

Systemic Treatments for Advanced Prostate Cancer: Relationship Between Health Insurance Plan and Treatment Costs

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The costs of cancer care are skyrocketing. The introduction of new and expensive drugs is a significant contributor to these escalating costs. It is estimated that by 2025 the average new self-administered anticancer medication will cost \$300,000 per year.¹ These high costs can result in significant societal and patient harm, including altered medication, worse health outcomes, reduced spending on food and other essential goods and services, and psychological stress.² The high costs of cancer drugs have been under increased scrutiny as many argue that the high prices are not associated with relative improvements in health outcomes.^{3,4} This has incited renewed interest in promoting value-based purchasing of pharmaceuticals by payers.⁵

Value-based insurance design (VBID) is a strategy to promote the use of value-based care by reducing patient cost sharing for high-value services and increasing patient cost sharing for low-value services.⁶ When several treatment alternatives of equal effectiveness but varying costs are available to a patient, VBID could lower costs by using differential cost sharing to direct patients to lower-cost alternatives.⁷ In the context of pharmaceuticals, pharmacy benefit managers (PBMs) are the entities through which VBID would be implemented. Health plans or self-insured employers contract with PBMs to manage their drug benefit in exchange for payments and fees, and PBMs in turn negotiate with manufacturers over formulary placement and with retailers over reimbursement of dispensed drugs.⁸ These negotiations determine the availability of and relative out-of-pocket (OOP) pricing for potential treatment alternatives. When treatment alternatives include both oral and injectable drugs, the implementation of VBID is more complicated because it requires coordination across the pharmaceutical benefit for oral therapies and the medical benefit for injectables.

Relatively little is known, however, about the extent to which these negotiations lead to cost sharing consistent with VBID and whether this varies by health plan type. Although the concern of soaring medication costs impacts numerous cancer types,⁹ in this article we focus on metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is responsible for the second-highest national OOP payments among all malignancies (\$2.26 billion

ABSTRACT

OBJECTIVES: The high costs of cancer care can cause significant harm to patients and society. Prostate cancer, the leading nonskin malignancy in men, is responsible for the second-highest out-of-pocket (OOP) payments among all malignancies. Multiple first-line treatment options exist for metastatic castration-resistant prostate cancer (mCRPC); although their costs vary substantially, comparative effectiveness data are limited. There is little evidence of how gross payments made by insurers and OOP payments made by patients differ by treatment and health plan type and how these payment differences relate to utilization.

STUDY DESIGN: Retrospective cohort study.

METHODS: We used IBM MarketScan databases from 2013-2019 to identify men with prostate cancer who initiated treatment with 1 of 6 drugs approved for first-line treatment of mCRPC. We calculated and compared gross and OOP payments and drug utilization across drug and insurance plan types.

RESULTS: We identified 4298 patients who met our inclusion criteria. Insurer payments varied substantially by first-line therapy but were similar across different health plan types, except for docetaxel. OOP payments for a given first-line therapy, in contrast, varied by health plan type. Utilization of first-line therapies varied by plan type in unadjusted analyses, but not after adjusting for patient characteristics.

CONCLUSIONS: The extent to which patient OOP payments for drugs reflect differences in gross payments made by insurers varies across health insurance plan types. However, even though OOP payments for the same treatment differ across plan types, treatment choice is not significantly different across type of health insurance after controlling for patient characteristics.

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annually in 2019).¹⁰ Since 2010, several drugs have been introduced that improve long-term survival for patients with mCRPC: docetaxel, cabazitaxel, sipuleucel-T, abiraterone, enzalutamide, and radium-223. However, although reported survival outcomes are similar across these drugs, their prices vary substantially.¹¹ Thus, mCRPC is a context in which health plans or PBMs could direct patients to lower-priced and equally effective treatments through VBID.

Therefore, we examined the differences in gross payments (ie, payments from insurers on a beneficiary's behalf) and OOP payments (ie, payments by patients), overall and by health plan type, for 6 drugs used as first-line treatment in mCRPC. We also examined the extent to which treatment choices vary by plan type. The objective of our analysis was to understand the extent to which patient OOP payments in the context of mCRPC reflect the principles of VBID and to provide patients, clinicians, and policy makers with improved insight into the relationships among health insurance plan type, health care payments, and utilization.

METHODS

Data and Study Population

Our primary data set was the IBM MarketScan Commercial and Medicare Supplemental databases (hereafter, MarketScan) from 2013 to 2019. MarketScan includes claims for inpatient and outpatient services and prescription drugs from approximately 350 payers for a large convenience sample of more than 40 million people with employer-sponsored health insurance. It also includes a subset of the Medicare population: participants 65 years and older with employer-sponsored Medicare supplemental health insurance.

Our study population included male patients who initiated treatment with at least 1 of 6 focus drugs used to treat mCRPC (docetaxel, abiraterone, enzalutamide, sipuleucel-T, cabazitaxel, and radium-223) between July 1, 2013, and June 30, 2019. This cohort has been previously described.¹¹ Abiraterone and enzalutamide are oral medications, and the other 4 are administered via injection. We defined the index date as the date of the first claim for a focus drug. We excluded patients who were not continuously enrolled in the MarketScan databases for at least 6 months before and after the index date, patients without a prostate cancer diagnosis (*International Classification of Diseases, Ninth Revision*, and/or *International Statistical Classification of Diseases, Tenth Revision*, code within 6 months before or 1 month after the index date), patients with other cancer diagnoses during the 6 months before the index period, patients with capitated insurance plans or those with invalid costs (defined as negative service or pharmacy costs on any given day during the study period or negative cost for focus drug), patients with only 1 claim for a medication given via injection (docetaxel, cabazitaxel) and no other focus drug claims, patients

TAKEAWAY POINTS

We examine how insurer and patient out-of-pocket (OOP) payments for advanced prostate cancer differ by drug and health plan type and describe the relationship between these payments and utilization.

- ▶ The extent to which patient OOP payments reflect differences in gross drug payments by insurers varies across health insurance plan types.
- ▶ Although OOP payments for the same treatment differ across plan types, treatment choice is not significantly different across plan types after controlling for patient characteristics.
- ▶ For patients and clinicians, insurance type can impact OOP payments; choosing a different treatment option may significantly reduce OOP spending.
- ▶ For policy makers, reducing the burden of cancer care requires improved mechanisms to understand both the financial and nonfinancial differences in treatment options.

who used more than 1 focus drug on the index date, and patients with claims with negative days of supply for the focus drug.

Outcomes

Our outcomes of interest were gross and OOP drug payments and treatment choice for first-line treatment within 6 months of the index date by insurance type.

For gross drug payments, we summarized OOP payments, coordination of benefits and other savings, and net payments from service and outpatient pharmacy claims of the first-line treatments within 6 months of the index date. These are all the payments that contribute to total payments for the drug alone in MarketScan. We calculated OOP payments by summing the deductible, coinsurance, and co-payment amounts of the paid claims for the first-line treatments within 6 months of the index date. First-line treatment utilization included the following drugs: docetaxel, abiraterone, enzalutamide, sipuleucel-T, cabazitaxel, and radium-223.

Independent Variables

Our primary independent variable of interest was the type of health plan in which the patient was enrolled. We used the MarketScan categorization to identify 4 categories: high-deductible health plan (HDHP) or consumer-driven health plan (CDHP); comprehensive; health maintenance organization (HMO) or exclusive provider organization (EPO); and preferred provider organization (PPO) or point-of-service (POS) health plan.

Statistical Methods

We used descriptive statistics to summarize patient characteristics by plan type. We then presented the unadjusted mean gross and OOP drug payments and treatment utilization by insurance category. All costs reported were after excluding outliers (< 1st percentile or > 99th percentile of cost).

Next, we used multivariable generalized linear models (GLMs) with a γ distribution and a log link to assess the associations between gross drug payments, first-line treatment choice, and insurance type, controlling for sample characteristics. We identified comorbidities using 6-month preindex claims. Sample characteristics included age

group, index year, household urban vs rural residency, geographic region, employment status, hypertension, diabetes, arrhythmia, cerebrovascular disease or myocardial infarction, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, renal disease, liver disease, and rheumatologic disease. We also included an interaction between first-line treatment choice and insurance type in our multivariable analyses. We calculated regression-adjusted mean costs using the GLMs to evaluate the average marginal effects for each first-line treatment choice and insurance type. We excluded patients whose first-line treatment was either radium-223 or cabazitaxel from our regression results because the small sample sizes in these cohorts resulted in the inability of our model to converge and unstable estimates.

For OOP payments, we fit 2-part models because of the large fraction of observations with zero payments. The 2-part model consisted of (1) a logistic regression to model the probability of having nonzero OOP payments using the entire sample and (2) a GLM using a γ distribution with a log link to model the OOP payments among patients with nonzero OOP payments. We then estimated the overall regression-adjusted mean costs using the product of expectations from the first and second parts of the model. Nonparametric bootstrap with 1000 replicates was used to estimate the 95% CIs of the regression-adjusted mean costs for each first-line treatment choice and insurance type.

Further, to evaluate first-line treatment utilization, we fit a multinomial logistic regression model with treatment choice as the outcome and indicators of plan type as the independent variables of interest. Adjusted estimates controlled for patient age, region of residence, employment status, year, and the presence of health conditions. We estimated ORs and 95% CIs with docetaxel as the reference drug.

All statistical analyses were performed using SAS 9.4 (SAS Institute) and Stata 17 (StataCorp LLC). Statistical tests were 2-sided and assessed at the level of significance of .05. This study was deemed exempt from review by Duke University's Institutional Review Board.

RESULTS

We identified 4298 patients who met our inclusion criteria. **Table 1** and **eAppendix Table 1** (eAppendix available at ajmc.com) present patient characteristics by insurance type. Patients were most commonly enrolled in a PPO or POS health plan (55.3%), followed by comprehensive (27.6%) and HDHP or CDHP (8.7%), and were least likely to be enrolled in an HMO or EPO (7.6%). Patients with HDHP or CDHP enrollment were younger (mean age, 59.3 years), had the highest percentage of active full-time or part-time employment (81%), and had the lowest mean National Cancer Institute (NCI) comorbidity index (0.7), whereas patients with comprehensive plans were older (mean age, 77.3 years) and had the highest percentage of retirees (95.6%) and the highest mean NCI index (1.6).

Although gross insurer payments varied substantially across first-line therapies, they were similar for each first-line therapy

across insurance plan types (**Figure 1**, **eAppendix Table 2**, and **eAppendix Table 3 [A]**). The exception was docetaxel, for which 6-month regression-adjusted mean gross payments were highest for CDHP/HDHPs (\$14,740) and lowest for comprehensive plans (\$6207). Interestingly, no single plan type had the highest or lowest gross payments consistently across drugs. Sipuleucel-T had the highest regression-adjusted mean gross payments across plan types (\$116,491-\$118,640), followed by enzalutamide (\$51,504-\$62,443), abiraterone (\$47,653-\$52,573), and then docetaxel (\$6207-\$14,740) (**Figure 1**).

In contrast to gross payments, OOP payments for each first-line therapy varied substantially by plan type. **Figure 2** and **eAppendix Table 3 (B)** illustrate the 6-month regression-adjusted mean OOP payments by drug and insurance type, and **eAppendix Table 4** demonstrates the results of the 2-part regression model examining the relationship among OOP drug payments, first-line treatment, and insurance type. Overall, individuals enrolled in a CDHP or HDHP paid the most OOP for each first-line therapy, and those with comprehensive plans paid the least.

In addition, among patients enrolled in a given type of plan, OOP payments differed by type of first-line therapy. For patients enrolled in a CDHP or HDHP, regression-adjusted mean 6-month OOP payments ranged from \$606 for docetaxel to \$1809 for enzalutamide. In other words, OOP payments for enzalutamide were approximately 3 times those for docetaxel. For patients with comprehensive plans, regression-adjusted mean 6-month OOP payments ranged from \$126 for docetaxel to \$403 for sipuleucel-T. Regression-adjusted differences in OOP payments across first-line therapies were greatest for individuals enrolled in EPO/HMO plans, ranging from \$265 for docetaxel to \$1633 for enzalutamide.

We also found that patient OOP payments were lowest for the first-line therapy with the lowest gross payments but were not highest for the first-line therapy with the highest gross payments. In particular, both gross and OOP payments were lowest for patients using docetaxel. For sipuleucel-T, in contrast, gross payments, but not OOP payments, were higher than those for other first-line therapies.

Treatment patterns varied significantly by insurance type in unadjusted (**Figure 3**) but not regression-adjusted (**Table 2**) analyses. For example, 37% of patients in a CDHP or HDHP used docetaxel as the first line-treatment for mCRPC compared with 12.7% of patients with comprehensive health plans, and 33.8% of patients with comprehensive insurance used sipuleucel-T as first-line therapy compared with 16.6% of patients in a CDHP or HDHP ($P < .001$). However, after controlling for patient and clinical characteristics, there were no statistically significant differences in the type of first-line therapy received.

DISCUSSION

We evaluated whether health insurance plan type was associated with differences in payments made by insurers on their beneficiaries' behalf (ie, gross payments), payments made by patients (ie, OOP

TABLE 1. Patient Characteristics by Insurance Type*

| Characteristic | CDHP or HDHP (n = 373) | EPO or HMO (n = 325) | POS or PPO (n = 2376) | Comprehensive (n = 1185) | Unknown (n = 39) | Total (N = 4298) |
|-----------------------------------|---------------------------|-------------------------|--------------------------|-----------------------------|---------------------|---------------------|
| Age in years | | | | | | |
| Mean (SD) | 59.3 (5.8) | 67.3 (10.3) | 68.1 (11.1) | 77.3 (8.3) | 68.2 (13.2) | 69.8 (11.2) |
| Median | 60.0 | 66.0 | 66.0 | 78.0 | 63.0 | 69.0 |
| IQR | 56.0-63.0 | 60.0-75.0 | 60.0-77.0 | 72.0-83.0 | 58.0-80.0 | 61.0-79.0 |
| Range | 43.0-87.0 | 40.0-95.0 | 36.0-97.0 | 48.0-99.0 | 49.0-95.0 | 36.0-99.0 |
| NCI comorbidity index | | | | | | |
| Mean (SD) | 0.7 (1.1) | 1.2 (1.5) | 1.1 (1.5) | 1.6 (1.7) | 1.5 (2.0) | 1.2 (1.6) |
| Median | 0.0 | 0.0 | 0.0 | 1.3 | 1.3 | 0.0 |
| IQR | 0.0-1.3 | 0.0-1.9 | 0.0-1.7 | 0.0-2.6 | 0.0-2.1 | 0.0-1.9 |
| Range | 0.0-6.0 | 0.0-7.8 | 0.0-9.2 | 0.0-9.2 | 0.0-7.8 | 0.0-9.2 |
| Year of first-line therapy, n (%) | | | | | | |
| 2013 | 20 (5.4%) | 33 (10.2%) | 250 (10.5%) | 166 (14.0%) | 5 (12.8%) | 474 (11.0%) |
| 2014 | 42 (11.3%) | 74 (22.8%) | 450 (18.9%) | 274 (23.1%) | 7 (17.9%) | 847 (19.7%) |
| 2015 | 54 (14.5%) | 36 (11.1%) | 430 (18.1%) | 269 (22.7%) | 7 (17.9%) | 796 (18.5%) |
| 2016 | 73 (19.6%) | 48 (14.8%) | 384 (16.2%) | 213 (18.0%) | 5 (12.8%) | 723 (16.8%) |
| 2017 | 69 (18.5%) | 42 (12.9%) | 371 (15.6%) | 157 (13.2%) | 7 (17.9%) | 646 (15.0%) |
| 2018 | 80 (21.4%) | 59 (18.2%) | 338 (14.2%) | 78 (6.6%) | 6 (15.4%) | 561 (13.1%) |
| 2019 | 35 (9.4%) | 33 (10.2%) | 153 (6.4%) | 28 (2.4%) | 2 (5.1%) | 251 (5.8%) |
| Urban vs rural, n (%) | | | | | | |
| Rural | 57 (15.3%) | 32 (9.8%) | 343 (14.4%) | 205 (17.3%) | 5 (12.8%) | 642 (14.9%) |
| Urban | 311 (83.4%) | 256 (78.8%) | 1725 (72.6%) | 891 (75.2%) | 32 (82.1%) | 3215 (74.8%) |
| Unknown | 5 (1.3%) | 37 (11.4%) | 308 (13.0%) | 89 (7.5%) | 2 (5.1%) | 441 (10.3%) |
| Region, n (%) | | | | | | |
| 1 (Northeast) | 57 (15.3%) | 43 (13.2%) | 648 (27.3%) | 173 (14.6%) | 10 (25.6%) | 931 (21.7%) |
| 2 (North Central) | 93 (24.9%) | 135 (41.5%) | 583 (24.5%) | 478 (40.3%) | 7 (17.9%) | 1296 (30.2%) |
| 3 (South) | 148 (39.7%) | 82 (25.2%) | 843 (35.5%) | 344 (29.0%) | 15 (38.5%) | 1432 (33.3%) |
| 4 (West) | 75 (20.1%) | 65 (20.0%) | 285 (12.0%) | 187 (15.8%) | 7 (17.9%) | 619 (14.4%) |
| 5 (unknown) | 0 (0.0%) | 0 (0.0%) | 17 (0.7%) | 3 (0.3%) | 0 (0.0%) | 20 (0.5%) |
| Employment status, n (%) | | | | | | |
| Active full time/part time | 302 (81.0%) | 118 (36.3%) | 776 (32.7%) | 19 (1.6%) | 11 (28.2%) | 1226 (28.5%) |
| Retiree | 52 (13.9%) | 67 (20.6%) | 1195 (50.3%) | 1133 (95.6%) | 18 (46.2%) | 2465 (57.4%) |
| Long-term disability | 0 (0.0%) | 5 (1.5%) | 11 (0.5%) | 7 (0.6%) | 0 (0.0%) | 23 (0.5%) |
| Other/unknown | 19 (5.1%) | 135 (41.5%) | 394 (16.6%) | 26 (2.2%) | 10 (25.6%) | 584 (13.6%) |

CDHP, consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; NCI, National Cancer Institute; POS, point of service; PPO, preferred provider organization.

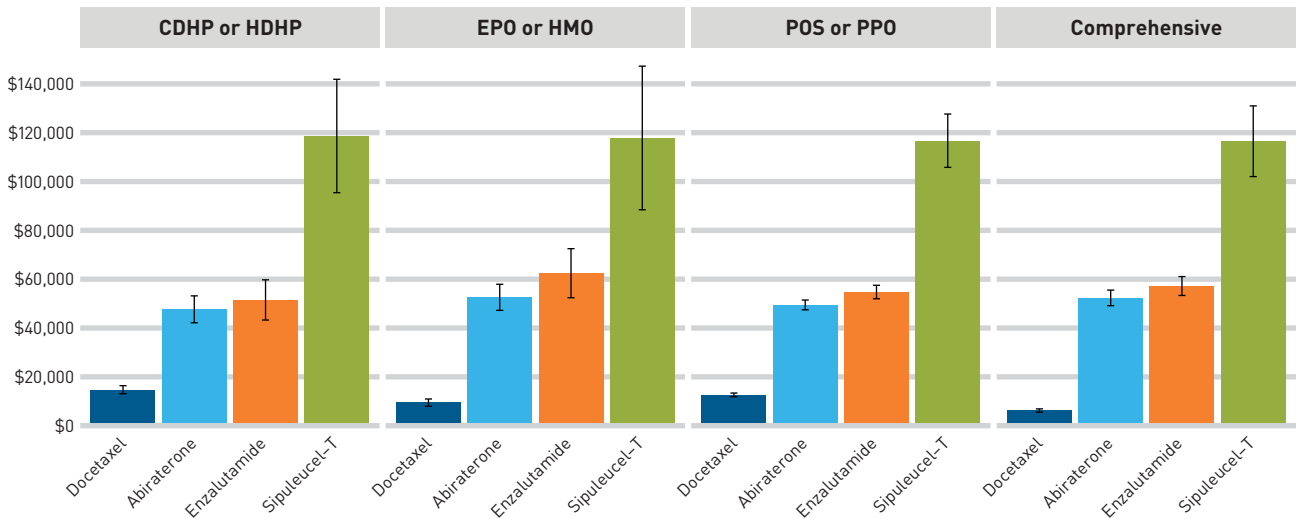
*In some cases, percentages do not add up to 100% due to rounding.

payments), and drug utilization. We report 3 key findings. First, gross payments varied dramatically across drugs but not much across plan types. Second, patients paid different amounts OOP for drugs depending upon both their treatment choice and the type of plan in which they were enrolled. Third, treatment receipt varied by insurance type in unadjusted but not adjusted analyses.

Consistent with prior work, we found that prices for drugs intended for patients with mCRPC were high, as measured by gross payments on the part of insurers.¹¹⁻¹⁴ We expanded upon this prior work by also demonstrating few differences in gross payments by insurance plan type among patients with employer-sponsored

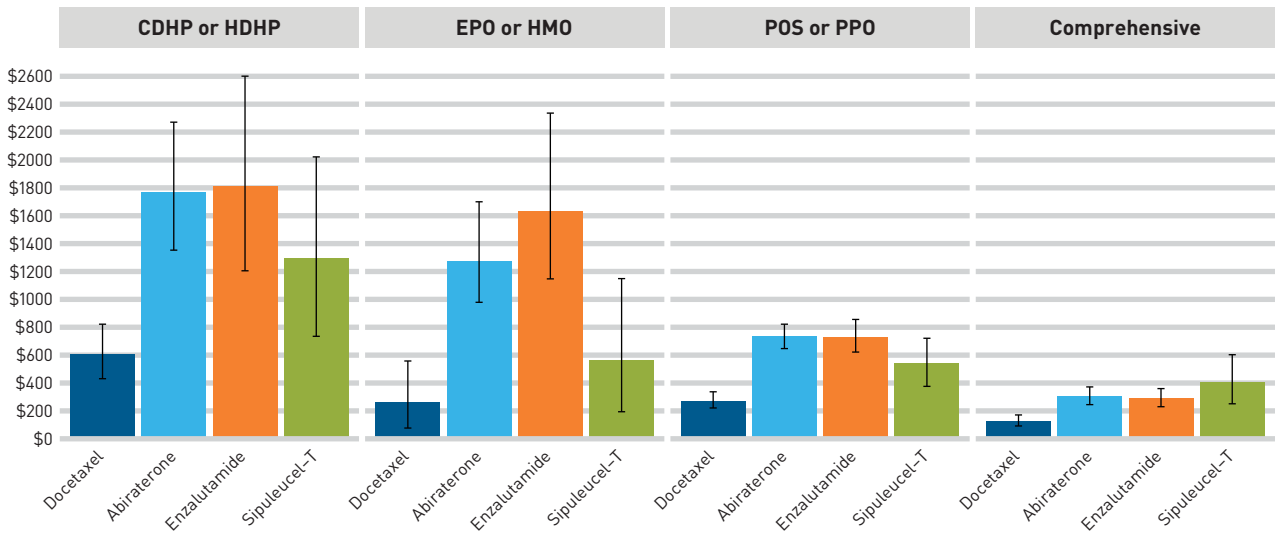
insurance. We note that it is plausible that net payments made by insurance companies on behalf of their beneficiaries vary across plan types as complex pricing arrangements frequently obscure the full set of financial transactions made among insurers, beneficiaries, PBMs, pharmaceutical manufacturers, and pharmacies.⁸ For example, spread pricing, whereby PBMs charge insurance companies (payers) more than what they pay the pharmacy for a particular drug,¹⁵ could vary by plan type in ways our analysis could not detect. Our results, however, suggest that different types of insurance plans pay similarly for the same drugs before accounting for drug rebates made to insurance companies.

FIGURE 1. Regression-Adjusted Gross Drug Payment by Drug and Plan Type



CDHP, consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

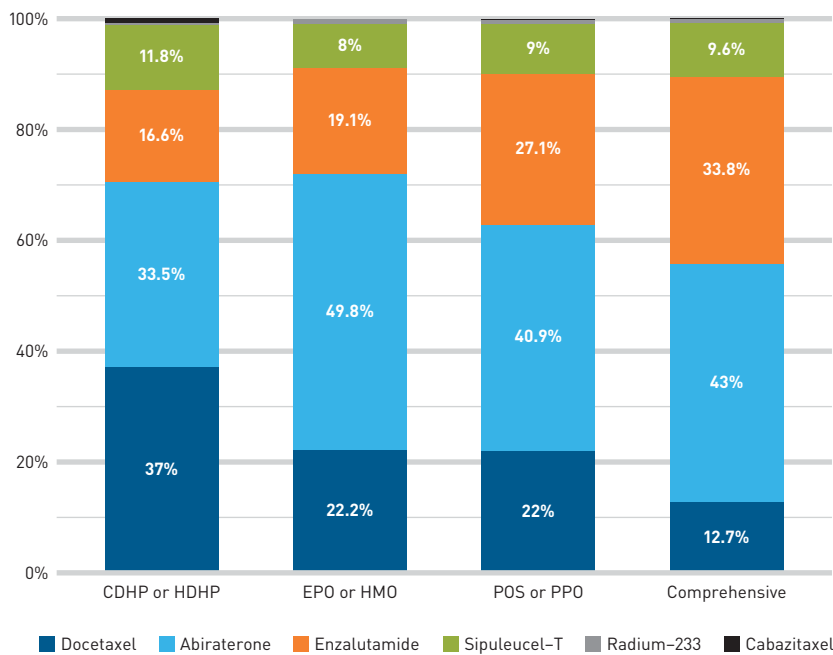
FIGURE 2. Regression-Adjusted Out-of-Pocket Drug Payment by Drug and Plan Type



CDHP, consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

In contrast to the similarity in gross drug payments across types of insurance plans, there were significant differences in what patients paid OOP, even for the same drug, depending upon their health plan type. This was not surprising, as health plans have different mechanisms to influence health care utilization and to steer patients toward lower-cost drugs,¹⁶ but our findings are novel in that we characterize the OOP payments and compare them with

gross payments across multiple drugs for advanced prostate cancer. Although cost sharing—having different OOP payments based on the type and cost of the drug—is a well-established mechanism for insurance companies to realize these goals, the results of our analyses were not completely consistent with insurers relying primarily on cost sharing (ie, the patient OOP amounts) to steer patients toward lower-priced treatments. For example, although

FIGURE 3. Treatment Choice by Plan Type

CDHP, consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

OOP payments were lowest for docetaxel, the first-line treatment with the lowest insurer gross payment, in all types of plans, OOP payments for sipuleucel-T, the first-line treatment with the highest insurer gross payments, were not higher than those for either abiraterone or enzalutamide for each type of plan.

Our evaluation further demonstrates that specific plan types were associated with consistent differences in OOP payments. Individuals enrolled in a CDHP or HDHP paid the most OOP for drugs, no matter which drug they received. In contrast, patients with comprehensive insurance plans tended to have the lowest OOP payments. Individuals with EPO or HMO insurance had the largest cost-sharing differentials across drug types; this finding suggests that EPO and/or HMO health plans were using OOP drug payments to create stronger financial incentives to encourage enrollees to use a lower-cost drug than other health plan types. Our results suggest that EPO and/or HMO plans may be more likely than POS/PPO or comprehensive plans to structure their benefit design, in the form of patient cost sharing, to steer patients to lower-priced drugs. However, despite the large difference in insurer gross payments for sipuleucel-T, we found that patients on average do not pay more OOP when they use this drug. Most types of plans may have other mechanisms, such as prior authorization, to control use of the most expensive therapies.

Given different OOP payments across drugs, yet similar clinical indications and survival outcomes, we would expect differences

in drug utilization by insurance type. Based on our analyses, however, it was not clear whether insurance plan type contributed to differences in utilization. Although insurance plan type was associated with type of first-line therapy received in unadjusted analyses, these differences were largely explained by differences in patient characteristics. In our sample, individuals in comprehensive health plans tended to be older, have more comorbidities, and be more likely to be retired than patients in HDHPs. Our analyses indicate that there were not important differences in treatment type receipt after controlling for patient characteristics, but they were not designed to test why that may be the case. Although it is possible that ultimately patient and provider treatment decisions are not responsive to the financial incentives created by cost sharing in this setting, it is also possible that people select insurance plans in ways that are correlated with treatment decisions.

Limitations

Our evaluation has several limitations. First, we may have overestimated how much insurers are actually paying for the drugs because we were

not able to account for drug rebates made to insurance companies by drug manufacturers.⁸ Similarly, we may have overestimated OOP payments because we were not able to account for patients who used drug assistance programs.^{8,17} Second, although we attempted to capture data for patients with mCRPC, some patients may have been treated in the nonmetastatic or non-castration-resistant state. However, prior work has used similar criteria when evaluating patients with mCRPC.¹⁸ Third, we do not know if there were specific clinical characteristics for which one drug may have been prescribed over another drug. However, we accounted for relevant comorbidities when considering prescribing, and prior research demonstrates that treatment for advanced prostate cancer varies based on nonclinical factors such as clinician specialty, practice location, and patient race and income.¹⁸⁻²¹ Fourth, we did not observe the full set of cost sharing the patient faced but rather the OOP price they paid conditional on their benefit design. This made it difficult to estimate causal relationships in this setting. Fifth, we were unable to determine whether race or ethnicity was associated with OOP payments because our data source (MarketScan) did not include information on patients' race.

These limitations notwithstanding, our findings have important implications for patients, physicians, and policy makers. First, our results demonstrate that relatively few patients face cost sharing that exposes them to higher OOP payments for more expensive drugs, as measured by gross payments to the insurer. Although patients in

TABLE 2. Multinomial Logistic Regression for First-Line Treatment Receipt^{a,b}

| Effect | OR (95% CI) | | |
|--|----------------------------|---------------------------|---------------------------|
| | Abiraterone vs docetaxel | Enzalutamide vs docetaxel | Sipuleucel-T vs docetaxel |
| CDHP or HDHP vs comprehensive insurance | 0.89 [0.61-1.31] | 1.05 [0.68-1.62] | 1.29 [0.77-2.19] |
| EPO or HMO vs comprehensive insurance | 1.39 [0.94-2.05] | 1.00 [0.63-1.56] | 0.89 [0.5-1.58] |
| POS or PPO vs comprehensive insurance | 1.13 [0.86-1.48] | 1.17 [0.89-1.54] | 1.00 [0.70-1.42] |
| Aged 55-64 vs <55 years | 1.49 [1.10-2.02] | 1.23 [0.85-1.78] | 1.73 [1.06-2.84] |
| Aged 65-74 vs <55 years | 3.30 [2.26-4.81] | 2.88 [1.86-4.47] | 2.98 [1.67-5.33] |
| Aged 75-84 vs <55 years | 6.42 [4.22-9.77] | 7.02 [4.38-11.27] | 4.86 [2.61-9.06] |
| Aged ≥85 vs <55 years | 31.23 [15.33-63.65] | 34.8 [16.57-73.09] | 11.14 [4.49-27.65] |
| Northeast region vs South region | 1.34 [1.04-1.74] | 1.23 [0.93-1.62] | 1.27 [0.89-1.81] |
| North Central region vs South region | 0.97 [0.78-1.21] | 0.82 [0.64-1.04] | 0.89 [0.65-1.22] |
| West region vs South region | 1.12 [0.85-1.46] | 0.76 [0.56-1.03] | 1.12 [0.76-1.63] |
| Unknown vs rural | 1.34 [0.86-2.07] | 1.52 [0.96-2.42] | 2.20 [1.16-4.17] |
| Urban vs rural | 1.01 [0.79-1.30] | 0.96 [0.73-1.25] | 1.47 [1.00-2.14] |
| Long-term disability vs active full time/part time | 0.67 [0.23-1.90] | 1.32 [0.42-4.14] | 0.44 [0.05-3.67] |
| Other/unknown vs active full time/part time | 0.79 [0.60-1.05] | 1.24 [0.89-1.72] | 1.07 [0.71-1.61] |
| Retiree vs active full time/part time | 1.09 [0.84-1.43] | 1.89 [1.39-2.56] | 1.27 [0.87-1.85] |
| Index year 2014 vs 2013 | 0.44 [0.30-0.65] | 0.86 [0.55-1.36] | 0.71 [0.44-1.15] |
| Index year 2015 vs 2013 | 0.19 [0.13-0.28] | 0.96 [0.62-1.49] | 0.36 [0.22-0.60] |
| Index year 2016 vs 2013 | 0.14 [0.10-0.21] | 0.79 [0.51-1.23] | 0.24 [0.14-0.40] |
| Index year 2017 vs 2013 | 0.29 [0.20-0.44] | 0.91 [0.57-1.47] | 0.25 [0.14-0.45] |
| Index year 2018 vs 2013 | 0.53 [0.35-0.80] | 1.29 [0.79-2.12] | 0.44 [0.25-0.79] |
| Index year 2019 vs 2013 | 0.65 [0.39-1.07] | 1.67 [0.93-3.00] | 0.49 [0.24-1.01] |
| Arrhythmia: yes vs no | 1.02 [0.79-1.32] | 1.05 [0.80-1.38] | 1.01 [0.71-1.44] |
| Diabetes: yes vs no | 1.26 [1.00-1.57] | 1.52 [1.20-1.93] | 1.28 [0.94-1.74] |
| Liver disease: yes vs no | 0.85 [0.63-1.14] | 0.70 [0.50-0.98] | 0.62 [0.38-1.00] |
| Osteoporosis: yes vs no | 1.27 [0.78-2.05] | 1.59 [0.97-2.61] | 2.68 [1.55-4.62] |
| COPD: yes vs no | 0.69 [0.51-0.93] | 0.63 [0.46-0.86] | 0.84 [0.56-1.27] |
| CVDMI: yes vs no | 0.68 [0.48-0.97] | 0.78 [0.54-1.11] | 0.69 [0.43-1.12] |
| HTN: yes vs no | 0.77 [0.64-0.93] | 0.76 [0.62-0.94] | 1.02 [0.78-1.33] |
| CHF: yes vs no | 1.00 [0.64-1.56] | 1.41 [0.90-2.21] | 0.55 [0.28-1.08] |
| PVD: yes vs no | 1.16 [0.82-1.66] | 1.06 [0.73-1.53] | 0.94 [0.58-1.54] |
| Renal disease: yes vs no | 1.04 [0.73-1.50] | 1.06 [0.73-1.54] | 1.55 [0.99-2.43] |
| Rheumatic disease: yes vs no | 0.68 [0.32-1.41] | 0.65 [0.29-1.44] | 0.11 [0.01-0.89] |

CDHP, consumer-directed health plan; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVDMI, cerebrovascular disease or myocardial infarction; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; HTN, hypertension; POS, point of service; PPO, preferred provider organization; PVD, peripheral vascular disease.

^aBold text indicates significance at $P < .05$.

^bCabazitaxel and radium-223 were not included in the regression analysis because the algorithm could not converge to find the maximum likelihood estimates. The reference drug choice for calculating the ORs was docetaxel.

HMOs and CDHPs had the strongest incentives to choose therapies with lower gross payments, they represented only 16% of patients in our sample. Patients were much more likely to be enrolled in either PPOs or CDHPs, where differences in OOP payments for alternative treatments were lower. We note that patients using sipuleucel-T, the most expensive drug to insurers as measured by gross payments, faced the highest OOP payments only when they were enrolled in comprehensive health plans. This likely indicates an important role for other mechanisms, such as utilization review, to steer patients to lower-cost alternatives in other types of plans. Although research suggests that VBID, particularly in the form of lowering cost sharing for essential medications, can increase adherence, improve patients' outcomes, and lower medical expenditures,⁷ our results suggest that VBID's potential has not been realized in this particular context.

For patients, our results demonstrate that insurance type can drastically impact OOP payments and therefore influence patient financial burden. In addition, choosing a different treatment option may significantly reduce OOP spending. Therefore, adequate insurance coverage and thorough education about the differences between plan types and treatment options are critical for reducing OOP payments and potential financial toxicity from cancer care. For clinicians, decreasing cancer care spending will require an understanding of drug-specific gross payment information, but lowering patient financial burden requires an appreciation of an individual's insurance benefit design, which could be facilitated through the use of price transparency and real-time benefit design tools integrated within the electronic health record. Although it is currently challenging for clinicians to obtain plan-specific payment information for many drugs, in addition to the aforementioned price transparency and real-time benefit design tools, financial distress screening and/or proactive referral to financial counselors to discuss costs of care and help patients attain adequate insurance coverage could also reduce financial burden.

For policy makers, our results demonstrate that decreasing the costs of cancer care in the US will require lower drug prices and better mechanisms for patients to understand both

the financial and nonfinancial differences in their treatment options, such as with the use of price transparency, real-time benefit design tools, and care navigators. However, with regard to the Inflation Reduction Act of 2022, although negotiating prices for some drugs covered under Medicare Part B and Part D will be important to reduce federal health spending, our results suggest that changes in gross payments may not directly lead to reductions in OOP payments. Additional research is needed to determine the comparative effectiveness of the first-line medications, how VBID impacts health care access and patient quality of life with drugs that are not completely interchangeable, the extent to which insurance plan type impacts drug utilization, differing amounts of cost sharing by race, and the impact of payment differences on utilization for advanced prostate cancer treatments for individuals enrolled in traditional Medicare and/or comparison with Medicare Advantage.

CONCLUSIONS

The extent to which patients pay for more costly drugs for the treatment of advanced prostate cancer in the form of high OOP payments varies across health insurance plan types. However, the amount of cost sharing often does not reflect the amount that insurers pay for the drugs on a beneficiary's behalf. Although there are differences in OOP payments by drug type, treatment choice is not significantly different across insurance plans after controlling for patient characteristics. ■

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eAppendix Table 1. Patient characteristics by insurance type

| | CDHP, or HDHP (N=373) | EPO or HMO (N=325) | POS or PPO (N=2376) | Comprehensive (N=1185) | Unknown (N=39) | Total (N=4298) |
|-----------------------------------|-----------------------------|-----------------------|------------------------|---------------------------|-------------------|-------------------|
| Type of first-line therapy | | | | | | |
| Docetaxel | 138 (37.0%) | 72 (22.2%) | 523 (22.0%) | 151 (12.7%) | 14 (35.9%) | 898 (20.9%) |
| Cabazitaxel | 3 (0.8%) | 0 (0.0%) | 8 (0.3%) | 1 (0.1%) | 0 (0.0%) | 12 (0.3%) |
| Abiraterone | 125 (33.5%) | 162 (49.8%) | 972 (40.9%) | 510 (43.0%) | 18 (46.2%) | 1787 (41.6%) |
| Enzalutamide | 62 (16.6%) | 62 (19.1%) | 643 (27.1%) | 401 (33.8%) | 6 (15.4%) | 1174 (27.3%) |
| Sipuleucel-T | 44 (11.8%) | 26 (8.0%) | 213 (9.0%) | 114 (9.6%) | 1 (2.6%) | 398 (9.3%) |
| Radium-233 | 1 (0.3%) | 3 (0.9%) | 17 (0.7%) | 8 (0.7%) | 0 (0.0%) | 29 (0.7%) |
| Age | | | | | | |
| Mean (SD) | 59.3 (5.8) | 67.3 (10.3) | 68.1 (11.1) | 77.3 (8.3) | 68.2 (13.2) | 69.8 (11.2) |
| Median | 60.0 | 66.0 | 66.0 | 78.0 | 63.0 | 69.0 |
| Q1, Q3 | 56.0, 63.0 | 60.0, 75.0 | 60.0, 77.0 | 72.0, 83.0 | 58.0, 80.0 | 61.0, 79.0 |
| Range | (43.0-87.0) | (40.0-95.0) | (36.0-97.0) | (48.0-99.0) | (49.0-95.0) | (36.0-99.0) |
| Age | | | | | | |
| Less than 55 | 64 (17.2%) | 27 (8.3%) | 217 (9.1%) | 4 (0.3%) | 4 (10.3%) | 316 (7.4%) |
| 55 - 64 | 286 (76.7%) | 121 (37.2%) | 911 (38.3%) | 82 (6.9%) | 19 (48.7%) | 1419 (33.0%) |
| 65 - 74 | 15 (4.0%) | 89 (27.4%) | 529 (22.3%) | 339 (28.6%) | 3 (7.7%) | 975 (22.7%) |
| 75 - 84 | 6 (1.6%) | 69 (21.2%) | 509 (21.4%) | 512 (43.2%) | 7 (17.9%) | 1103 (25.7%) |
| 85 and older | 2 (0.5%) | 19 (5.8%) | 210 (8.8%) | 248 (20.9%) | 6 (15.4%) | 485 (11.3%) |
| Year of first-line therapy | | | | | | |
| 2013 | 20 (5.4%) | 33 (10.2%) | 250 (10.5%) | 166 (14.0%) | 5 (12.8%) | 474 (11.0%) |
| 2014 | 42 (11.3%) | 74 (22.8%) | 450 (18.9%) | 274 (23.1%) | 7 (17.9%) | 847 (19.7%) |
| 2015 | 54 (14.5%) | 36 (11.1%) | 430 (18.1%) | 269 (22.7%) | 7 (17.9%) | 796 (18.5%) |
| 2016 | 73 (19.6%) | 48 (14.8%) | 384 (16.2%) | 213 (18.0%) | 5 (12.8%) | 723 (16.8%) |
| 2017 | 69 (18.5%) | 42 (12.9%) | 371 (15.6%) | 157 (13.2%) | 7 (17.9%) | 646 (15.0%) |
| 2018 | 80 (21.4%) | 59 (18.2%) | 338 (14.2%) | 78 (6.6%) | 6 (15.4%) | 561 (13.1%) |
| 2019 | 35 (9.4%) | 33 (10.2%) | 153 (6.4%) | 28 (2.4%) | 2 (5.1%) | 251 (5.8%) |
| Urban vs. rural | | | | | | |
| Rural | 57 (15.3%) | 32 (9.8%) | 343 (14.4%) | 205 (17.3%) | 5 (12.8%) | 642 (14.9%) |
| Urban | 311 (83.4%) | 256 (78.8%) | 1725 (72.6%) | 891 (75.2%) | 32 (82.1%) | 3215 (74.8%) |

| | CDHP, or HDHP (N=373) | EPO or HMO (N=325) | POS or PPO (N=2376) | Comprehensive (N=1185) | Unknown (N=39) | Total (N=4298) |
|---|-----------------------------|-----------------------|------------------------|---------------------------|-------------------|-------------------|
| Unknown | 5 (1.3%) | 37 (11.4%) | 308 (13.0%) | 89 (7.5%) | 2 (5.1%) | 441 (10.3%) |
| Region | | | | | | |
| 1-Northeast Region | 57 (15.3%) | 43 (13.2%) | 648 (27.3%) | 173 (14.6%) | 10 (25.6%) | 931 (21.7%) |
| 2-North Central Region | 93 (24.9%) | 135 (41.5%) | 583 (24.5%) | 478 (40.3%) | 7 (17.9%) | 1296 (30.2%) |
| 3-South Region | 148 (39.7%) | 82 (25.2%) | 843 (35.5%) | 344 (29.0%) | 15 (38.5%) | 1432 (33.3%) |
| 4-West Region | 75 (20.1%) | 65 (20.0%) | 285 (12.0%) | 187 (15.8%) | 7 (17.9%) | 619 (14.4%) |
| 5-Unknown Region | 0 (0.0%) | 0 (0.0%) | 17 (0.7%) | 3 (0.3%) | 0 (0.0%) | 20 (0.5%) |
| Employment status | | | | | | |
| Active full time/part time | 302 (81.0%) | 118 (36.3%) | 776 (32.7%) | 19 (1.6%) | 11 (28.2%) | 1226 (28.5%) |
| Retiree | 52 (13.9%) | 67 (20.6%) | 1195 (50.3%) | 1133 (95.6%) | 18 (46.2%) | 2465 (57.4%) |
| Long-term disability | 0 (0.0%) | 5 (1.5%) | 11 (0.5%) | 7 (0.6%) | 0 (0.0%) | 23 (0.5%) |
| Other/unknown | 19 (5.1%) | 135 (41.5%) | 394 (16.6%) | 26 (2.2%) | 10 (25.6%) | 584 (13.6%) |
| Hypertension | 156 (41.8%) | 173 (53.2%) | 1273 (53.6%) | 706 (59.6%) | 19 (48.7%) | 2327 (54.1%) |
| Diabetes | 78 (20.9%) | 94 (28.9%) | 645 (27.1%) | 383 (32.3%) | 11 (28.2%) | 1211 (28.2%) |
| Arrhythmia | 45 (12.1%) | 53 (16.3%) | 421 (17.7%) | 293 (24.7%) | 9 (23.1%) | 821 (19.1%) |
| Congestive heart failure (CCS) | 5 (1.3%) | 19 (5.8%) | 105 (4.4%) | 87 (7.3%) | 5 (12.8%) | 221 (5.1%) |
| Osteoporosis | 11 (2.9%) | 13 (4.0%) | 111 (4.7%) | 84 (7.1%) | 1 (2.6%) | 220 (5.1%) |
| Seizures | 0 (0.0%) | 2 (0.6%) | 9 (0.4%) | 13 (1.1%) | 0 (0.0%) | 24 (0.6%) |
| Metastatic cancer | 326 (87.4%) | 268 (82.5%) | 1975 (83.1%) | 945 (79.7%) | 36 (92.3%) | 3550 (82.6%) |
| Acute Myocardial Infarction | 2 (0.5%) | 2 (0.6%) | 15 (0.6%) | 12 (1.0%) | 0 (0.0%) | 31 (0.7%) |
| History of Myocardial Infarction | 2 (0.5%) | 2 (0.6%) | 27 (1.1%) | 32 (2.7%) | 0 (0.0%) | 63 (1.5%) |
| Cerebrovascular disease or acute MI or history of MI | 8 (2.1%) | 19 (5.8%) | 189 (8.0%) | 134 (11.3%) | 5 (12.8%) | 355 (8.3%) |
| Congestive Heart Failure (NCI) | 7 (1.9%) | 21 (6.5%) | 134 (5.6%) | 120 (10.1%) | 6 (15.4%) | 288 (6.7%) |
| Peripheral Vascular Disease | 11 (2.9%) | 25 (7.7%) | 199 (8.4%) | 158 (13.3%) | 5 (12.8%) | 398 (9.3%) |
| Cerebrovascular Disease | 5 (1.3%) | 15 (4.6%) | 152 (6.4%) | 98 (8.3%) | 5 (12.8%) | 275 (6.4%) |
| Chronic Obstructive Pulmonary Disease | 19 (5.1%) | 32 (9.8%) | 225 (9.5%) | 172 (14.5%) | 4 (10.3%) | 452 (10.5%) |
| Dementia | 0 (0.0%) | 0 (0.0%) | 20 (0.8%) | 13 (1.1%) | 0 (0.0%) | 33 (0.8%) |
| Hemiplegia or Paraplegia | 4 (1.1%) | 3 (0.9%) | 12 (0.5%) | 9 (0.8%) | 0 (0.0%) | 28 (0.7%) |
| Diabetes | 58 (15.5%) | 71 (21.8%) | 543 (22.9%) | 340 (28.7%) | 10 (25.6%) | 1022 (23.8%) |

| | CDHP, or HDHP (N=373) | EPO or HMO (N=325) | POS or PPO (N=2376) | Comprehensive (N=1185) | Unknown (N=39) | Total (N=4298) |
|--------------------------------------|-----------------------------|-----------------------|------------------------|---------------------------|-------------------|-------------------|
| Moderate-Severe Renal Disease | 14 (3.8%) | 33 (10.2%) | 192 (8.1%) | 167 (14.1%) | 3 (7.7%) | 409 (9.5%) |
| Liver disease | 37 (9.9%) | 31 (9.5%) | 195 (8.2%) | 69 (5.8%) | 4 (10.3%) | 336 (7.8%) |
| Peptic Ulcer Disease | 3 (0.8%) | 3 (0.9%) | 11 (0.5%) | 8 (0.7%) | 0 (0.0%) | 25 (0.6%) |
| Rheumatologic Disease | 1 (0.3%) | 7 (2.2%) | 34 (1.4%) | 15 (1.3%) | 0 (0.0%) | 57 (1.3%) |
| AIDS | 2 (0.5%) | 0 (0.0%) | 6 (0.3%) | 0 (0.0%) | 0 (0.0%) | 8 (0.2%) |
| NCI comorbidity index | | | | | | |
| Mean (SD) | 0.7 (1.1) | 1.2 (1.5) | 1.1 (1.5) | 1.6 (1.7) | 1.5 (2.0) | 1.2 (1.6) |
| Median | 0.0 | 0.0 | 0.0 | 1.3 | 1.3 | 0.0 |
| Q1, Q3 | 0.0, 1.3 | 0.0, 1.9 | 0.0, 1.7 | 0.0, 2.6 | 0.0, 2.1 | 0.0, 1.9 |
| Range | (0.0-6.0) | (0.0-7.8) | (0.0-9.2) | (0.0-9.2) | (0.0-7.8) | (0.0-9.2) |

eAppendix Table 2. Gamma regression to assess the association of 6-month gross drug payment with first-line therapy receipt, insurance type, and the interaction of insurance type with first-line therapy

| Covariates | Cost Ratio (95% CI) | P-value |
|---|----------------------------|----------------|
| Age 55 - 64 vs. Less than 55 | 0.94 (0.86,1.02) | 0.11 |
| Age 65 - 74 vs. Less than 55 | 0.88 (0.8,0.97) | 0.008 |
| Age 75 - 84 vs. Less than 55 | 0.85 (0.77,0.93) | <.001 |
| Age 85 and older vs. Less than 55 | 0.8 (0.71,0.89) | <.001 |
| Year 2014 vs. 2013 | 1.08 (1,1.16) | 0.05 |
| Year 2015 vs. 2013 | 1.1 (1.02,1.19) | 0.01 |
| Year 2016 vs. 2013 | 1.18 (1.09,1.28) | <.001 |
| Year 2017 vs. 2013 | 1.2 (1.1,1.3) | <.001 |
| Year 2018 vs. 2013 | 1.2 (1.1,1.31) | <.001 |
| Year 2019 vs. 2013 | 1 (0.9,1.11) | >0.99 |
| Urban vs. rural | 0.95 (0.9,1) | 0.06 |
| North Central Region vs. Northeast Region | 0.99 (0.93,1.04) | 0.64 |
| South Region vs. Northeast Region | 1.03 (0.98,1.09) | 0.24 |
| West Region vs. Northeast Region | 0.96 (0.9,1.03) | 0.23 |
| Long-term disability vs. Active full time/part time | 1 (0.77,1.31) | 0.98 |
| Other/unknown vs. Active full time/part time | 0.94 (0.87,1) | 0.06 |
| Retiree vs. Active full time/part time | 0.94 (0.88,1) | 0.07 |
| Hypertension | 1.02 (0.98,1.06) | 0.42 |
| Diabetes | 1 (0.95,1.05) | 0.96 |
| Arrhythmia | 1 (0.95,1.05) | 0.92 |
| Osteoporosis | 1.05 (0.96,1.15) | 0.28 |
| Cerebrovascular Disease or Myocardial Infarction | 0.94 (0.87,1.01) | 0.09 |
| Congestive Heart Failure | 0.99 (0.91,1.08) | 0.83 |
| Peripheral Vascular Disease | 1.03 (0.96,1.1) | 0.49 |
| Chronic Obstructive Pulmonary Disease | 1.02 (0.96,1.09) | 0.56 |
| Moderate-Severe Renal Disease | 0.96 (0.9,1.03) | 0.30 |
| Liver Disease | 0.98 (0.92,1.06) | 0.67 |
| Rheumatologic Disease | 1.02 (0.86,1.21) | 0.82 |
| Comprehensive vs. CDHP or HDHP for Docetaxel | 0.42 (0.36,0.49) | <.001 |
| EPO or HMO vs. CDHP or HDHP for Docetaxel | 0.64 (0.53,0.77) | <.001 |
| POS or PPO vs. CDHP or HDHP for Docetaxel | 0.86 (0.76,0.97) | 0.01 |
| Comprehensive vs. CDHP or HDHP for Abiraterone | 1.1 (0.96,1.26) | 0.17 |
| EPO or HMO vs. CDHP or HDHP for Abiraterone | 1.1 (0.95,1.29) | 0.21 |
| POS or PPO vs. CDHP or HDHP for Abiraterone | 1.04 (0.92,1.17) | 0.55 |
| Comprehensive vs. CDHP or HDHP for Enzalutamide | 1.11 (0.93,1.33) | 0.24 |
| EPO or HMO vs. CDHP or HDHP for Enzalutamide | 1.21 (0.97,1.52) | 0.10 |
| POS or PPO vs. CDHP or HDHP for Enzalutamide | 1.06 (0.9,1.26) | 0.48 |
| Comprehensive vs. CDHP or HDHP for Sipuleucel-T | 0.98 (0.78,1.24) | 0.88 |
| EPO or HMO vs. CDHP or HDHP for Sipuleucel-T | 0.99 (0.72,1.36) | 0.97 |
| POS or PPO vs. CDHP or HDHP for Sipuleucel-T | 0.98 (0.79,1.22) | 0.88 |

| Covariates | Cost Ratio (95% CI) | P-value |
|--|----------------------------|----------------|
| Abiraterone vs. Docetaxel for Comprehensive | 8.43 (7.46,9.53) | <.001 |
| Enzalutamide vs. Docetaxel for Comprehensive | 9.22 (8.13,10.45) | <.001 |
| Sipuleucel-T vs. Docetaxel for Comprehensive | 18.77 (15.95,22.09) | <.001 |
| Abiraterone vs. Docetaxel for EPO or HMO | 5.56 (4.61,6.7) | <.001 |
| Enzalutamide vs. Docetaxel for EPO or HMO | 6.6 (5.28,8.26) | <.001 |
| Sipuleucel-T vs. Docetaxel for EPO or HMO | 12.46 (9.29,16.71) | <.001 |
| Abiraterone vs. Docetaxel for POS or PPO | 3.92 (3.64,4.21) | <.001 |
| Enzalutamide vs. Docetaxel for POS or PPO | 4.34 (4,4.7) | <.001 |
| Sipuleucel-T vs. Docetaxel for POS or PPO | 9.25 (8.28,10.32) | <.001 |
| Abiraterone vs. Docetaxel for CDHP or HDHP | 3.23 (2.77,3.78) | <.001 |
| Enzalutamide vs. Docetaxel for CDHP or HDHP | 3.49 (2.89,4.23) | <.001 |
| Sipuleucel-T vs. Docetaxel for CDHP or HDHP | 8.05 (6.45,10.05) | <.001 |

eAppendix Table 3 (A). Unadjusted and regression-adjusted mean costs of the 6-month first-line treatment gross payment by first-line treatment and insurance type

| Insurance type | Type of first-line therapy | Unadjusted mean cost (SD) | Unadjusted median cost (25th and 75th percentiles) | Regression-adjusted mean cost (95% CI) |
|-----------------------|-----------------------------------|----------------------------------|---|---|
| CDHP, or HDHP | Sipuleucel-T | 129425.3 (23547.6) | 127848.8 (114914.5, 141122.3) | 118640.4 (95420.3, 141860.5) |
| | Enzalutamide | 56203.2 (18616.6) | 59236.6 (46828.7, 71093.2) | 51503.5 (43268.3, 59738.8) |
| | Abiraterone | 51977.7 (19653.0) | 57766.2 (40847.7, 66989.3) | 47652.9 (42140.9, 53164.9) |
| | Docetaxel | 16792.6 (22635.5) | 7260.5 (3483.9, 19672.6) | 14739.9 (13088.2, 16391.7) |
| Comprehensive | Sipuleucel-T | 110080.6 (32307.0) | 113392.1 (106405, 123370.7) | 116490.6 (102015.2, 130965.9) |
| | Enzalutamide | 53500.0 (19556.7) | 58369 (41889.8, 67415.9) | 57201.9 (53329.6, 61074.2) |
| | Abiraterone | 47741.8 (17069.9) | 52047.3 (37459.3, 59502.7) | 52331.6 (49140.6, 55522.6) |
| | Docetaxel | 6073.0 (8549.1) | 3647.5 (2123.5, 5966) | 6206.8 (5527.1, 6886.4) |
| EPO or HMO | Sipuleucel-T | 113808.2 (41255.8) | 113297.5 (107692, 129998.7) | 117838.2 (88420.8, 147255.6) |
| | Enzalutamide | 61701.0 (26350.2) | 65169.6 (52751.7, 71112.9) | 62442.9 (52394.1, 72491.6) |
| | Abiraterone | 51663.0 (24092.9) | 52996.7 (37793.2, 62464.7) | 52573.2 (47230.7, 57915.8) |
| | Docetaxel | 10319.2 (14629.2) | 3829.2 (2563.2, 12280.9) | 9457.5 (7975, 10939.9) |
| POS or PPO | Sipuleucel-T | 115690.6 (31877.7) | 116682.5 (108470.6, 129862.2) | 116715.1 (105792, 127638.1) |
| | Enzalutamide | 54565.8 (23016.5) | 60203.6 (39846.1, 68947.2) | 54737.2 (51975.1, 57499.3) |
| | Abiraterone | 49559.5 (18616.0) | 52567.1 (38345.4, 62577.4) | 49453.8 (47445.6, 51462) |
| | Docetaxel | 13530.8 (17487.8) | 6878.5 (3256.3, 17721.9) | 12622.5 (11874.6, 13370.5) |

eAppendix Table 3 (B). Unadjusted and regression-adjusted mean costs of the 6-month first-line treatment out-of-pocket payment by first-line treatment and insurance type

| Insurance | First-line treatment | Unadjusted mean cost (SD) | Unadjusted median cost (25th and 75th percentiles) | Regression-adjusted mean cost (95% CI) |
|------------------|-----------------------------|----------------------------------|---|---|
| CDHP, or HDHP | Sipuleucel-T | 1231.8 (1680.3) | 504.4 (0, 1792) | 1293.5 (735.2, 2022.2) |
| | Enzalutamide | 1390.7 (1699.3) | 707 (227.3, 1813.6) | 1809.1 (1204.8, 2601.2) |
| | Abiraterone | 1727.0 (2019.7) | 834.4 (75.6, 3124.1) | 1769.9 (1352.6, 2271.3) |
| | Docetaxel | 538.3 (884.6) | 129.3 (0, 707.8) | 606.4 (431, 821.7) |
| Comprehensive | Sipuleucel-T | 392.5 (965.9) | 159.1 (0, 384.7) | 403.1 (251.3, 602.5) |
| | Enzalutamide | 298.8 (715.2) | 90.7 (43.1, 201) | 292.3 (230.3, 359.5) |
| | Abiraterone | 333.4 (772.7) | 113.4 (53.9, 226.8) | 306.5 (245.2, 371.9) |
| | Docetaxel | 110.1 (193.5) | 38.2 (0, 138.1) | 125.7 (92.3, 171.2) |
| EPO or HMO | Sipuleucel-T | 1084.4 (1918.8) | 18.9 (0, 2277.2) | 562.5 (194.4, 1148.5) |
| | Enzalutamide | 2211.2 (2738.7) | 674.5 (189, 4252) | 1632.7 (1146.6, 2335.5) |
| | Abiraterone | 1804.0 (2487.4) | 399 (142.5, 3294.4) | 1276.2 (978.7, 1699.9) |
| | Docetaxel | 286.5 (1118.2) | 0 (0, 190) | 265.2 (77.2, 558.2) |
| POS or PPO | Sipuleucel-T | 505.4 (1139.2) | 0 (0, 161.8) | 538.3 (375.8, 721) |
| | Enzalutamide | 628.6 (1293.6) | 131 (0, 491.6) | 727.4 (622.1, 855.5) |
| | Abiraterone | 730.3 (1394.6) | 209.4 (27, 647.4) | 734 (646.6, 821.8) |
| | Docetaxel | 239.0 (543.1) | 0 (0, 248.7) | 271.9 (221.3, 336.5) |

eAppendix Table 4. Multivariable two-part model to compare 6-month out-of-pocket drug payment and first-line treatment, insurance type and the interaction between first-line treatment receipt and insurance types.

| Covariates | Odds Ratio (OR) (95% CI) | P-value | Cost Ratio (CR) (95% CI) | P-value |
|---|-------------------------------------|----------------|-------------------------------------|----------------|
| Age 55 - 64 vs. Less than 55 | 1.2 (0.89,1.62) | 0.24 | 1.05 (0.87,1.27) | 0.62 |
| Age 65 - 74 vs. Less than 55 | 0.98 (0.68,1.4) | 0.89 | 1.19 (0.94,1.5) | 0.15 |
| Age 75 - 84 vs. Less than 55 | 1.21 (0.82,1.78) | 0.33 | 1.4 (1.1,1.79) | 0.006 |
| Age 85 and older vs. Less than 55 | 0.74 (0.48,1.15) | 0.18 | 1.64 (1.26,2.15) | <.001 |
| Year 2014 vs. 2013 | 1.13 (0.81,1.59) | 0.47 | 0.94 (0.8,1.09) | 0.40 |
| Year 2015 vs. 2013 | 0.69 (0.49,0.96) | 0.03 | 0.86 (0.72,1.01) | 0.07 |
| Year 2016 vs. 2013 | 0.54 (0.38,0.75) | <.001 | 0.62 (0.52,0.74) | <.001 |
| Year 2017 vs. 2013 | 0.49 (0.34,0.7) | <.001 | 0.96 (0.8,1.16) | 0.68 |
| Year 2018 vs. 2013 | 0.46 (0.32,0.67) | <.001 | 1.29 (1.07,1.56) | 0.007 |
| Year 2019 vs. 2013 | 0.6 (0.38,0.93) | 0.02 | 0.85 (0.67,1.07) | 0.17 |
| Urban vs. rural | 1 (0.79,1.27) | >0.99 | 1 (0.88,1.13) | 0.95 |
| North Central Region vs. Northeast Region | 8.67 (6.77,11.09) | <.001 | 0.86 (0.75,0.99) | 0.03 |
| South Region vs. Northeast Region | 3.07 (2.48,3.8) | <.001 | 0.84 (0.73,0.97) | 0.02 |
| West Region vs. Northeast Region | 4.19 (3.18,5.52) | <.001 | 0.96 (0.82,1.13) | 0.66 |
| Long-term disability vs. Active full time/part time | 0.63 (0.21,1.86) | 0.40 | 0.45 (0.24,0.82) | 0.009 |
| Other/unknown vs. Active full time/part time | 1.1 (0.83,1.44) | 0.52 | 1.45 (1.22,1.73) | <.001 |
| Retiree vs. Active full time/part time | 0.85 (0.67,1.1) | 0.22 | 0.91 (0.77,1.06) | 0.23 |
| Hypertension | 1.07 (0.9,1.27) | 0.47 | 1 (0.91,1.1) | 0.95 |
| Diabetes | 0.87 (0.71,1.06) | 0.15 | 0.98 (0.88,1.09) | 0.68 |
| Arrhythmia | 0.78 (0.63,0.98) | 0.03 | 1.02 (0.9,1.16) | 0.71 |
| Osteoporosis | 1.05 (0.71,1.56) | 0.81 | 0.85 (0.7,1.04) | 0.12 |
| Cerebrovascular Disease or Myocardial Infarction | 1.38 (1.01,1.88) | 0.05 | 0.91 (0.77,1.07) | 0.24 |
| Congestive Heart Failure | 0.9 (0.63,1.28) | 0.55 | 1.11 (0.92,1.35) | 0.28 |
| Peripheral Vascular Disease | 0.82 (0.62,1.1) | 0.19 | 0.88 (0.75,1.04) | 0.13 |
| Chronic Obstructive Pulmonary Disease | 1.08 (0.82,1.41) | 0.60 | 0.85 (0.74,0.99) | 0.03 |
| Moderate-Severe Renal Disease | 1 (0.75,1.35) | 0.97 | 0.86 (0.74,1.01) | 0.06 |
| Liver Disease | 1 (0.75,1.34) | 0.99 | 1.04 (0.87,1.23) | 0.66 |
| Rheumatologic Disease | 1.29 (0.63,2.64) | 0.49 | 1.19 (0.82,1.73) | 0.36 |
| Comprehensive vs. CDHP or HDHP for Docetaxel | 1.13 (0.65,1.95) | 0.67 | 0.2 (0.14,0.29) | <.001 |
| EPO or HMO vs. CDHP or HDHP for Docetaxel | 0.42 (0.23,0.79) | 0.007 | 0.65 (0.39,1.08) | 0.10 |

| Covariates | Odds Ratio (OR) (95% CI) | P-value | Cost Ratio (CR) (95% CI) | P-value |
|---|-------------------------------------|----------------|-------------------------------------|----------------|
| POS or PPO vs. CDHP or HDHP for Docetaxel | 0.53 (0.35,0.81) | 0.003 | 0.59 (0.43,0.8) | <.001 |
| Comprehensive vs. CDHP or HDHP for Abiraterone | 2.23 (1.18,4.22) | 0.01 | 0.16 (0.12,0.21) | <.001 |
| EPO or HMO vs. CDHP or HDHP for Abiraterone | 3.01 (1.23,7.38) | 0.02 | 0.63 (0.45,0.89) | 0.008 |
| POS or PPO vs. CDHP or HDHP for Abiraterone | 0.79 (0.46,1.36) | 0.39 | 0.43 (0.33,0.56) | <.001 |
| Comprehensive vs. CDHP or HDHP for Enzalutamide | 1.72 (0.64,4.63) | 0.28 | 0.15 (0.11,0.22) | <.001 |
| EPO or HMO vs. CDHP or HDHP for Enzalutamide | 1.24 (0.31,4.86) | 0.76 | 0.88 (0.55,1.41) | 0.60 |
| POS or PPO vs. CDHP or HDHP for Enzalutamide | 0.3 (0.12,0.75) | 0.010 | 0.49 (0.35,0.7) | <.001 |
| Comprehensive vs. CDHP or HDHP for Sipuleucel-T | 1.39 (0.64,3.04) | 0.41 | 0.27 (0.16,0.48) | <.001 |
| EPO or HMO vs. CDHP or HDHP for Sipuleucel-T | 0.83 (0.28,2.4) | 0.73 | 0.47 (0.21,1.08) | 0.07 |
| POS or PPO vs. CDHP or HDHP for Sipuleucel-T | 0.35 (0.17,0.71) | 0.004 | 0.72 (0.41,1.24) | 0.23 |
| Abiraterone vs. Docetaxel for Comprehensive | 9.16 (5.56,15.09) | <.001 | 1.53 (1.17,2.02) | 0.002 |
| Enzalutamide vs. Docetaxel for Comprehensive | 13.12 (7.51,22.91) | <.001 | 1.42 (1.07,1.88) | 0.01 |
| Sipuleucel-T vs. Docetaxel for Comprehensive | 1.01 (0.58,1.76) | 0.97 | 3.2 (2.2,4.65) | <.001 |
| Abiraterone vs. Docetaxel for EPO or HMO | 32.88 (13.51,80.01) | <.001 | 1.91 (1.16,3.12) | 0.01 |
| Enzalutamide vs. Docetaxel for EPO or HMO | 25.06 (7.88,79.74) | <.001 | 2.5 (1.44,4.34) | 0.001 |
| Sipuleucel-T vs. Docetaxel for EPO or HMO | 1.6 (0.6,4.28) | 0.35 | 1.68 (0.75,3.76) | 0.20 |
| Abiraterone vs. Docetaxel for POS or PPO | 6.8 (5.18,8.92) | <.001 | 1.43 (1.18,1.74) | <.001 |
| Enzalutamide vs. Docetaxel for POS or PPO | 4.84 (3.61,6.48) | <.001 | 1.53 (1.24,1.88) | <.001 |
| Sipuleucel-T vs. Docetaxel for POS or PPO | 0.53 (0.36,0.77) | <.001 | 2.81 (2.01,3.92) | <.001 |
| Abiraterone vs. Docetaxel for CDHP or HDHP | 4.63 (2.47,8.65) | <.001 | 1.95 (1.36,2.78) | <.001 |
| Enzalutamide vs. Docetaxel for CDHP or HDHP | 8.59 (3.32,22.24) | <.001 | 1.83 (1.21,2.77) | 0.004 |
| Sipuleucel-T vs. Docetaxel for CDHP or HDHP | 0.82 (0.39,1.7) | 0.60 | 2.31 (1.35,3.93) | 0.002 |

eAppendix Figure. Study Cohort Flow Diagram

