these patients.

In a second model (Fig. 1B), the relationship between AR-V7 prevalence and assay cost was examined after assuming a fixed price of drug (\$20,000 USD/3-month supply). Using the post-abiraterone or -enzalutamide population as an example (30% AR-V7 prevalence), the cost of the assay could be increased up to \$6,000 USD and still remain cost-neutral, representing a sixfold increase over its current price. Indeed, even for the abiraterone- and enzalutamide-naïve patients (10% AR-V7 prevalence), an assay cost of up to \$2,000 USD would be cost-effective. Therefore, the current assay price of approximately \$1,000 USD results in a cost savings in all scenarios examined.

DISCUSSION

The expensive price, combined with the perception of limited benefit, make oncology drugs a commonly used example of how the rising cost of medical treatment is draining the

healthcare system. Much has been written about the reasons for such high prices including research and development costs, Medicare rules forbidding price negotiations, US patent laws on pharmaceutical products, the ban on importing foreign drugs, and the often lengthy process for drug approval [20,21]. The development of orally administered anticancer drugs (such as abiraterone and enzalutamide) has increased in the last decade, putting much of the burden of healthcare coverage in the US on Medicare part D. Although the Affordable Care Act (ACA) made provisions to protect Medicare beneficiaries from the rising cost of oral oncolytics, experts predict that out-of-pocket expenses will remain high even when the ACA takes full effect [22].

Efforts to curb drug costs by regulating the pharmaceutical industry have been difficult. Recently, recommendations have been made to allow health insurers to negotiate drug price, restrict products from their formulary based on value, and provide greater information on pricing and alternative therapy options [23]. Such approaches may indirectly result in more reasonable pricing of oncology drugs. Here, we have explored the potential cost savings of implementing a diagnostic test to better select prostate cancer treatments and improve their relative value. The AR-V7 assay, currently available in a CLIA-certified molecular diagnostics laboratory at Johns Hopkins, is priced to cover the cost of labor, reagents, instrument depreciation and molecular pathologist's professional interpretive fee. Assuming that this price is fixed at approximately \$1,000 USD per test (or modestly increased, say to \$2,000 USD, in a commercial setting), there exists a financial incentive to health insurers to reimburse providers for AR-V7 testing rather than covering abiraterone or enzalutamide empirically for all eligible mCRPC patients. Not included in our analysis are the costs of monitoring/treating known side effects and toxicities of both abiraterone (i.e., abnormal liver function tests, hypertension, electrolyte imbalance) and enzalutamide (i.e., hypertension, seizure). Expenditures on the management of these toxicities are not reflected in the upfront cost of drug and would substantially add to the total cost of treatment. Therefore, we have erred on underestimating the financial impact of AR-V7 testing in our analysis.

With respect to drug cost, the manufacturers of abiraterone and enzalutamide may even consider a cost-reduction in an effort to improve the cost-benefit ratio of AR-V7 testing. However, given the relatively low cost of the AR-V7 assay compared to current drug costs, any price reduction of abiraterone or enzalutamide would have to be substantial and of unclear financial impact to the manufacturer. Moreover, our analysis used a conservative estimate of drug cost (\$20,000/3-month supply), which reflects drug pricing at the time of FDA approval [24,25]. Enzalutamide and abiraterone prices have since increased which may result in additional cost savings of AR-V7 testing. In clinical practice, providers may discontinue therapy following a rising PSA after 2 months on treatment rather than three. In our model, assuming the cost of a 2-month drug supply to be ~ \$13,000 USD, the incidence of AR-V7 required to "break even" is 7–8%, which is less than the incidence found in the abiraterone- and enzalutamide-naïve patients (10%). Should this AR-V7 test have no effect on drug pricing, the selection of a patient population that is more likely to have a treatment response to abiraterone/enzalutamide may increase the value of each drug.

Another compelling argument to get patients on the proper drug is the relative value of each treatment. Except for docetaxel, the relative value of therapies for mCRPC is low, suggesting

that drug prices are overinflated [26]. Relative value, in this context, accounts for both the cost per life-year gained as well as the cost per probability of survival. Those treatments that have larger impacts on survival at lower cost are of more relative value. One potential consequence of AR-V7 testing would be lowering the cost per life-year gained for either abiraterone or enzalutamide, since AR-V7(+) patients may be treated preferentially with chemotherapy instead of hormonal therapy. By removing the AR-V7(+) patients (i.e., the non-responders) from the equation, the total spending on either abiraterone or enzalutamide would be reduced. Assuming no effect on life-years gained or the probability of survival (only non-responders excluded from treatment), the relative value of each drug should improve due to decreased total drug spending (i.e., reduced cost per life-year gained and cost per probability of survival). In this instance, the total cost of drug would be reduced since non-responders would no longer be treated with enzalutamide/ abiraterone. Using relative value as a metric to evaluate drug pricing, any increase in relative value due to AR-V7 testing may provide some justification for the current cost of abiraterone or enzalutamide.

Given the cost savings shown here, and assuming that the clinical utility of AR-V7 is further confirmed over the next several years, we propose a conceptual testing algorithm (Fig. 2) that could be applied to different mCRPC populations during the course of treatment. Since AR-V7 detection did not appear to be associated with resistance to taxanes in prior studies [8,9,11], patients that are [1] abiraterone/enzalutamide-naïve or [2] post-abiraterone or -enzalutamide with a positive AR-V7 result could subsequently be treated preferentially with taxane-based chemotherapy. In addition, post-abiraterone and -enzalutamide patients may also be considered for testing, should an AR-V7—directed clinical trial be available. Intriguingly, following taxane chemotherapy, some patients who initially have AR-V7(+) CTCs may revert back to an AR-V7(−) state [10]. Given this finding, it might be reasonable to also consider AR-V7 testing after progression on both first- or second-line chemotherapy. Those patients who are found to have AR-V7(−) CTCs after taxane therapy may be considered for abiraterone or enzalutamide at that time, although clinical confirmation of this hypothesis is currently lacking.

There are several weaknesses of this study, and certain caveats that must be acknowledged. Prior to implementing diagnostic testing outside of a research study, clinical outcomes using an AR-V7—informing approach must be shown to be at least noninferior to outcomes using an AR-V7—agnostic approach. Should AR-V7 testing result in worse clinical outcomes (e.g., shorter overall survival), then the potential harm of testing would outweigh the cost savings and would not be recommended. Additionally, the true response rate of AR-V7(+) patients to abiraterone/enzalutamide is not fully known, and might be higher than the 5% rate that was assumed here. In the meantime, larger cohorts of mCRPC patients are being evaluated for AR-V7 and studied in a blinded prospective fashion, which should provide further insight into disease response to various agents. If the response rate of AR-V7(+) patients to abiraterone/enzalutamide is higher than anticipated, this potential harm (i.e., withholding effective therapy in a subset of patients) will need to be accounted for in future cost analyses. Currently, the preliminary data showing low response rates in such patients make AR-V7 testing more appealing given the minimal harm in avoiding abiraterone/enzalutamide treatment in this setting [6–8]. Lastly, we have not accounted for potential quality-of-life improvements in the absence of an objective response for AR-V7(+) patients

treated with abiraterone or enzalutamide; loss of such benefits could also be considered as a harm of testing.

In conclusion, our cursory economic analysis suggests that AR-V7 testing could result in a substantial cost savings to the United States healthcare system of \$150 Million USD per year. Further studies are needed to clinically confirm AR-V7 as a biomarker for hormonal therapy resistance and to determine the effect of AR-V7 testing on overall survival in patients with mCRPC.

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IMPLICATIONS FOR PRACTICE

A splice variant of the androgen receptor, AR-V7, has been implicated in resistance to AR-directed therapy in metastatic castration-resistant prostate cancer patients, but does not negatively predict response to chemotherapy. In a CLIA-certified laboratory at Johns Hopkins, we have developed a clinical assay to detect AR-V7 mRNA in circulating tumor cells. The clinical use of AR-V7 testing may result in a cost savings to the health care system by avoiding the expenditures on futile therapy.

Fig. 1.

Prevalence of AR-V7 in mCRPC patients required to "Break Even" at different costs of drug and assay. **A:** At increasing costs of drug, the required prevalence of AR-V7 in a population at which the cost of testing equals the cost of treating non-responders (i.e., AR-V7(+)) patients) is shown. In this model, the assay price is fixed at \$1,000 USD per test. Any AR-V7 prevalence above or below the "break even" threshold at a given drug price would result in a net cost-savings or cost-loss, respectively. The estimated AR-V7 prevalence for each mCRPC population is also depicted, at the current cost of abiraterone and enzalutamide. **B:** The AR-V7 prevalence in a population required to be cost-neutral is shown at increasing

costs of the AR-V7 assay, across a range of AR-V7 prevalence rates. In this model, the cost of drug is fixed at \$20,000 USD per 3-month supply. The expected AR-V7 prevalence in [1] abiraterone- and enzalutamide-naïve (10%) and [2] post-abiraterone or -enzalutamide (30%) mCRPC patients are also displayed.

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Fig. 2.

Proposed AR-V7 testing algorithm in mCRPC patients. Multiple potential testing nodes are shown. The clinical states of mCRPC are defined by the number and types of prior novel hormonal therapies that were administered. As determined by the Johns Hopkins CTC-based test, AR-V7 prevalence increases with additional lines of hormonal therapy. Abiraterone and enzalutamide-naïve mCRPC patients, as well as those patients progressing on either abiraterone or enzalutamide, could be offered AR-V7 testing. AR-V7(+) patients could then proceed to treatment with chemotherapy rather than hormonal therapy. Patients progressing on first- or second-line chemotherapy could also be considered for testing, with AR-V7(-) patients being potentially eligible for novel hormonal therapy (although this hypothesis remains to be confirmed). Following treatment with both abiraterone and enzalutamide, patients could again be offered AR-V7 testing if an AR-V7-directed clinical trial might be available.

TABLE I

Cost Savings From AR-V7 Testing in mCRPC Patients in the United States Per Year

mCRPC patients eligible for abiraterone/enzalutamide	30,000
AR-V7 prevalence	30%
Cost per AR-V7 assay	\$1,000
Abiraterone/enzalutamide cases avoided	9,000
Cost per abiraterone/enzalutamide avoided	\$20,000
Expenditures on abiraterone/enzalutamide avoided	\$180,000,000
Cost of testing entire population for AR-V7	\$30,000,000
Net cost savings	\$150,000,000