Health Economics

WILEY

Health Economics

RESEARCH ARTICLE OPEN ACCESS

Behavioral Responses to Healthcare Funding Decisions and Their Impact on Value for Money: Evidence From Australia

Peter Ghijben[1] | Dennis Petrie[1] | Silva Zavarsek[2] | Gang Chen[1] | Emily Lancsar[3]

[1]Centre for Health Economics, Monash Business School, Monash University, Caulfield, Australia | [2]Deakin Health Economics, School of Health and Social Development, Institute for Health Transformation, Deakin University, Burwood, Australia | [3]Department of Health Economics Wellbeing and Society, College of Health & Medicine, The Australian National University, Acton, Australia

Correspondence: Peter Ghijben (peter.ghijben@monash.edu)

Received: 29 October 2023 | **Revised:** 23 February 2025 | **Accepted:** 27 February 2025

Funding: The authors received no specific funding for this work.

Keywords: allocative efficiency | information | public health insurance | uncertainty

ABSTRACT

Value for money is fundamental to health insurance schemes given insurers must choose which treatments to fund. Assessing value for money *ex ante* is challenging, however, because costs and outcomes depend on how treatments are used. Estimates often rely on evidence from early randomized controlled trials conducted prior to regulatory approval, where provider and patient behaviors are tightly controlled. This approach ignores how different supply conditions and incentives in practice influence behaviors. This paper considers how provider and patient incentives can differ between trial and practice settings and analyses how healthcare use changed when new prostate cancer treatments were funded on the public health insurance scheme in Australia. We find evidence that doctors treated patients with worse prognosis compared to the trials, patients ceased prior treatment and switched to the new treatments earlier than expected, and treatment duration was longer than expected. These and other behavioral responses reduced value for money *ex post*. Our findings suggest that health insurers should carefully consider the supply conditions and incentives in practice when funding new treatments.

JEL Classification: I130, D610, D800, D820

1 | Introduction

Value for money is fundamental to investment decisions in health insurance schemes (Briggs 2016; Drummond et al. 2015). Public and private insurers need to consider the likely costs and outcomes of supplying new treatments and make funding decisions. "Early" randomized controlled trials (RCTs), conducted prior to regulatory approval, often inform these decisions but have limitations. The comparative evidence may not align with the way new treatments will substitute for existing therapies in practice due to evolving treatment patterns or local-specific treatment guidelines. Even when comparators do align, the way new treatments are used in practice may differ. While behaviors are heavily controlled in early RCTs (Ford and Norrie 2016; Schwartz and Lellouch 1967), patients and providers ultimately decide how new treatments are used in practice after insurers set the supply conditions (Maynard and Kanavos 2000). These differences could have important implications for both costs and outcomes and, thus, there is a critical need to better understand how behaviors in practice impact the value for money of new treatments.

Early RCTs are primarily designed to prove the efficacy and safety of new treatments for regulatory purposes while minimizing costs (Kennedy-Martin et al. 2015; Silverman 2009). This often means; weak comparators, such as placebos, are chosen; only those patients most likely to benefit and least likely to suffer adverse events are included; and strict trial protocols are enforced that encourage adherence, careful management of adverse events and limit differences across groups in terms of other healthcare use. While some of these design features help ensure that differences in outcomes could only be caused by the new treatment itself (high internal validity with a clear causal pathway), they also heavily restrict patient and provider behaviors and limit the potential for moral hazard. Thus, the same outcomes may not be achieved when treating a broader range of patients under real-world conditions in practice (low external validity).

Insurers are acutely aware of this issue but face pressure to make supply decisions for new efficacious treatments with limited evidence on their value for money under local real-world conditions. Current guidelines for assessing value for money emphasize the need to adjust or calibrate early RCT evidence to local market conditions using the best available real-world data (Australian Government 2016; Canadian Agency for Drugs and Technologies in Health 2017; Drummond et al. 2015; Gold 1996; National Institute for Health and Care Excellence 2022). Real-world data is mostly utilized descriptively by insurers and use varies considerably depending in part on data availability (Makady et al. 2018). Attempts to use real-world evidence in decision-analytic models often combine early RCT evidence on the relative effectiveness and safety of new treatments with locally estimated parameters such as the cost of treating adverse events, underlying risks, and mortality rates (Ades et al. 2006). While these adjustments are useful, they are unlikely to fully account for the behavioral differences between early RCTs and local real-world conditions. Hence, even when local real-world data are available, insurers still face considerable uncertainty on the funding implications for costs and outcomes (Berger et al. 2017).

Conducting subsequent "pragmatic" RCTs that mimic real-world supply conditions with less stringent protocols could provide more evidence on the likely behavioral responses and impact on real-world cost and outcomes (Ford and Norrie 2016). This trial design can increase the externality validity of the evidence whilst maintaining adequate internal validity. However, conducting pragmatic RCTs after early RCTs could come at considerable societal cost not only in terms of direct trial costs but also the opportunity cost of needing to wait many years for the evidence to develop. It may also be unethical or infeasible to randomize individuals to the control group when efficacious treatments are available. In addition, if insurers want to know the value for money implications under alternative supply conditions in their local context, then these pragmatic trials would need many arms, further adding to the cost and potential delay.

An alternative strategy for insurers is to fund new treatments under certain supply conditions and conduct post-market comparative analyses to assess the real-world impact on costs and outcomes in the local healthcare system (Pratt et al. 2024). Current post-market analyses typically examine the utilization and incidence of adverse events of new treatments and, in some cases, the improvement in health outcomes. However, post-market analyses rarely consider both costs and outcomes (Cipriani et al. 2020; Kemp-Casey et al. 2019; Raj et al. 2019). This limited scope has been partly attributable to data availability and potential for bias due to confounding, which necessitates careful study design (Facey et al. 2020; Makady et al. 2018). However, the data linkage landscape in many countries is rapidly evolving to support more detailed and robust observational studies and the development of the trial-emulation study design provides a clear framework for estimating causal effects (Hernán and Robins 2016; Hernán et al. 2022). Although a post-market analysis only provides evidence under the current supply conditions, an understanding of the behavioral responses in practice can still provide insurers with useful insights to adjust supply conditions or renegotiate with suppliers. A better understanding of the likely behavioral responses in practice and their implications for costs and outcomes may also be useful when considering the funding of new treatments with similar characteristics.

In this paper, we consider an empirical example when new prostate cancer treatments were funded on the public health insurance scheme in Australia. We examine how healthcare utilization changed over the disease pathway as a result of the funding decision to provide insights into the behavioral responses. We compare this to what was observed in the early RCTs and explore how these behavioral responses impacted on the value for money of the new treatments in terms of cost per Quality Adjusted Life Years (QALYs) under the Australian supply conditions. In summary, we find doctors treated a broader range of patients including more with poor prognosis, prior treatments were ceased earlier than expected as patients switched to the new treatments sooner than expected (a response not even possible to observe in RCTs), and patients remained on the new treatments longer than expected. These responses highlight the greater risk of moral hazard in practice compared to heavily controlled trials. We find these and other behavioral responses had large impacts on the value for money for the new treatments.

2 | Behavioral Responses to New Treatments

In this section, we outline an empirical example to consider how funding new treatments can influence behaviors in practice and highlight key differences from early RCTs. In the early 2010s, many countries, including Australia, approved subsidized access to three life-extending treatments for metastatic prostate cancer after first-line treatment with docetaxel (Bencina et al. 2023). These decisions were made based largely on evidence from three early RCTs (De Bono et al. 2011, 2010; Scher et al. 2012).

Prostate cancers are typically slow-growing, and for many patients with localized disease, surgery and radiotherapy are curative. If local therapies fail, pharmacological treatments, such as long-term testosterone suppressants, slow disease progression but eventually the cancer may become metastatic and spread from the prostate (Park and Eisenberger 2015). Prior to funding the three new treatments, first-line treatment

(docetaxel) was the only life-extending treatment available for patients with metastatic disease (Australian Cancer Network Management of Metastatic Prostate Cancer Working Party 2010). This relatively low cost intravenous chemotherapy is generally poorly tolerated and usually only given as a short-term course until further disease progression or patients experience severe toxicity. Doctors closely monitor patients to help decide when to stop treatment (i.e. when the associated adverse events likely outweigh the potential gains from continued use). Patients can experience pain as the disease progresses and spreads to other regions, particularly to the bones, with some patients using long-acting opioids and palliative therapies (including other chemotherapies) to improve their quality of life (Logothetis et al. 2012).

The new life-extending but high cost treatments included two hormonal drugs (abiraterone and enzalutamide) formulated as tablets and another intravenous chemotherapy (cabazitaxel). The early RCTs, relied upon by public insurance agencies, offered eligible patients (those without complex comorbidities or short life expectancy) the chance (50%–67%, depending on the RCT) to receive one as second-line treatment[1] after completing the first-line chemotherapy (docetaxel) or palliative treatments. Earlier data from small samples indicated that treatment with one of these three treatments might delay disease progression compared to no treatment (Engels et al. 2005; Fujimoto et al. 2010; Reid et al. 2010). The RCTs provided the new treatments at no cost but enforced strict stopping criteria at disease progression, based on frequent (e.g. every 3 to 4 weeks) monitoring of symptoms, pathology, and imaging. On average, the results for all three treatments indicated that when used in this way, second-line treatment improved survival for these patients by approximately 4 months. The results also indicated that the new hormonal drugs were generally well tolerated and had fewer adverse events than the new chemotherapy (Bahl et al. 2014).

The recommendation to fund these treatments in Australia by the Pharmaceutical Benefits Advisory Committee (referred to herein as the funding committee), was made in the context of *"considerable uncertainty regarding the clinical place in therapy"* due the changing market (Australian Government 2011a). The funding committee considered that the new chemotherapy (cabazitaxel) would likely replace palliative care in Australian patients *"fit [enough] for further chemotherapy"* and the new hormonal treatments would likely replace supportive care (placebo in the RCTs) in patients *"unfit for chemotherapy"* (Australian Government 2011a, 2012). Compared to the early RCT evidence, however, the committee also identified risks that some patients may be treated with both the new chemotherapy and new hormonals *"either sequentially or in combination"*, continued use of the new hormonals *"beyond disease progression until death"* given their good safety profile, and longer use of the new chemotherapy given the potential for *"further dose reductions"* (or dose interruptions) to manage adverse events (Australian Government 2012). These possible behavioral responses and their implications for both costs and outcomes in the Australian context were not captured by any of the early RCT evidence considered by the funding committee.

The Australian funding committee ultimately made a pragmatic decision to fund all three new treatments, with relatively broad funding criteria compared to the trial protocols. Funding was still restricted to patients with metastatic prostate cancer after first-line docetaxel, but doctors could prescribe treatment to a broader range of patients and had more discretion in deciding when to stop treatment.[2] Sequential use of treatments (as second- and third-line treatments) was also permitted provided patients only used one of the new hormonal treatments. There were no monitoring requirements but the duration of each prescription implied a degree of monitoring (i.e. every 3 weeks on chemotherapy and every 3 months on hormonal treatment) (Australian Government 2013, 2014). The funding criteria were generally consistent with international guidelines at that time (Chopra and Rashid 2015; Heidenreich et al. 2014).[3]

We now expand on the considerations noted by the funding committee above on how the demand and supply conditions in practice would likely have influenced the use of the new treatments compared to the early RCTs. In Australia, the broader eligibility criteria and low out-of-pocket costs meant that doctors would likely treat patients with worse prognosis compared to trial participants. Similarly, doctors and patients may have decided to use the new treatments earlier in practice as there were fewer barriers to access, better evidence of the treatments' benefits, and a guarantee the patient would receive the new treatments (rather than potentially be randomized to the control arm). As noted by the funding committee, we might expect patients would remain on the hormonal treatments for longer due to the less stringent stopping criteria or less frequent and enforced patient monitoring. Also, with low out-of-pocket costs, few adverse events (low non-monetary costs) and no further treatment options available, there may have been an incentive to remain on the hormonals after disease progression if doctors and patients perceived even small benefits from continued use. We expect this behavioral response to be weaker for the new chemotherapy owing to frequent monitoring (before every dose), poor tolerability, and inconvenience of ongoing administration (large non-monetary costs). All these factors highlight that, while the potential for moral hazard was heavily restricted in the RCTs, the potential for moral hazard once funded under the Australian supply conditions was much greater.

In addition to the new treatments themselves, we would also likely expect to find impacts on other behaviors that were heavily controlled in the RCTs. With the new efficacious treatments available, doctors and patients would likely have switched from first-line chemotherapy before its toxicity needed careful management. As a result, the value of monitoring while on first-line chemotherapy may have decreased but the value of monitoring after first-line chemotherapy may have increased, to inform subsequent treatment decisions. We might also expect to find changes in other healthcare use due to delayed disease progression and improved survival as well as potential substitution effects with concomitant therapies. Economic modeling using RCT evidence on delayed progression and extended survival combined with local real-world data on the costs prior to and post progression could have at least partially accounted for this last point. Although, ultimately the extent to which these behaviors occurred and their implications for costs and outcomes is an empirical question.

3 | Methods

3.1 | Data and Empirical Strategy

To estimate the causal impact of funding these new prostate cancer treatments on healthcare use, related costs and outcomes in Australia, we used a target trial emulation framework (Hernán and Robins 2016; Hernán et al. 2022). We developed a protocol for the empirical analysis (or target trial) to mimic the key elements of an RCT comparing outcomes in patients treated with any of the new treatments (i.e. after the funding decision) compared untreated controls without access (i.e. before the funding decision). The empirical analysis was not designed to replicate the original RCTs, which only considered a single treatment for second-line therapy after first-line chemotherapy. A direct comparison between the empirical analysis and original RCTs was not conducted because of differences in the baseline/time-zero (i.e. initiation of first-line vs. second-line therapy) and insufficient data to accurately identify those patients treated in practice who closely matched patients enrolled in the RCTs.[4] We do, however, explore the differences in costs and outcomes across key subgroups, defined by baseline/time-zero characteristics, to assess the potential impact of patient selection in the RCTs.

We provide a summary of the study design, empirical strategy and baseline characteristics of the comparison groups below, but full details from a previous analysis are published elsewhere (Ghijben et al. 2021). That analysis focused on estimating the impact on survival and QALYs, and found that the average benefit to patients treated in practice was less than expected by the Australian funding committee. In this paper, we estimate the impact on resource use and associated behaviors.

We use individual-level administrative data between 2009 and 2015 for prostate cancer patients linked across three national databases.[5] The data contains basic patient characteristics and medical utilization funded by the Australian federal government, which accounts for at least 60%–65% of total health expenditure (Australian Institute of Health and Welfare 2021). This includes the majority of medicines and medical services provided in the community, outpatient clinics, and privately owned hospitals. The data excludes healthcare funded by state governments, such as services provided in government owned hospitals, and other non-subsidized services.[6]

We identified all potentially eligible patients and defined time-zero as the date when first-line docetaxel was initiated. Patients were categorized into the pre-funding cohort and post-funding cohort, based on their docetaxel initiation date. We defined two enrollment windows to maximize follow-up and minimize potential contamination. Pre-funding patients were censored when the new treatments were registered, while post-funding patients were censored at the end of the available data.

The rational for defining time-zero based on prior treatment initiation was three-fold. First, we could accurately identify all patients across both cohorts at their first-line treatment in the administrative data which avoided the need to impute the hypothetical initiation of second-line treatment for the pre-funding cohort. Second, this excluded "prevalent" patients at the funding decision who may have received delayed access to the new treatments. The average treatment effects for treated prevalent patients are less relevant than treated "incident" patients when considering value for money, given that future patients will not experience delayed access to treatment. Finally, this allowed us to investigate the potential impacts of the funding decision on prior treatment use.

Given that some patients in the post-funding cohort did not receive any of the new treatments, the main identification challenge was to accurately match treated patients after the funding decision to their equivalent treated-controls before the funding decision. For this, we used an *untreated* matching approach to overcome potential bias from unobserved factors being related to both treatment selection and outcomes (Ghijben et al. 2021). This approach uses the outcomes of contemporaneous *untreated* patients to improve matching between treated patients after the funding decision with treated-controls before the funding decision. While this approach considerably reduces bias related to unobserved treatment selection, the causal effects may still be subject to bias if unobserved factors related to outcomes or healthcare use are changing over time.[7]

To operationalize this matching technique, we estimate two sets of matching weights. First, we match the pre-funding cohort (consisting of both treated-controls and *untreated*-controls) to the post-funding cohort (consisting of both treated patients and *untreated* patients) in terms of baseline characteristics using inverse probability weights. To calculate the weights (w_{1i}), we used a probit model to predict the probability or propensity score ($\hat{p}$) of being in the post-funding cohort for each patient i conditional on their baseline characteristics.[8] The weights applied to the pre-funding cohort were calculated based on Equation (1).

$$w_{1i} = \frac{\hat{p}_i}{1 - \hat{p}_i} \tag{1}$$

After the first matching step, both cohorts are of equal size and the key assumption here is that the only systematic difference is the availability of the new treatments. Aside from the new treatments, we did not expect any systematic differences given the short remaining life-expectancy (20 months without the new treatments), the short time frame between the groups (32 months), and no other changes to the recommended treatment pathway for these patients over this period.

In the second step, we matched *untreated* patients in the post-funding cohort to equivalent *untreated*-control patients in the weighted pre-funding cohort using coarsened exact matching (Iacus et al. 2012), accounting for both baseline characteristics and outcomes. This step uses the assumed independence between the funding decision and the outcomes of *untreated* patients both before and after the funding decision to improve the matching to *untreated*-controls (consistent with an instrumental variable approach). Specifically, we defined 24 "matching bins" that accounted for key outcomes, time on first-line chemotherapy and survival. Here, we assumed *untreated* patients in the post-funding cohort and *untreated*-controls in the pre-funding cohort would receive similar treatment and have similar survival. Compared to the treated patients in our sample,

the *untreated* patients were older, had more comorbidities and much shorter median survival. Hence, the decision to remain *untreated* in the post-funding for many was likely due to poor prognosis following first-line chemotherapy. Similar patients with poor prognosis (*untreated*-controls) were also likely to be present in the pre-funding cohort. The coarsened exact matching weights (w_{2ij})—used to identify the *untreated*-controls in the pre-funding cohort—were calculated based on Equation (2).

$$w_{2ij} = \frac{N_{uj}\ w_{1ij}}{\sum_{i=1}^{Ncj} w_{1ij}} \tag{2}$$

The N_{cj} patients in the pre-funding cohort c in each matching bin j are re-weighted proportionally to their initial weights w_{1ij} (estimated in Equation 1), such that their new weights w_{2ij} sum to the total of the N_{uj} *untreated* patients u in the post-funding cohort in bin j. The final weights (w_{3i})—used to identify the treated-controls in the pre-funding cohort—were calculated based on Equation (3), which is given by the difference between the total cohort weight from Equation (1) and the weight for the *untreated*-controls from Equation (2).

$$w_{3i} = w_{1i} - w_{2i} \tag{3}$$

3.2 | Estimating the Impact of Funding on Healthcare Use Behaviors

We compare monthly healthcare use for the treated patients with their matched treated-controls. We do this prior to baseline to confirm that there are no differences between the groups unrelated to the new treatments,[9] and post baseline to understand the behavioral impacts of the funding decision (such as whether the new treatments substitute, complement, or delay existing therapies). Specifically, we consider healthcare use each month for those still alive (conditional on survival) in addition to overall use for the cohort (unconditional on survival). Examining both conditional and unconditional use lets us better understand the role that extended survival played in increasing healthcare costs.

We define 14 healthcare categories relevant for prostate cancer to investigate the impact on different behaviors. We explore the use of the newly funded treatments (*new hormonals* and *new chemotherapy*) including the order and duration of treatments. We also explore the use of other prostate cancer therapies in the treatment pathway, where *first-line chemotherapy, opioids, surgery/radiotherapy,* and *palliative chemotherapy* capture impacts to prior, concurrent and/or subsequent therapies. We further assume medical consultations (*general practitioner* and *specialist*), *pathology* and *imaging/diagnostic procedures* reflect decisions around monitoring of patients, and use of background *testosterone suppressants* capture impacts on background compliance rates. We consider the use of other healthcare services in umbrella categories (*other medicines*, *other medical services,* and *chemotherapy administration*[10]). Where possible, we report healthcare use in natural units (such as the number of scripts or visits) or as a common monetary unit (2015 Australian dollars) for more heterogeneous categories. Aside from the new treatments, there were no major changes to other healthcare services available over this period.[11]

While we observe most patients until their death, some patients remained alive at the end of the follow-up. For these censored patients we predict both their death and their healthcare use after censoring until death. We first estimate their time to death using parametric survival functions and then predict healthcare use in missing future months based on the observed use for similar patients. We selected the best fitting parametric functions for the treated and *untreated*-controls (considering the gamma, loglog, lognormal, Weibull, and exponential, using the AIC and BIC), though the results were robust to the choice of function form with minimal differences in mean predictions. Overall, we predict resource use for approximately 30% of the person-months in the analysis at the tail of the survival distributions (Supporting Information S1: Appendix Figure A1).

For the new treatments, we estimate future use with a discrete event simulation model to account for the sequential nature of the treatments (Karnon 2003). This type of model predicts the time to the next discrete event over a lifetime, such as stopping and starting treatment. Here, we estimated eight unique parametric functions based on time-on-treatment and time-to-next-treatment data, accounting for the different treatment pathways —second-line hormonal or second-line chemotherapy. Since time to death was modeled using a separate parametric function, death was treated as a censoring event rather than a failure event in the time-on-treatment and time-to-next-treatment data. To predict number of scripts from time on treatment, we use ordinary least squares regressions controlling for time on treatment. Further detail and the results of the discrete event simulation model are provided in the Appendix (see Supporting Information S1: Appendix Tables A1–A3). The average number of scripts using observed data only (accounting for use before censoring) was only 10%–14% smaller than the predictions (accounting for use before and after censoring), illustrating that the extrapolated resource use was not a major driver of the results.

For other healthcare categories with censored data, we predict use after censoring using a parametric extension to the Kaplan-Meier sample average estimator (Lin et al. 1997). We use observed data in uncensored patients to estimate regression models to predict healthcare use in each month from censoring until death controlling for patient characteristics (including age, on/off treatment, time from baseline, time to death, pre- or post-funding cohort). We also included a linear time trend to test our assumption that there were no other major changes taking place unrelated to the availability of the new treatments. We found no evidence of resource use changing over time due to unobserved characteristics, which supported the assumption required for our analysis. To test the same assumption for prior docetaxel use, which was not censored, we compared the change in prior docetaxel cycles per patient within each cohort over time controlling for baseline characteristics, and similarly found no changes over time due to unobserved characteristics. Further detail and the results of the estimated regressions are provided in the Appendix (see Supporting Information S1: Appendix Tables A4–A6). Given the multiple parts of the estimation process, we estimate confidence intervals (CIs) around these

predictions using the bootstrapping method, sampling with replacement within the pre- and post-funding periods (Efron and Tibshirani 1994).

3.3 | Value for Money

To explore the impact of behavioral responses on value for money, we estimate the incremental cost-effectiveness ratio associated with the funding decision (i.e. the new treatments), in terms of cost per QALY. We convert all healthcare use into 2015 Australian dollars and combine the results with survival outcomes and QALYs[12] estimated previously (Ghijben et al. 2021). Since the unit prices of the new treatments at listing were confidential,[13] we estimate their unit prices based on public statements from the funding committee (details provided below). For other resource categories, we estimate the unit price based on average costs recorded in the dataset for the 2015 calendar year (Table 1). Finally, we discount costs and outcomes at 5% per annum in-line with the approach used for these funding decisions.

When making this decision, the funding committee assumed each of the three new treatments were similar or equivalent in terms of both costs and outcomes, for both second-line or third-line treatment. Based on the available evidence, the committee considered that each treatment improved average survival by approximately "*4.26 months*" and had a cost-effectiveness ratio of *"$45,000 to $75,000 per QALY*" (Australian Government 2011b, 2012, 2013, 2014; Sandblom et al. 2004; Wilson et al. 2014). The funding committee did not publicly cite the corresponding change in QALYs, which we estimated to equal approximately 0.27 QALYs after discounting, based on the literature (Wilson et al. 2014) and other statements.[14] The average duration of treatment was considered to be "*7.5 scripts*" per course of hormonal treatment and *"6 cycles"* (i.e. scripts) per course of new chemotherapy (Australian Government 2011a). The new chemotherapy was also considered to have additional healthcare costs associated with *"administration costs"* (estimated at A$100 per infusion); costs for *"pre-medication"* (estimated at A$40 per infusion); costs for *"adverse events … associated with hospitalization*" (estimated at A$600 per course); and concomitant *"granulocyte colony stimulating factor … [of] less than A$500"* (estimated at A$450 per course) (Australian Government 2011a, 2011b, 2012).

From these statements, we estimated the unit cost of the new hormonal treatments assuming a funding threshold of A$50,000 per QALY, which was a commonly cited but implicit Australian funding threshold at that time (Wang et al. 2018). The economic model for the new hormonal treatment (abiraterone vs. placebo), considered by the funding committee, did not include any non-drug costs (or none were stated to be included). Thus, the unit cost was simply calculated by multiplying the funding threshold by the average QALYs divided by the average units per course, equal to A$1800 per script (i.e. A$50,000/QALY * 0.27 QALYs/7.5 scripts). We then calculated the corresponding unit cost of the new chemotherapy as A$1935 per script from the cost-equivalence assumptions with the new hormonal treatments and accounting for the additional costs (i.e. [A $13,500—A$1890]/6.0 scripts). This is consistent with the Australian funding committee's approach to fund therapies with similar effectiveness on a cost-minimization basis.

We provide a reference point for the original funding decision. Incremental costs were estimated assuming patients had remained on the new treatments as expected by the committee. Incremental QALYs were estimated based on the expected change in QALYs given the incremental costs and the funding threshold, which assumes similar benefit for second- and third-line use. We also tested the sensitivity of our results to these assumptions in three scenarios; (i) raising the funding threshold to A$60,000 per QALY based on the mid-point of the published range, (ii) assuming a + A$1000 change in background/net costs, and (iii) assuming a −A$1000 change in background/net costs.[15]

3.4 | Exploring the Effects Across Subgroups

It is useful to consider the differences in the costs and outcomes for key subgroups as defined by baseline characteristics. Due to data limitations preventing a direct comparison with the trial population, subgroup analysis provides insight into the role of patient selection in the RCTs and the impact of treating a different population in practice. Examining subgroups can also

TABLE 1 | Unit costs applied in the analysis of value-for-money.

Resource item	Units cost	Source
First-line chemotherapy (docetaxel), scripts	A$170.81	Average cost in 2015;
New hormonals (abiraterone, enzalutamide), scripts	A$1800.00	Estimated approximate unit price to government
New chemotherapy (cabazitaxel), scripts	A$1935.00	Estimated approximate unit price to government
Opioids, scripts	A$56.20	Average cost in 2015;
Palliative chemotherapy, scripts	A$214.57	Average cost in 2015;
Testosterone suppressants, scripts[a]	A$369.54	Average cost in 2015;
Pathology, tests	A$18.30	Average cost in 2015;
General practitioner, visits	A$50.33	Average cost in 2015;
Specialist, visits	A$80.81	Average cost in 2015;

[a]Standardized scripts, where one script reflects 1 month of treatment.

provide evidence on whether to adjust access to the new treatments for some patients. Additionally, public insurance agencies may want to incorporate equity concerns into such decisions and be willing to pay more for health gains in specific patient groups (Cookson et al. 2017). Given our use of administrative data, we are somewhat restricted in the types of subgroups we can consider. We provide subgroup estimates based on age at baseline (< 75 years old vs. those 75 years or older); the presence of significant pain at baseline, defined by the concurrent use of long-acting opioids (with pain vs. without pain); and presence of comorbidities at baseline, defined by the pharmacy-based comorbidity index ("less" comorbidities with an index score < 3 vs. "more" comorbidities with an index score ≥ 3) (Sarfati et al. 2014).

4 | Results

4.1 | Patient Characteristics at Baseline

The matched sample included 1048 treated patients after the funding decision and 1048 control patients (weighted up from 693 patients) before the funding decision. There were no significant differences between these groups in baseline characteristics or prior healthcare use, despite not matching on healthcare use (Table 2).

4.2 | Impact of Funding on Behaviors

We first consider the duration of first-line chemotherapy. When the new treatments became available, doctors and patients stopped the first-line chemotherapy sooner, corresponding to a significant 0.9 (95% CI 0.6, 1.2) reduction in the average number of scripts (Table 3). This translates into approximately one less 3-week cycle and reflects a preference for discontinuing the poorly tolerated first-line treatment and starting the well-tolerated and effective hormonals.

Next, we consider the patients' characteristics when they started the new treatments and compare this with the early RCTs. First, we found evidence of less delay to second-line treatment in practice compared with the RCTs (De Bono et al. 2011, 2010; Scher et al. 2012). Fewer patients had undergone multiple courses of prior chemotherapy (2% vs. ~ 30%) and the time from the last dose of prior chemotherapy to the first dose of a new treatment was shorter (median of 2 vs. 4 months). We also found patients were, on average, 4 years older when treated in practice (median 73 years vs. ≤ 69 years) and a higher proportion had clinically significant pain, as defined by long-acting opioid use (64% vs. ≤ 45%). Overall, this suggests that in practice patients were being treated earlier in their disease pathway, in addition to the new treatments being used by a broader population (e.g. older patients and more with pain). However, it is difficult to disentangle the extent to which these two factors influence costs and outcomes.

Doctors and patients overwhelmingly chose hormonal treatment over chemotherapy as their new second-line therapy (95.5% vs. 4.5%, respectively), which reflects a preference for the better-tolerated and more easily administered alternative. Disease progression, while on the new hormonals, likely prompted nearly half (43.3%) of the patients to switch to the new chemotherapy as third-line therapy and some patients (8.1%) even switched back to hormonals after that. Other patients

TABLE 2 | Patient characteristics at baseline.[a]

	Treated (95% CI), $N = 1048$	Controls (95% CI), $N = 1048$
Patient characteristics[b]		
Age, mean	71.8 (71.4, 72.3)	71.8 (71.3, 72.4)
≥ 75 years, %	40.0 (37.0, 42.9)	38.0 (34.7, 42.0)
Pharmacy-based comorbidity index, mean	1.8 (1.7, 1.9)	1.8 (1.7, 1.9)
Long-acting opioids (significant pain), %	53.5 (50.5, 56.6)	53.9 (50.3, 57.3)
Prior chemotherapy, %	2.0 (1.2, 2.8)	3.0 (1.7, 4.2)
Average monthly healthcare use in the 12 months prior to baseline		
Opioids, scripts	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)
Testosterone suppressants, scripts[c]	0.9 (0.8, 0.9)	0.9 (0.8, 0.9)
Specialist, visits	1.1 (1.0, 1.1)	1.1 (1.0, 1.1)
General practitioner, visits	1.2 (1.2, 1.3)	1.2 (1.2, 1.3)
Pathology, tests	3.7 (3.5, 3.9)	3.9 (3.7, 4.1)
Imaging and diagnostics, cost (A$)	188.0 (178.8, 197.2)	182.2 (172.7, 191.6)
Surgery and radiotherapy, cost (A$)	118.6 (105.0, 132.3)	117.4 (103.6, 131.2)
Other medicines, cost (A$)	155.6 (145.4, 165.8)	151.2 (140.7, 161.7)
Other medical services, cost (A$)	16.6 (15.2, 17.9)	16.0 (14.6, 17.5)

[a]Initiation of first-line chemotherapy (docetaxel).
[b]Refer to Ghijben et al. (2021) for additional characteristics.
[c]Standardized scripts, where one script reflects 1 month of treatment.

TABLE 3 | Unconditional mean per patient use of healthcare services.

Resource category	Treated (95% CI)	Controls (95% CI)	Difference (95% CI)
First-line chemotherapy (docetaxel), scripts	5.6 (5.4, 5.8)	6.4 (6.2, 6.6)	−0.9 (−1.2, −0.6)
New hormonals, scripts	10.3 (9.8, 10.8)	0	10.3 (9.8, 10.8)
New chemotherapy (cabazitaxel), scripts	3.1 (2.8, 3.4)	0	3.1 (2.8, 3.4)
Palliative chemotherapy, scripts	2.8 (2.0, 3.8)	2.7 (1.8, 3.7)	0.1 (−0.5, 0.7)
Opioids, scripts	25.0 (22.0, 28.4)	20.9 (17.6, 24.6)	4.1 (1.6, 6.5)
Testosterone suppressants, scripts	22.8 (21.2, 24.5)	16.8 (15.0, 18.7)	6.0 (3.8, 8.1)
General practitioner, visits	37.7 (33.7, 42.5)	27.5 (23.1, 32.6)	10.2 (7.2, 13.4)
Specialist, visits	44.1 (39.6, 49.4)	40.1 (34.4, 46.8)	4.0 (−0.5, 8.5)
Pathology, tests	146.7 (135.9, 161.4)	126.3 (112.5, 144.1)	20.4 (8.7, 31.6)

remained on hormonal treatment until death or stopped all active treatments prior to death. Overall, these behaviors led to patients remaining on the new treatments for longer than expected compared to the early RCT evidence. Conditional on starting treatment, patients used on average 10.3 scripts of the new hormonals and 6.3 scripts of the new chemotherapy compared to 7.5 scripts and 6.0 scripts, respectively, as expected from the RCT evidence (Supporting Information S1: Appendix Table A3).

We also found other important changes in monitoring-related behaviors after the funding decision. Conditional on survival, specialist visits (Figure 1A) and pathology tests (Figure 1B) became less frequent in the 18 months after starting first-line chemotherapy. This suggests reduced patient monitoring and testing when deciding to discontinue first-line chemotherapy and switch to the hormonals. Treatment decisions related to discontinuing first-line chemotherapy and commencing subsequent treatments became easier when the new treatments became available, meaning the value of monitoring decreased. Conditional on survival, pathology tests (Figure 1B) and imaging/diagnostics procedures (Figure 1C) became more frequent after the first 18 months which suggests more intense monitoring when deciding on the timing of the switch from the hormonals to the new chemotherapy. The additional or sustained rate of monitoring in the long-term, however, highlights the value of monitoring to inform ongoing use of the new treatments. This long-term effect resulted in an overall increase in specialist visits, pathology tests and imaging/diagnostic procedures. In contrast, conditional on survival, there was no change in general practitioner visits (Supporting Information S1: Appendix Figure A2D), suggesting general practitioners continued to monitor their patients at a relatively constant rate until death. Overall use of general practitioner consultations, unconditional on survival, increased due to improved survival (Table 3).

Similarly, we also found other important changes in treatment-related behaviors after the funding decision. Conditional on survival, the new treatments delayed the use of palliative chemotherapies (Figure 1D), likely by slowing disease progression. However, there was no change in palliative chemotherapy use overall, suggesting the new treatments only postponed rather than avoided palliative care[16] (Table 3). For opioids, there was only a slight reduction in use conditional on survival, likely due to the new treatments delaying the onset of significant pain (Supporting Information S1: Appendix Figure A2C). But this reduction was more than offset by an increase in overall use owing to longer survival with pain, corresponding to 4.1 (95%CI 1.6, 6.5) additional opioid scripts, on average, over their lifetime (Table 3). In contrast, we found no impacts on the use of other treatments conditional on survival (such as testosterone suppressants, surgical procedures/radiotherapy, other medicines or other medical services), suggesting relatively constant use of other care irrespective of disease progression (Supporting Information S1: Appendix Figure A2). Overall use, unconditional on survival, was higher for all of these categories due to improved survival (Table 3).

4.3 | Impact of Behaviors on Value for Money

To explore the potential impact on value for money, we consider how these behavioral responses influenced healthcare costs, discounted at 5% (Table 4). We find that funding the new treatments increased costs by A$29,435 per patient on average. This was mostly comprised of new drug costs (A$17,915 per patient for the hormonals and A$5746 per patient for the new chemotherapy). While there were some cost savings (−A$149 per patient) related to early stopping of first-line chemotherapy, these were minor because of their low cost to government.[17] For monitoring costs, initial savings in the first year were more than offset by increased use in subsequent years (net increase of A$1822 per patient).[18] Given palliative chemotherapy was slightly delayed rather than avoided, we find no impact for costs (−A$4 per patient). Although pain progression was slightly delayed, the increase in survival led to higher opioid costs overall (A$203 per patient). We found that other health care costs were relatively constant, conditional on survival, therefore the longer survival with the new treatments resulted in substantially higher costs (A$3901 per patient).[19] The incremental costs without discounting were similar given the relatively short time horizon of the analysis (Supporting Information S1: Appendix Table A7).

Next, we compare the costs and outcomes observed in practice to the reference case informed by the early RCT evidence, using a stepped approach and discounted at 5% (Figure 2). Based on the proportion of patients who received second- and third-line treatment, and the key assumptions of the Australian funding committee, we expected to observe an average incremental cost of

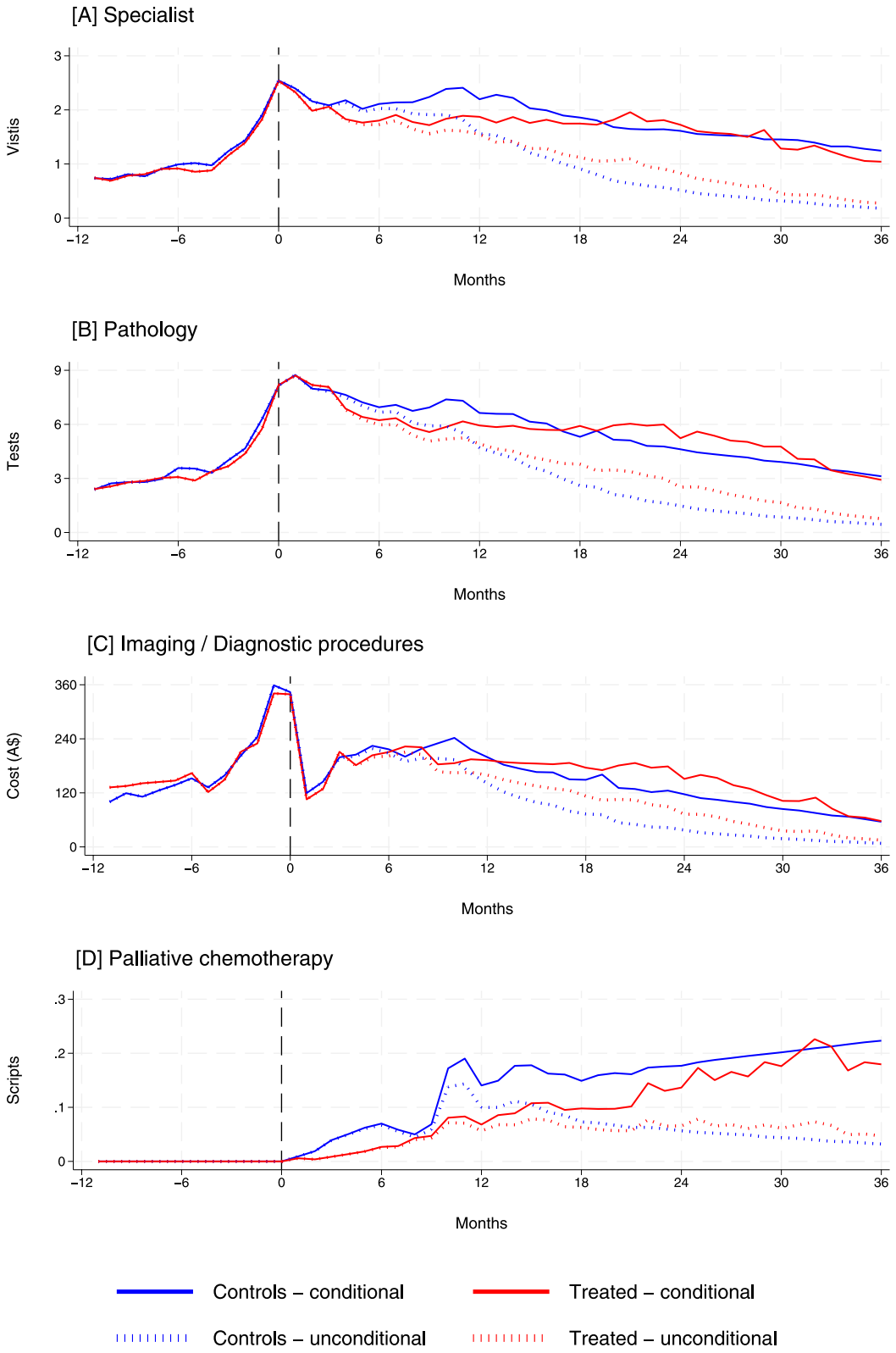

FIGURE 1 | Average use of healthcare services in treated patients and matched controls. The conditional and unconditional curves report the average healthcare utilization per month for those currently still alive and for the total cohort, including the dead, respectively. A difference in the conditional curves at a given point in time indicates that the funding decisions changed average health use due to either a change in health status or change in behaviors. The unconditional curves reflect the budgetary impact for government associated with healthcare service use with the area between the curves reflecting the impact on government costs associated with the funding decision. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 | Average incremental costs per treated patient (discounted at 5%).

	Treated (95% CI)	Controls (95% CI)	Incremental (95% CI)
Costs total (A$,000)	55.84 (53.56, 58.05)	26.40 (24.49, 28.85)	29.44 (26.91, 31.62)
New 2nd and 3rd line treatments			
Hormonals (abiraterone, enzalutamide)	17.92 (17.04, 18.72)	0	17.92 (17.04, 18.72)
Chemotherapy (cabazitaxel)	5.75 (5.24, 6.25)	0	5.75 (5.24, 6.25)
Existing treatments			
First-line chemotherapy (docetaxel)	0.95 (0.92, 0.98)	1.10 (1.06, 1.14)	−0.15 (−0.20, −0.10)
Palliative chemotherapy	0.55 (0.39; 0.74)	0.55 (0.37; 0.74)	−0.00 (−0.13; 0.12)
Opioids	1.33 (1.18, 1.50)	1.13 (0.95, 1.32)	0.20 (0.07, 0.33)
Testosterone suppressants	8.04 (7.51, 8.60)	5.99 (5.40, 6.63)	2.05 (1.32, 2.78)
Surgery and radiotherapy	2.56 (2.20, 3.01)	1.81 (1.39, 2.30)	0.75 (0.42, 1.08)
Other medical services	0.30 (0.25, 0.36)	0.25 (0.17, 0.34)	0.06 (−0.00, 0.11)
Other medicines	4.97 (3.98, 6.42)	4.24 (3.33, 5.38)	0.73 (0.15, 1.32)
Chemotherapy administration	1.63 (1.50, 1.82)	1.32 (1.13, 1.58)	0.32 (0.14, 0.50)
Monitoring			
Pathology	2.69 (2.51, 2.93)	2.31 (2.08, 2.61)	0.37 (0.17, 0.56)
Imaging and diagnostics	3.93 (3.69, 4.24)	3.22 (2.88, 3.59)	0.70 (0.39, 0.97)
General practitioner	1.80 (1.63, 2.01)	1.33 (1.13, 1.57)	0.47 (0.33, 0.61)
Specialist	3.43 (3.11, 3.81)	3.15 (2.72, 3.66)	0.28 (−0.07, 0.62)

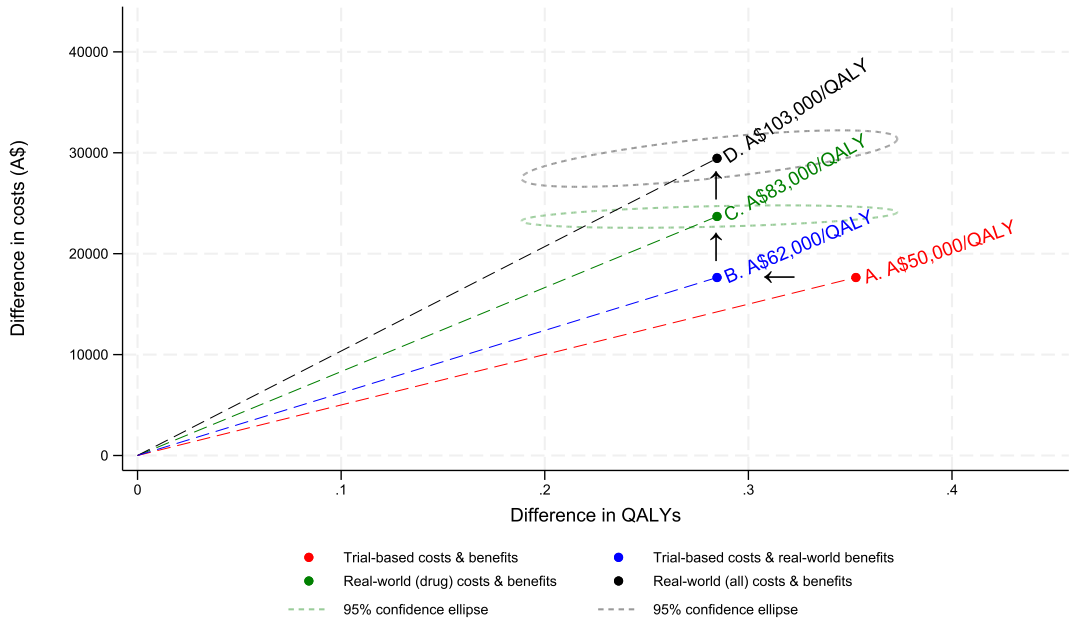

FIGURE 2 | Value for money estimates of the funding decision, stepped analysis (discounted at 5%). The figure illustrates the change in the estimated incremental cost-effectiveness ratio of the funding decision when considering the behavioral responses observed in practice and their implications for both healthcare resource use and health outcomes. Point "A" shows the difference in costs and QALYs for the new treatments compared to usual care based on the clinical trial evidence and a funding threshold of A$50,000/QALY. In practice, the difference in QALYs was less than expected (Point "B") and the difference in costs was higher than expected (Points "C" and "D"). [Colour figure can be viewed at wileyonlinelibrary.com]

approximately $17,640 and an incremental benefit of approximately 0.35 QALYs (Point A in Figure 2). In practice, despite longer use of the new treatments compared to the RCTs, we previously estimated lower discounted average benefits for those who received the new treatments of 0.28 QALYs (Supporting Information S1: Appendix Table A8). This lower benefit was likely in part due to doctors treating more patients with poor prognosis but also due to some patients, treated with both the hormonal and new chemotherapy, spending longer alive in the end-stage of their disease (Ghijben et al. 2021). Hence, even

before considering the full cost implications, these treatment behaviors increased the incremental cost-effectiveness ratio of the funding decision to A$62,000 per QALY (Point B in Figure 2).

Next, we consider the estimated higher costs for the new treatments owing to longer use. Compared to the expectations of the funding committee, the additional use of the new treatments corresponded to higher costs per patient of approximately 35% (A$6050). Which increased the incremental cost-effectiveness ratio to A$83,000 per QALY (Point C in Figure 2). It is hard to disentangle the extent to which this longer use was due to starting the new treatments earlier versus their extended use beyond progression. While the funding committee had at least noted the potential for the latter, they did not consider the potential for earlier use and, at that time, had no evidence about the extent to which longer use would increase costs.

The net cost implication for all other behavioral responses (i.e. less first-line chemotherapy, additional monitoring and costs associated with longer survival) further increased costs per patient by A$6250 and increased the incremental cost-effectiveness ratio to A$103,000 per QALY. The majority of this increase in costs was for healthcare categories where, conditional on survival, use did not change (general practitioner, testosterone suppressants, surgery/radiation, other medicines, other medical services). Even for healthcare categories where the new treatment decreased use in the short term, the longer survival increased overall costs. Given this real-world data on background costs existed at the time of the decision, not accounting for these costs had important implications for the results. The uncertainty around the estimated incremental cost-effectiveness ratio of the funding decision was small relative to the overall change from the reference point (Figure 2).

Our conclusions were largely unchanged when we adjusted some of our key assumptions (Supporting Information S1: Appendix Figure A3). The results were not very sensitive to assuming that a A$60,000 (rather than A$50,000) per QALY threshold was used by the funding committee when deriving the unit costs of the new treatments. This change slightly increased the unit costs of the new treatments and scaled up the cost implications of the extended use of the new treatments, with the final incremental cost-effectiveness ratio (A$121,000 per QALY) more than double the reference point. Similarly, assuming that the funding committee had accounted for a modest change in background costs (± A$1000) had minimal impact on the results, given the amount assumed was very small relative to our estimated increase in costs.

4.4 | Variation Across Subgroups

We now consider the extent to which the incremental costs and outcomes varied across subgroups defined by baseline characteristics (Figure 3). We find little difference in costs and outcomes for younger versus older patients, likely because those "fit enough" for first-line chemotherapy could have then received the new treatments. We observed larger differences between patients with and without significant pain—as defined by the use of long-acting opioids. The new treatments were associated with smaller health gains in those with significant pain, likely due to their more advanced disease. While their incremental costs were also lower, this was not fully proportional to the smaller health gains, leading to a slight increase in the cost per QALY. A similar pattern was observed between patients with more versus less comorbidities, however, there were no differences in cost per QALY. Overall, we do not find major differences in the cost per QALY across subgroups, suggesting that the increase in the cost per QALY compared to the early RCT evidence was not due to treating a broader patient population.

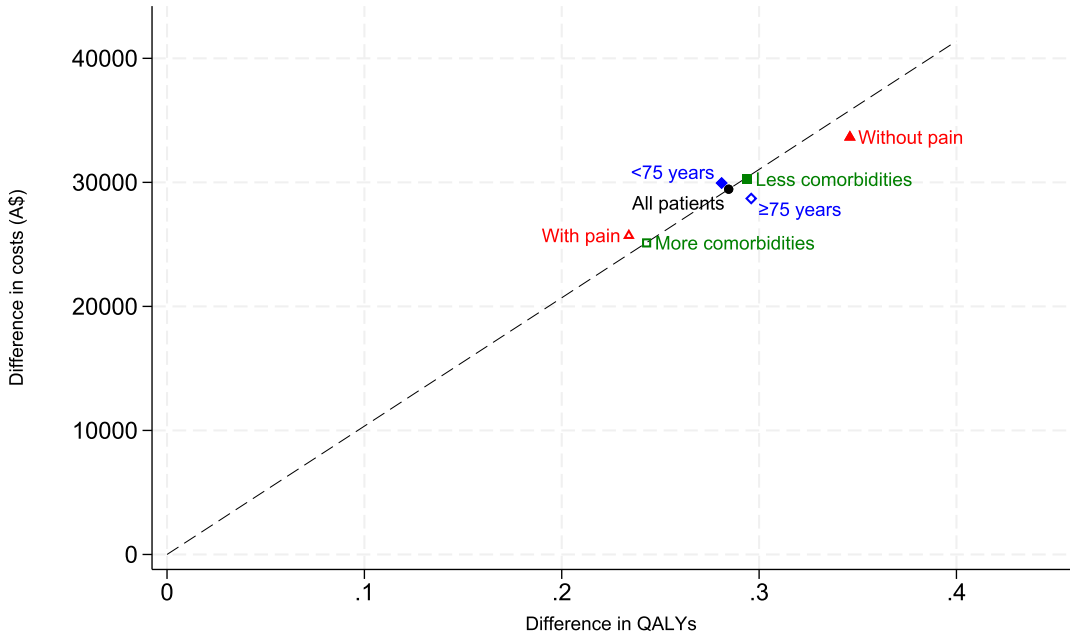

FIGURE 3 | Value for money estimates of the funding decision, by subgroup (discounted at 5%). [Colour figure can be viewed at wileyonlinelibrary.com]

5 | Discussion

This paper has considered the limitations of using early RCT evidence to inform funding decisions when behaviors in practice may depend on the local supply conditions and differ to those observed in the RCTs. Insurers are regularly confronted with this issue and while some attempts are often made to address potential concerns, significant uncertainties may remain. We consider how the provider and patient incentives in early RCTs differ from practice and how these may lead to different behaviors, costs, and outcomes. We then used a target trial emulation framework to estimate the incremental costs and outcomes of an Australian funding decision for three new treatments for metastatic prostate cancer. We found behavioral responses that were absent in the RCTs, highlighting how information and incentives can influence healthcare use and impact on the value for money of new treatments.

When three new prostate cancer treatments were funded under certain supply conditions in Australia, we found that treated patients, on average, benefited less and incurred higher costs than anticipated based on early RCTs. Although doctors treated a broader range of patients than those in the RCTs, including more with worse prognosis, this had minimal impact on the average incremental cost-effectiveness, as these patients experienced lower benefits but also incurred lower costs. A significant proportion of the higher costs in practice were related to the extended use of the new treatments. This extended use was due to two key reasons. First, patients switched earlier than expected from first-line treatment to second-line treatment. The earlier switch was likely driven by the higher perceived net patient benefit of starting the well-tolerated and easily administered hormonal treatment compared to remaining on the poorly-tolerated and inconvenient first-line chemotherapy. The second reason for extended use was likely due to the limited restrictions on when the new treatment needed to be ceased. With no further life extending treatments available, patients likely continued to use the new treatments even after progression. Extended use was more pronounced for hormonal treatment, which had less adverse events than the new chemotherapy. This highlights that treatments with low non-monetary and monetary costs for patients have a high potential for moral hazard.

Another significant factor driving higher costs in practice was the extended survival combined with high background treatment and monitoring costs for these patients. This aligns with research emphasizing the importance of background costs (Perry-Duxbury et al. 2020; P. van Baal et al. 2016; P. H. van Baal et al. 2011). While the early RCTs did not report these costs, and they may have been irrelevant for the Australian context, real-world data could have provided valuable insights. By leveraging administrative data, insurers can ensure more precise calculations of background costs associated with different diseases or stages of disease. Such estimates, however, may not capture behavioral effects that could influence background costs. For example, we observed a decrease in patient monitoring when transitioning from the prior first-line treatment to the new treatments, compared to palliative care. Before the new treatments were funded, the clinical decision to stop first-line treatment required careful consideration of the trade-off between potential adverse events and the possibility of continued benefit. This highlights that the incentive to monitor patients depends on the value of information for guiding future treatment decisions. In our example, the cost implications of this behavioral response were minimal and outweighed by the monitoring during extended treatment and survival.

Several limitations of our empirical analysis must be acknowledged, both for interpreting the results but also to guide similar research in the future. Given only administrative data was available, we needed to define most of the baseline characteristics and likely quality of life (i.e. QALYs) based on medication or medical service use. This limited our ability to match on observed characteristics, to investigate additional subgroup effects, and to accurately identify the QALY impacts of the new treatments. The dataset also did not capture most hospital costs, which may be considerable at the end of life and it is thus unknown how these would have differed across the groups. More detailed patient data would have allowed for a more comprehensive analysis that could better explain differences between the trial and practice settings due to treating broader populations versus changes in how the treatments are used. It was also necessary to extrapolate survival and healthcare use in censored patients, however, in this case it only accounted for 30% of patient-months in the analysis. This extrapolation required a number of modeling assumptions. The discrete event simulation and the Kaplan-Meier sample average estimator methods both assume no fundamental differences between censored and uncensored patients in terms of healthcare use over time. We do not expect significant differences between these patients, but they may differ by a small amount. Comparison to the funding committee's reference point was also made difficult as not all of the evidence relied on for the decision was made publicly available.

Despite these limitations, our empirical analysis addressed several uncertainties that the funding committee could not resolve prior to making their decision. A key question is, if the committee had this evidence in 2015, when it could have been produced,[20] what would their policy response have been? Given that there was no particular subgroup which had a relative low value use compared to others, tightening up eligibility criteria based on patient characteristics did not seem particularly worthwhile. Consideration could have been given to making extended use more difficult (e.g. restricting hormonal treatments to a maximize number of doses or provide guidelines on when treatments should be ceased) and/or threaten to withdraw the current subsidy and re-negotiate the unit price with the companies involved. Even if the decision based on this new evidence was to do nothing, such an analysis may still have value. If this analysis was planned from the start, then the funding committee may have been more inclined to fund these treatments earlier and able to assess the real-world evidence sooner as well. In this example, the funding committee delayed their final decision for more than a year—partly related to the uncertainty on how the new treatments would be used in practice. In addition, the evidence provided here may have helped the committee to consider the likely behavioral consequences when considering similar medicines.

More broadly, analyzing the comparative impact of funding decisions on costs and outcomes can provide valuable insights for funding committees. Variations across subgroups may reveal areas of low value use or issues such as low uptake and reduced benefits in specific populations. It may also highlight where further interventions are needed to change behavior, such as the implementation and dissemination of clinical guidelines or requiring written or verbal approval from the insurer to encourage efficient and equitable use. While the evidence produced may also lead to re-negotiating price and coverage agreements with pharmaceutical companies, such negotiations may be complex due to political pressures and the involvement of multiple stakeholders. Governments may also face challenges in isolating the benefits of individual treatments, especially when multiple treatments are funded simultaneously, as in the empirical example.

Before conducting a post-market comparative analysis, insurers must first consider the feasibility of the study and whether meaningful effects could be estimated (ENCePP 2018). Careful planning is necessary to estimate robust causal effects from observational data, which depends on the quality of available data and comparisons of interest. Considerations include the assumptions necessary to identify reliable control patients, the duration of follow-up to observe a sufficient number of health events, and the potential that other practice changes unrelated to the new treatment(s) have occurred. Insurers must also consider the likely value of conducting a post-market comparative analysis and compare this against other options, such as, pragmatic trials (Garrison Jr et al. 2007). The concept of "value of information" may be useful, even when unexpected factors might complicate a formal analysis. Additional research may have limited value in several scenarios. First, when new evidence is unlikely to change the decision because the current option is already clearly more or less cost-effective than alternatives, and behavioral uncertainties are unlikely to alter this conclusion. This is unlikely for new innovative treatments as unit prices are often approved close to the insurer's funding threshold. Second, when any change in decision would likely only lead to small improvements in outcomes or modest cost savings. This may be difficult to determine *a priori* but would be more likely when the potential for moral hazard is low. Finally, when changing a decision is politically difficult and unlikely to occur irrespective of any new evidence. This is more likely when the funding decision is driven by equity considerations, when alternative treatments are unavailable, or when the treatment targets a priority disease.

This paper has added to the current policy landscape aimed at utilizing real-world data to improve healthcare funding decisions (NICE 2022; Pratt et al. 2024). When translating RCT evidence to practice for healthcare funding decisions, more attention is needed on how providers and patients may respond to supply conditions in the local healthcare system. There is a wealth of existing economic research to draw upon that underscores the importance of supply conditions, insurance coverage, guidelines, and co-payments on healthcare use and outcomes (Arrow 1963; Brot-Goldberg et al. 2017; Card et al. 2008; Cutler and Zeckhauser 2000; Einav and Finkelstein 2018; Guthrie et al. 2016; Irving et al. 2020; Manning et al. 1987; Pauly 1968; Zeckhauser 1970; Zweifel and Manning 2000). Utilizing administrative and other health data, such as patient registries, can provide valuable insights into current behaviors, resource use, and outcomes. Similarly, stated preference research may also help to predict behaviors. Despite efforts to address this important source of uncertainty, there is likely to be an ongoing need for post-market comparative analyses to inform adjustments to the supply conditions or prices paid for new treatments. More research is needed to further develop and refine such methods, potentially building on the approaches pioneered in this paper.

Acknowledgments

The authors are grateful to Services Australia, Australian Government, for providing access to the data used in this paper. The findings and views in this paper are those of the authors and are not attributed to Services Australia. The authors would like to acknowledge general support provided by the Center for Health Economics, Monash University. Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

Ethics Statement

Monash University Human Research Ethics Committee granted ethics approval for this study (CF15/4240-2015001816).

Consent

The authors have nothing to report.

Conflicts of Interest

E.L. and G.C. have nothing to declare. P.G., D.P., and S.Z. report grants from the Australian Government, outside the submitted work.

Data Availability Statement

This paper uses administrative patient-level data owned by the Australian Government. The data are not publicly available because they contain confidential health records of Australian patients. Access to the data requires a formal application to Services Australia.

Endnotes

[1] The three RCTs were conducted at a similar time (enrollment from 2007 to 2010), and so each new treatment was compared to best supportive care (no life-extending treatment) in the second-line setting.

[2] The funding criteria excluded use in patients confined to bed and required patients to stop treatment at disease progression, but did not define explicit stopping criteria.

[3] No economic evidence was presented to support the more flexible use of the new treatments.

[4] Other exclusion criteria used in the RCTs (such as, ECOG status, expected survival > 6 months, and specific comorbidities) were not available in the administrative data.

[5] Linked data from the Pharmaceutical Benefits Scheme, the Medicare Benefits Schedule and the Australian Death Registry. Linkage to the Medicare Benefits Schedule was only available for 82% of patients in the sample who had at least one claim of chemotherapy administration. The failure to claim administration costs for subsidized chemotherapy is likely due to clerical oversight or some use in state-government outpatient clinics. We assume patients with complete

data are representative of the whole population and impute healthcare use on the Medicare Benefits Schedule for the 18% of patients with missing data.

[6] For our sample of prostate cancer patients, the dataset likely misses changes to behaviors related to hospitalizations at the end of life. We expect these behaviors would likely mirror the use of palliative chemotherapy.

[7] Changes in unobservable factors over time related to outcomes would also reduce the performance of our matching approach, as it may not be possible to match *untreated* patients to *untreated*-controls using outcomes when their outcomes are not similar. In this empirical example, we included a time variable in all regression models to test this assumption and found no evidence of either survival or resource use changing over time due to unobserved factors.

[8] Baseline characteristics included age, private patient, PBCI, prior GnRH, prior anti-androgen, prior long-acting opioid, prior chemotherapy, and treated in a private hospital.

[9] Our matching weights are based on patient characteristics and outcomes of *untreated* patients, but not on prior healthcare use.

[10] Chemotherapy administration is claimed as a separate cost category to chemotherapy treatments and it is not always clear what type of chemotherapy is linked to which administration cost. Therefore we include this as a separate category.

[11] Medicines and medical services in the dataset are classified by a unique item code specific to the medicine or type of service. Nearly all of the item codes (> 98%) in the dataset were common to both comparison groups, indicating few changes in the available healthcare over time. Most new items in the post-funding period either replaced deleted items or were direct substitutes with other items (i.e. same cost) in the pre-funding period. The main exception was a rarely used but high cost palliative medicine for bone pain related to prostate cancer (denosumab, funded in December 2011), which was available in the post-funding period but unavailable in the pre-funding period. For simplicity, we exclude costs for this treatment from the analysis given use does not impact on survival (the main clinical outcome).

[12] Given we only had access to administrative data, QALYs were estimated based on likely health states given their medication use.

[13] The Australian government routinely negotiates confidential special pricing arrangements and risk-sharing agreements for high cost pharmaceuticals, which obscure the unit price paid by government (Robertson et al. 2009).

[14] The committee considered that each treatment (vs. placebo) improved average survival by 0.36 life years (or 4.3 months) with an average utility weight of 0.77 for non-progressed disease (Australian Government 2011b, 2012; Sandblom et al. 2004). The incremental 0.27 QALYs estimated from the literature was therefore consistent with these statements, assuming that the majority of survival gain was spent without disease progression. In practice, if patients with more progressed disease were treated, more of the survival gains may have been spent in a worse health state.

[15] The base case analysis assumes no change in background or net costs, but the funding committee could have considered various factors that may have influenced costs or QALYs. For example, there may be a net cost in terms of routine care from improved survival or a net cost savings associated with a reduction in supportive treatments or delays to end of life care. A similar model in the United Kingdom included a weekly survival cost of £87 (approx. A$170) after progression but treatment was estimated to result in a net cost savings of £452 (approx. A$875) (Connock et al. 2011). The net direction of these factors is unclear, however, either alone or combined we expect their impact to be small and therefore not to affect the overall conclusions drawn in this case.

[16] Because the new treatments may have also displaced the use of palliative chemotherapy (see Supporting Information S1: Appendix Table A4), it is hard to distinguish between this and the role they had in delaying the "need" for palliative chemotherapy.

[17] Early stopping of docetaxel also likely reduced chemotherapy administration costs but this was more than offset by the administration costs related to the new chemotherapy.

[18] General practitioner visits did not display the same pattern, instead there was a stable use of general practitioner visits, suggesting a supporting role rather than active role in treatment decisions.

[19] The overall impact on chemotherapy administration costs was driven by a combination of reduced docetaxel use, use of the new chemotherapy, and delayed palliative chemotherapy.

[20] Ideally, such an analysis would have been planned in advance, such that data extraction and data cleaning issues had already been resolved, and the evidence could have been produced as quickly as possible to inform future decisions.

References

Ades, A. E., M. Sculpher, A. Sutton, et al. 2006. "Bayesian Methods for Evidence Synthesis in Cost-Effectiveness Analysis." *PharmacoEconomics* 24: 1–19. https://doi.org/10.2165/00019053-200624010-00001.

Arrow, K. 1963. "Uncertainty and the Welfare Economics of Medical Care." *American Economic Review* 53: 941–973.

Australian Cancer Network Management of Metastatic Prostate Cancer Working Party 2010. Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer.

Australian Government. 2011a. Public Summary Document. Abiraterone November 2011 Pharmaceutical Benefits Advisory Committee Meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2011-11/Abiraterone_ZYTIGA_Janssen_Cilag_PSD_2011-11_FINAL.pdf.

Australian Government. 2011b. Public Summary Document. Cabazitaxel July 2011 Pharmaceutical Benefits Advisory Committee Meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2011-07/Cabazitaxel_JEVTANA_Sanofi-aventis_PSD_5-5_2011-07_final.pdf.

Australian Government. 2012. Public Summary Document. Abiraterone November 2012 Pharmaceutical Benefits Advisory Committee Meeting. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2012-11/abiraterone.pdf.

Australian Government. 2013. Schedule of Pharmaceutical Benefits. August 2013. https://www.pbs.gov.au/publication/schedule/2013/08/2013-08-01-general-schedule.pdf.

Australian Government. 2014. Schedule of Pharmaceutical Benefits. December 2014. https://www.pbs.gov.au/publication/schedule/2014/12/2014-12-01-general-schedule.pdf.

Australian Government. 2016. Guidelines for Preparing a Submission to the Pharmaceutical Benefits Advisory Committee (Version 5.0).

Australian Institute of Health and Welfare. 2021. *Health System Expenditure on Cancer and Other Neoplasms in Australia, 2015–16*. Cancer series no. 131. Cat. no. CAN 142. AIHW.

Bahl, A., S. Masson, A. Birtle, S. Chowdhury, and J. de Bono. 2014. "Second-Line Treatment Options in Metastatic Castration-Resistant Prostate Cancer: A Comparison of Key Trials With Recently Approved Agents." *Cancer Treatment Reviews* 40, no. 1: 170–177. https://doi.org/10.1016/j.ctrv.2013.06.008.

Bencina, G., E. Petrova, D. Sönmez, S. M. Pereira, I. Dimitriadis, and S. Salomonsson. 2023. "HTA and Reimbursement Status of Metastatic Hormone-Sensitive Prostate Cancer, Non-Metastatic Castration-Resistant Prostate Cancer, and Metastatic Castration-Resistant Prostate Cancer Treatments in Europe: A Patient Access Landscape Review."

Journal of Health Economics and Outcomes Research 10, no. 1: 102. https://doi.org/10.36469/001c.75208.

Berger, M. L., H. Sox, R. J. Willke, et al. 2017. "Good Practices for Real-World Data Studies of Treatment And/or Comparative Effectiveness: Recommendations From the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making." *Value in Health* 20, no. 8: 1003–1008. https://doi.org/10.1016/j.jval.2017.08.3019.

Briggs, A. 2016. "A View From the Bridge: Health Economic Evaluation —A Value-Based Framework?" *Health Economics* 25, no. 12: 1499–1502. https://doi.org/10.1002/hec.3448.

Brot-Goldberg, Z. C., A. Chandra, B. R. Handel, and J. T. Kolstad. 2017. "What Does a Deductible Do? The Impact of Cost-Sharing on Health Care Prices, Quantities, and Spending Dynamics." *Quarterly Journal of Economics* 132, no. 3: 1261–1318. https://doi.org/10.1093/qje/qjx013.

Canadian Agency for Drugs and Technologies in Health 2017. Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition).

Card, D., C. Dobkin, and N. Maestas. 2008. "The Impact of Nearly Universal Insurance Coverage on Health Care Utilization: Evidence From Medicare." *American Economic Review* 98, no. 5: 2242–2258. https://doi.org/10.1257/aer.98.5.2242.

Chopra, S., and P. Rashid. 2015. "Management of Castration-Resistant (Advanced) Prostate Cancer (CRPC): Rationale, Progress and Future Directions." *Australian Family Physician* 44, no. 5: 302–305.

Cipriani, A., J. P. Ioannidis, P. M. Rothwell, et al. 2020. "Generating Comparative Evidence on New Drugs and Devices After Approval." *Lancet* 395, no. 10228: 998–1010. https://doi.org/10.1016/s0140-6736(19)33177-0.

Connock, M., E. Cummins, D. Shyangdan, B. Hall, A. Grove, and A. Clarke. 2011. Abiraterone Acetate for the Treatment of Metastatic, Castrate-Resistant Prostate Cancer Following Previous Cytotoxic Chemotherapy: A Single Technology Appraisal. Warwick Evidence.

Cookson, R., A. J. Mirelman, S. Griffin, et al. 2017. "Using Cost-Effectiveness Analysis to Address Health Equity Concerns." *Value in Health* 20, no. 2: 206–212. https://doi.org/10.1016/j.jval.2016.11.027.

Cutler, D. M., and R. J. Zeckhauser. 2000. "The Anatomy of Health Insurance." In *Handbook of Health Economics*, Vol. 1, 563–643. Elsevier. https://doi.org/10.1016/s1574-0064(00)80170-5.

De Bono, J. S., C. J. Logothetis, A. Molina, et al. 2011. "Abiraterone and Increased Survival in Metastatic Prostate Cancer." *New England Journal of Medicine* 364, no. 21: 1995–2005. https://doi.org/10.1056/nejmoa1014618.

De Bono, J. S., S. Oudard, M. Ozguroglu, et al. 2010. "Prednisone Plus Cabazitaxel or Mitoxantrone for Metastatic Castration-Resistant Prostate Cancer Progressing After Docetaxel Treatment: A Randomised Open-Label Trial." *Lancet* 376, no. 9747: 1147–1154. https://doi.org/10.1016/s0140-6736(10)61389-x.

Drummond, M. F., M. J. Sculpher, K. Claxton, G. L. Stoddart, and G. W. Torrance. 2015. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press.

Efron, B., and R. Tibshirani. 1994. *An Introduction to the Bootstrap*. Chapman & HallHall. CRC Monographs on Statistics & Applied Probability.

Einav, L., and A. Finkelstein. 2018. "Moral Hazard in Health Insurance: What We Know and How We Know It." *Journal of the European Economic Association* 16, no. 4: 957–982. https://doi.org/10.1093/jeea/jvy017.

ENCePP 2018. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on Methodological Standards in Pharmacoepidemiology (Revision 6). EMA/95098/2010. http://www.encepp.eu/standards_and_guidances.

Engels, F., A. Sparreboom, R. Mathot, and J. Verweij. 2005. "Potential for Improvement of Docetaxel-Based Chemotherapy: A Pharmacological Review." *British Journal of Cancer* 93, no. 2: 173–177. https://doi.org/10.1038/sj.bjc.6602698.

Facey, K. M., P. Rannanheimo, L. Batchelor, M. Borchardt, and J. de Cock. 2020. "Real-World Evidence to Support Payer/HTA Decisions About Highly Innovative Technologies in the EU—Actions for Stakeholders." *International Journal of Technology Assessment in Health Care* 36, no. 4: 459–468. https://doi.org/10.1017/s026646232000063x.

Ford, I., and J. Norrie. 2016. "Pragmatic Trials." *New England Journal of Medicine* 375, no. 5: 454–463. https://doi.org/10.1056/NEJMra1510059.

Fujimoto, N., M. Shiota, T. Kubo, and T. Matsumoto. 2010. "Novel Therapeutic Strategies Following Docetaxel-Based Chemotherapy in Castration-Resistant Prostate Cancer." *Expert Review of Clinical Pharmacology* 3, no. 6: 785–795. https://doi.org/10.1586/ecp.10.119.

Garrison Jr., L. P., P. J. Neumann, P. Erickson, D. Marshall, and C. D. Mullins. 2007. "Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-world Data Task Force Report." *Value in Health* 10, no. 5: 326–335. https://doi.org/10.1111/j.1524-4733.2007.00186.x.

Ghijben, P., D. Petrie, S. Zavarsek, G. Chen, and E. Lancsar. 2021. "Healthcare Funding Decisions and Real-World Benefits: Reducing Bias by Matching Untreated Patients." *PharmacoEconomics* 39, no. 7: 741–756. https://doi.org/10.1007/s40273-021-01020-x.

Gold, M. R. 1996. *Cost-Effectiveness in Health and Medicine*. Oxford University Press.

Guthrie, B., K. Kavanagh, C. Robertson, et al. 2016. "Data Feedback and Behavioural Change Intervention to Improve Primary Care Prescribing Safety (EFIPPS): Multicentre, Three Arm, Cluster Randomised Controlled Trial." *BMJ* 354: i4079. https://doi.org/10.1136/bmj.i4079.

Heidenreich, A., P. J. Bastian, J. Bellmunt, et al. 2014. "EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer." *European Urology* 65, no. 2: 467–479. https://doi.org/10.1016/j.eururo.2013.11.002.

Hernán, M. A., and J. M. Robins. 2016. "Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available." *American Journal of Epidemiology* 183, no. 8: 758–764. https://doi.org/10.1093/aje/kwv254.

Hernán, M. A., W. Wang, and D. E. Leaf. 2022. "Target Trial Emulation: A Framework for Causal Inference From Observational Data." *JAMA* 328, no. 24: 2446–2447.

Iacus, S. M., G. King, and G. Porro. 2012. "Causal Inference Without Balance Checking: Coarsened Exact Matching." *Political Analysis* 20, no. 1: 1–24. https://doi.org/10.1093/pan/mpr013.

Irving, A. H., A. Harris, D. Petrie, A. Higgins, J. Smith, and Z. K. McQuilten. 2020. "Impact of Patient Blood Management Guidelines on Blood Transfusions and Patient Outcomes During Cardiac Surgery." *Journal of Thoracic and Cardiovascular Surgery* 160, no. 2: 437–445.e420. https://doi.org/10.1016/j.jtcvs.2019.08.102.

Karnon, J. 2003. "Alternative Decision Modelling Techniques for the Evaluation of Health Care Technologies: Markov Processes Versus Discrete Event Simulation." *Health Economics* 12, no. 10: 837–848. https://doi.org/10.1002/hec.770.

Kemp-Casey, A., N. Pratt, E. Ramsay, and E. E. Roughead. 2019. "Using Post-Market Utilisation Analysis to Support Medicines Pricing Policy: An Australian Case Study of Aflibercept and Ranibizumab Use." *Applied Health Economics and Health Policy* 17, no. 3: 411–417. https://doi.org/10.1007/s40258-018-0440-4.

Kennedy-Martin, T., S. Curtis, D. Faries, S. Robinson, and J. Johnston. 2015. "A Literature Review on the Representativeness of Randomized Controlled Trial Samples and Implications for the External Validity of Trial Results." *Trials* 16: 1–14. https://doi.org/10.1186/s13063-015-1023-4.

Lin, D., E. Feuer, R. Etzioni, and Y. Wax. 1997. "Estimating Medical Costs From Incomplete Follow-Up Data." *Biometrics* 53, no. 2: 419–434. https://doi.org/10.2307/2533947.

Logothetis, C. J., E. Basch, A. Molina, et al. 2012. "Effect of Abiraterone Acetate and Prednisone Compared With Placebo and Prednisone on Pain Control and Skeletal-Related Events in Patients With Metastatic Castration-Resistant Prostate Cancer: Exploratory Analysis of Data From the COU-AA-301 Randomised Trial." *Lancet Oncology* 13, no. 12: 1210–1217. https://doi.org/10.1016/s1470-2045(12)70473-4.

Makady, A., A. van Veelen, P. Jonsson, et al. 2018. "Using Real-World Data in Health Technology Assessment (HTA) Practice: A Comparative Study of Five HTA Agencies." *PharmacoEconomics* 36, no. 3: 359–368. https://doi.org/10.1007/s40273-017-0596-z.

Manning, W. G., J. P. Newhouse, N. Duan, E. B. Keeler, and A. Leibowitz. 1987. "Health Insurance and the Demand for Medical Care: Evidence From a Randomized Experiment." *American Economic Review*: 251–277.

Maynard, A., and P. Kanavos. 2000. "Health Economics: An Evolving Paradigm." *Health Economics* 9, no. 3: 183–190. https://doi.org/10.1002/(sici)1099-1050(200004)9:3<183::aid-hec515>3.0.co;2-i.

National Institute for Health and Care Excellence 2022. NICE Health Technology Evaluations: The Manual.

NICE 2022. NICE Real-World Evidence Framework. https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837.

Park, J. C., and M. A. Eisenberger. 2015. "Advances in the Treatment of Metastatic Prostate Cancer." *Mayo Clinic Proceedings* 90, no. 12: 1719–1733. https://doi.org/10.1016/j.mayocp.2015.10.010.

Pauly, M. V. 1968. "The Economics of Moral Hazard: Comment." *American Economic Review* 58, no. 3: 531–537.

Perry-Duxbury, M., M. Asaria, J. Lomas, and P. van Baal. 2020. "Cured Today, Ill Tomorrow: A Method for Including Future Unrelated Medical Costs in Economic Evaluation in England and Wales." *Value in Health* 23, no. 8: 1027–1033. https://doi.org/10.1016/j.jval.2020.05.006.

Pratt, N., C. Vajdic, X. Camacho, N. Donnolley, and S. Pearson. 2024. Optimising the Availability and Use of Real World Data and Real World Evidence to Support Health Technology Assessment in Australia. https://www.health.gov.au/sites/default/files/2024-07/hta-policy-and-methods-review-optimising-the-availability-and-use-of-real-world-data-and-real-world-evidence-to-support-health-technology-assessment.pdf.

Raj, N., S. Fernandes, N. R. Charyulu, A. Dubey, G. S. Ravi, and S. Hebbar. 2019. "Postmarket Surveillance: A Review on Key Aspects and Measures on the Effective Functioning in the Context of the United Kingdom and Canada." *Therapeutic Advances in Drug Safety* 10: 2042098619865413. https://doi.org/10.1177/2042098619865413.

Reid, A. H., G. Attard, D. C. Danila, et al. 2010. "Significant and Sustained Antitumor Activity in Post-Docetaxel, Castration-Resistant Prostate Cancer With the CYP17 Inhibitor Abiraterone Acetate." *Journal of Clinical Oncology* 28, no. 9: 1489–1495. https://doi.org/10.1200/jco.2009.24.6819.

Robertson, J., E. J. Walkom, and D. A. Henry. 2009. "Transparency in Pricing Arrangements for Medicines Listed on the Australian Pharmaceutical Benefits Scheme." *Australian Health Review* 33, no. 2: 192–199. https://doi.org/10.1071/ah090192.

Sandblom, G., P. Carlsson, K. Sennfält, and E. Varenhorst. 2004. "A Population-Based Study of Pain and Quality of Life During the Year Before Death in Men With Prostate Cancer." *British Journal of Cancer* 90, no. 6: 1163–1168. https://doi.org/10.1038/sj.bjc.6601654.

Sarfati, D., J. Gurney, J. Stanley, B. T. Lim, and C. McSherry. 2014. "Development of a Pharmacy-Based Comorbidity Index for Patients With Cancer." *Medical Care* 52, no. 7: 586–593. https://doi.org/10.1097/mlr.0000000000000149.

Scher, H. I., K. Fizazi, F. Saad, et al. 2012. "Increased Survival With Enzalutamide in Prostate Cancer After Chemotherapy." *New England Journal of Medicine* 367, no. 13: 1187–1197. https://doi.org/10.1056/nejmoa1207506.

Schwartz, D., and J. Lellouch. 1967. "Explanatory and Pragmatic Attitudes in Therapeutical Trials." *Journal of Chronic Diseases* 20, no. 8: 637–648. https://doi.org/10.1016/0021-9681(67)90041-0.

Silverman, S. L. 2009. "From Randomized Controlled Trials to Observational Studies." *American Journal of Medicine* 122, no. 2: 114–120. https://doi.org/10.1016/j.amjmed.2008.09.030.

van Baal, P., D. Meltzer, and W. Brouwer. 2016. "Future Costs, Fixed Healthcare Budgets, and the Decision Rules of Cost-Effectiveness Analysis." *Health Economics* 25, no. 2: 237–248. https://doi.org/10.1002/hec.3138.

van Baal, P. H., A. Wong, L. C. Slobbe, J. J. Polder, W. B. Brouwer, and G. A. de Wit. 2011. "Standardizing the Inclusion of Indirect Medical Costs in Economic Evaluations." *PharmacoEconomics* 29, no. 3: 175–187. https://doi.org/10.2165/11586130-000000000-00000.

Wang, S., D. Gum, and T. Merlin. 2018. "Comparing the ICERs in Medicine Reimbursement Submissions to NICE and PBAC—Does the Presence of an Explicit Threshold Affect the ICER Proposed?" *Value in Health* 21, no. 8: 938–943. https://doi.org/10.1016/j.jval.2018.01.017.

Wilson, L., J. Tang, L. Zhong, et al. 2014. "New Therapeutic Options in Metastatic Castration-Resistant Prostate Cancer: Can Cost-Effectiveness Analysis Help in Treatment Decisions?" *Journal of Oncology Pharmacy Practice* 20, no. 6: 417–425. https://doi.org/10.1177/1078155213509505.

Zeckhauser, R. 1970. "Medical Insurance: A Case Study of the Tradeoff Between Risk Spreading and Appropriate Incentives." *Journal of Economic Theory* 2, no. 1: 10–26. https://doi.org/10.1016/0022-0531(70)90010-4.

Zweifel, P., and W. G. Manning. 2000. "Moral Hazard and Consumer Incentives in Health Care." In *Handbook of Health Economics*, Vol. 1, 409–459. Elsevier. https://doi.org/10.1016/s1574-0064(00)80167-5.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.