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HEALTH POLICY ANALYSIS

Patient Access to New Cancer Drugs in the United States and Australia

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ABSTRACT

Objectives: In light of the current debate on the use value and potential impact of comparative effectiveness research on patient access, it may prove insightful to compare a health-care system that systematically bases its reimbursement decisions on comparative effectiveness evidence with the United States (US) system that hitherto has only been informed by such evidence on an ad hoc basis. **Methods:** For a set of 2000–2009 approved new molecular entities and biologics indicated for cancer, we compared patient access between US Medicare and Australian Pharmaceutical Benefits Scheme (PBS) beneficiaries. Here, access is defined in terms of marketing availability, payer coverage, and patient out-of-pocket costs. **Results:** Although 34 drugs and biologics were approved for cancer in the US, just more than one-third (35%) were ultimately covered by the Australian PBS. The PBS also placed more restrictions on use. On the other hand, prices and patient out-of-pocket costs were greater for the US Medicare population. **Conclusion:** Our analysis points to a possible trade-off in market access to oncology drugs. Although more oncology drugs are available in the US and a higher percentage of available drugs are covered, the evidence-based approach adopted by Australia has contributed to reduced prices, thereby improving affordability for payers and patients for those medications deemed cost-effective by the reimbursement authority.

Keywords: United States, Australia, access to health care, pharmaceuticals, cancer.

Introduction

In the United States (US), patient access to costly new cancer drugs is of keen interest and concern to patients, physicians, payers, developers, and policymakers. Because many newly approved cancer drugs have high per-unit prices, licensing by the regulatory authority is not sufficient to ensure population-wide access. New cancer treatments have been a focal point in the ongoing public debate on the merits of costly treatments that are perceived as offering relatively modest benefits [1].

The US Congressional Budget Office has defined comparative effectiveness research (CER) as "a rigorous evaluation of the impact of different treatment options that are available for treating a given medical condition for a particular set of patients" [2]. The goal of CER is to provide decision makers—patients, physicians, and payers—with clinical evidence to support treatment and coverage decisions. With few exceptions, payers have been reluctant to explicitly assess the comparative (cost) effectiveness of drugs and make reimbursement decisions accordingly [3,4].

There appears to be consensus on the need for an improved evidence base through CER. The extent to which there is agreement on CER, however, seems to end here. There is no consensus regarding what kind of impact CER should have on treatment and coverage decisions. This normative debate pits two opposing camps on either side of the philosophical divide. On the one hand, some maintain that treatment and coverage decisions, particularly with regard to expensive drugs, should be subject to explicit cost-effectiveness considerations, including the use of thresholds, because this presumably constitutes a rational way to contain cost growth [5]. Others, however, resist this notion, arguing that such thresholds are an ineffective way to contain costs. Further, they see thresholds as an impediment to innovation [6].

To inform the CER debate, we examined the Australian reimbursement decision-making process, which makes its resource allocation decisions explicit and evidence based. In this study, we compare patient access to newly approved cancer medications in the US and Australia. Broadly, our goals in this article are to 1) compare the Australian method of priority setting, which has built up an extensive evidence base and systematically uses CER evidence to guide treatment and coverage decisions, to the US system that until now gathers and implements CER evidence on an ad hoc basis and 2) examine the impact that systematic use of CER appears to have on patient access to cancer drugs approved from 2000 through 2009 in the US and Australia.

We recognize the inherent challenge of comparing different health-care systems. In all international comparisons, including the one presented here, one should continually be mindful of the political, social, and economic forces that shape policy outcomes. For example, the US and Australian health-care systems differ substantially in terms of regulatory processes and government involvement. Nonetheless, macro-level comparisons with respect to multiple health policy questions are conducted by researchers

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all the time to examine relative strengths and weaknesses of vastly different health-care systems [7–10].

US Health Technology Assessment (HTA) and reimbursement

We assume that the reader is familiar with the general contours of the US system. Suffice it to say, the US system reflects a great diversity of pricing and reimbursement mechanisms, in both the private and public sectors. Each US payer uses its own method for evaluating newly approved biopharmaceuticals, some with more evidence-based methods than others. Although many now appear to use cost-effectiveness in their formulary decisions, evidence suggests that it remains a secondary criterion at best [11]. Furthermore, public payers (i.e., Medicare and Medicaid) are legislatively barred from considering cost or cost-effectiveness [12]. Overall, until now, HTA has remained largely an academic exercise, with little impact on payer decisions, particularly at the national level [3]. Lack of systematization and standardization, widespread differences in organizational structure, a myriad of state and federal laws, and market competition all contribute to significant variation in payer policies, which, in turn, lead to variable levels of patient access.

Australian HTA and reimbursement

Health care in Australia is largely a public system [13,14]. The federal government operates a comprehensive national prescription drug reimbursement program known as the Pharmaceutical Benefits Scheme (PBS). Prescription drug coverage is provided to all residents and visitors through the PBS, which accounts for approximately 80% of all prescriptions [15,16]. In recent years, spending in Australia on cancer drugs has grown significantly. Since 2000, growth in expenditures on antineoplastic and immunomodulating agents has averaged over 20% annually [17].

A sponsor seeking PBS listing for a newly developed product must first obtain marketing approval from the Therapeutic Goods Administration (TGA), the Australian analogue to the US Food and Drug Administration (FDA). Once the product is registered, the sponsor must submit an application for funding consideration to the Pharmaceutical Benefit Advisory Committee (PBAC), an independent body tasked with making recommendations to the Health Minister about whether a drug should be reimbursed by the PBS. In making its recommendations, the PBAC considers several factors, including clinical need and comparative cost-effectiveness. There is a strong preference for randomized, controlled clinical trials that directly compare a newly approved drug to a comparator. Here, the choice of an existing treatment to which the new drug will be compared is critical. The most prescribed analogue used for the same indication is usually preferred. For example, if the drug is in a new pharmacological class, the drug most prescribed in the PBS for the same indication is the comparator. Alternatively, if no currently listed drug is available, the main comparator is usually standard nondrug treatment [16].

The PBAC does not adhere to fixed cost-effectiveness thresholds. Rather, a drug's cost-effectiveness is considered in combination with other factors, such as availability of alternative therapies, disease severity, and projected budget impact. For example, a higher cost-effectiveness ratio could be acceptable when the drug is indicated for a life-threatening condition, when there are no alternative therapies available, or when a rare disease is involved, in which case, the financial consequences of prescribing and reimbursing the drug for all eligible patients are limited.

Under the PBS, products fall into four categories as recommended by the PBAC: unrestricted, restricted, authority required, and denied coverage. Unrestricted means all TGA-approved indications are reimbursed. When evidence fails to show adequate cost-effectiveness or there are issues raised on other grounds, such as a high degree of uncertainty regarding cost-effectiveness or budget impact, a drug may be listed as restricted or authority required [15]. Restricted listings are generally limited to particular therapeutic uses, populations (e.g., pediatrics), or clinical settings. Drugs tagged with authority required are restricted to specific therapeutic uses and require previous PBS approval, which can be contingent on specific initiation rules, such as diagnostic tests or evidence of response (or lack thereof) to previous treatments [18]. In some cases, there are also criteria placed on the conditions for which continuation of an authority-required treatment is justified. In addition, listings may be subject to quantity limits depending on the indication.

Finally, the PBAC can reject a drug outright or defer issuing a final recommendation on a drug. A refusal to recommend effectively denies listing in the PBS, although sponsors can have applications reconsidered if new evidence is provided [9]. Deferrals require sponsors to clarify or provide additional data or information before the PBAC is able to make a fully informed recommendation.

If a positive recommendation is given, the decision is passed on to the Pharmaceutical Benefit Pricing Authority (PBPA). Similar to PBAC, the PBPA provides guidance to the Minister of Health and Ageing, specifically with respect to the price of drugs. In negotiating prices with the manufacturer, the PBPA explicitly considers clinical and cost-effectiveness. In this respect, pricing is partly value based; that is, it is adjusted in accordance with a drug's cost-effectiveness ratio. In addition, the PBPA considers prices of alternative brands and similar products in the relevant therapeutic group and expected use [16].

The final decision to list a drug in the PBS is made by the Minister of Health based on the recommendations from the PBAC and PBPA. Products not receiving a positive recommendation from the PBAC cannot be approved by the Minister. For drugs expected to affect the health or pharmaceutical budget by more than $10 million, the decision must be made at the cabinet level. All drugs receiving final approval by the Minister are published in a publicly available formulary called the Schedule of Pharmaceutical Benefits (hereafter referred to as Schedule of Benefits). The Schedule of Benefits serves as a positive list, meaning only listed products are subsidized.

Prescriptions under the PBS in Australia are subject to out-of-pocket cost sharing via fixed copayments per prescription. For general beneficiaries, the maximum amount is AU$33.30 (US$31.00), whereas other concessional beneficiaries (pensioners, seniors, the poor) are subject to a maximum of AU$5.40 (US$5.03). To limit out-of-pocket costs for general and concessional beneficiaries and their families, there is also a safety net threshold of AU$1281.30 (US$1192.89) and AU$324.00 (US$301.64). Once out-of-pocket costs reach these amounts in a calendar year, beneficiaries are able to apply for reduced copayments through the Safety Net Entitlement. Under this scheme, copayments are reduced to a maximum of AU$5.40 for general beneficiaries and eliminated for concessional beneficiaries.

Drugs approved by the TGA, but not subsidized by the PBS, are also available to beneficiaries through the private market, which represents approximately 11% of all prescriptions dispensed annually. Prices are not subject to PBS pricing mechanisms [19]. Costs for these drugs are either paid out-of-pocket by the patient or through private health insurance.

Methods

Our study examines access to medicines by insured individuals. We are aware of the special issues confronting the uninsured, but they are beyond the scope of this study. Recognizing "access" as a multidimensional concept, we operationalize it to include three subdimensions: market availability, including regulatory approval and time to reimbursement; insurer coverage and conditions of reimbursement; and patient out-of-pocket costs [6]. To conduct a like-with-like comparison, we strictly considered publicly insured beneficiaries in both countries. The US population that we looked at was Medicare beneficiaries. Our decision to examine Medicare

beneficiary access is a practical one for the following reasons. First, Medicare covers 56% of cancer patients in the US [20]. Second, Medicare Parts B and D drug coverage data sets are publicly available and nationally representative. Third, Medicare coverage policies often drive coverage decisions for private payers [21].

Availability

We began by identifying all therapeutic new molecular entities (NMEs) and biologics approved by the US FDA between 2000 and 2009 for cancer indications [22]. Chemotherapeutic agents and hormonal treatments were excluded. Subsequently, we searched the Australian Register of Therapeutic Goods (ARTG) for each US approved product using the active ingredient and brand name as search terms [23]. The ARTG is an online database containing all products approved by the TGA. Although many of these medicines have been approved for more than one indication, we only used the initial indication approved by the US FDA for our analysis.

Prices

Because our focus is on Medicare, our comparison looked at those prices used in Medicare Parts B and D in addition to a commonly used reference price (average wholesale price [AWP]), although we acknowledge that there are other sets of prices in the US that vary from these three [24]:

- AWP [25]. Often referred to as the "sticker price," these are the manufacturer-suggested prices that wholesalers charge pharmacies and other retailers. Although not directly used in determining prices in Medicare, it is nonetheless a widely used, albeit imperfect, benchmark for prescription drug prices [24].
- Average sales price (ASP) [26]. The ASP reflects the average sales price charged by manufacturers to all private purchasers inclusive of rebates and other discounts. Medicare Part B pays the ASP plus 6% for drugs administered by a physician in an outpatient setting. These prices, from April 2010, apply to 10 of the drugs included on the final list.
- Medicare Part D [27]. Prescription drug plans (PDPs) providing prescription drug coverage to seniors through Medicare Part D report to the Centers for Medicare and Medicaid Services (CMS) the prices of prescription drugs paid to retail pharmacies. Because prices vary by PDP, we included the lowest published retail pharmacy price among the top 10 PDPs in terms of lives covered in 2008 offering plans in Massachusetts [28]. Prices are from April 30, 2010, and comprise only products that are self-administered.

Australian prices were extracted from the May 2010 edition of the Schedule of Benefits published by the Department of Health and Ageing [29]. We converted all prices to US dollars using the April 30, 2010, mid-market rate (AU$1.000 = US$0.931) and the 2005 Organisation for Economic Co-operation and Development gross domestic product purchasing power parity benchmark (US = 1.0, AU = 1.39) [30,31].

We compared prices between countries on a price-per-dose basis. These were calculated according to the largest dose strength and corresponding package size available in both countries.

Coverage

For the purpose of comparing coverage of oncology drugs, we only considered the subset of products licensed in both countries.

The Medicare Part B drug benefit is administered by regional Medicare contractors, which do not subject Part B drugs to a formulary per se. This said, carriers at the regional level may tag certain Part B drugs with local coverage determinations (LCDs) as well as related policy articles. At the national level, the CMS may assign a national coverage determination to a Medicare Part B drug. Therefore, to fully evaluate coverage of Medicare Part B drugs, we searched the CMS coverage database, which contains a searchable archive of active Medicare carriers and Part B administrative contractors (MACs) that issue coverage determinations that specify the conditions under which a product or service is deemed "reasonable and necessary" for coverage [32].

For each drug, we used the brand and generic names (e.g., imatinib mesylate and Gleevec) as keywords to search the database. We counted each uniquely numbered LCD issued by carriers and Part B MACs. In some cases, contractors issued a single, broadly defined LCD and related policy articles that refined coverage for an individual product or service. We found six instances of this in the database and counted each as a single LCD. All LCDs were examined for specific coverage restrictions such as indication restrictions, quantity limits, and step therapy.

Part D coverage was assessed by examining formulary placement, cost sharing, and coverage restrictions with respect to each drug by the top 10 PDPs. Seven of the formularies that we examined were those with the highest Medicare beneficiary enrollment: a three-tier formulary, augmented by a fourth specialty tier used primarily for biotechnology or injectable drugs that often cost more than $500 per month per member. Two of the remaining three formularies had three tiers, whereas the other had five. Information for eight PDPs was obtained from the Medicare Prescription Drug Plan finder in the zip code 02111 (Boston, Massachusetts). The remaining two PDPs were not offered in Massachusetts, in which case, formularies were accessed directly from each plan's Web site.

We used the Schedule of Benefits and the PBS Web site to examine coverage, cost sharing, and reimbursement restrictions in Australia. Regarding the latter, we documented the number and types of rules governing the initiation and/or continuation of use of each drug.

We also calculated delays between regulatory approval and reimbursement in Australia. Here, two periods together comprise the total time from TGA approval to reimbursement. First, we calculated the number of months between TGA approval and the PBAC recommendation. Based on its assessment, the PBAC can either recommend, refuse to recommend, or defer a decision on a drug. Thus, we examined past PBAC recommendations to determine the date that a drug was recommended for the first indication approved by the US FDA [33]. The second period that we measured was the time between PBAC recommendation and listing in the PBS. Here, we used previous editions of the PBS to locate the date that a drug was first listed for the comparison indication.

For the US, we examined potential delays in full reimbursement, as a result of a lag between US FDA approval and final billing and reimbursement code determination. There often is a delay between US FDA approval and assignment of a definitive Health Care Procedure Coding System J code to each drug [34]. Such codes facilitate and ensure proper billing and payment.

Once a drug is approved by the US FDA, the CMS must decide whether a programmatic need exists to justify establishing a code. No specific timeframe exists between marketing approval and definitive coding. Delays between approval and reimbursement coding usually do not lead to an actual delay in reimbursement. This is because during the phase when a specific reimbursement code is not available, carriers typically use a nonspecific temporary code for billing and reimbursement purposes. This said, temporary coding can lead to confusion on the part of providers, for example, with respect to the size and number of vials reimbursed or the fact that multiple drugs may be assigned the same code.

Results

Availability

Between 2000 and 2009, the US FDA approved 34 NMEs and biologics for the treatment of cancer. Of these, 19 (56%) were approved by

Table 1 – Oncology NMEs approved in the United States and Australia.

Drug name (brand)	USFDA approval	TGA approval
Arsenic trioxide (Trisenox)	9/25/2000	5/13/2009
Imatinib mesylate (Gleevec)	5/10/2001	8/13/2001
Oxaliplatin (Eloxatin)	8/9/2002	2/27/2001
Fulvestrant (Faslodex)	4/25/2002	3/6/2006
Gefitinib (Iressa)	5/5/2003	4/28/2003
Bortezomib (Velcade)	5/13/2003	2/14/2006
Pemetrexed (Alimta)	2/4/2004	6/30/2004
Erlotinib (Tarceva)	11/18/2004	1/30/2006
Sorafenib (Nexavar)	12/20/2005	9/27/2006
Dasatinib (Sprycel)	6/28/2006	1/15/2007
Sunitinib (Sutent)	1/26/2006	9/14/2006
Nilotinib (Tasigna)	10/29/2007	1/17/2008
Temsirolimus (Torisel)	5/30/2007	6/4/2008
Lapatinib (Tykerb)	3/13/2007	6/28/2007
Alemtuzumab (Campath)	5/7/2001	5/10/2006
Bevacizumab (Avastin)	2/26/2004	2/24/2005
Cetuximab (Erbitux)	2/12/2004	9/25/2007
Panitumumab (Vectibix)	9/27/2006	5/14/2008
Everolimus (Afinitor)	3/30/2009	6/8/2009

NMEs, new molecular entities; TGA, Therapeutic Goods Administration; USFDA, U.S. Food and Drug Administration.

the Australian TGA. Table 1 displays these 19 products and their corresponding dates of approval. A full list of all US FDA approvals is provided in the Supplemental Materials found at doi:10.1016/j.val.2011.05.004.

Price

Table 2 shows a comparison of US and Australian prices for the 19 products licensed in both countries. Overall, intra-US prices varied widely, with the AWP being the highest for most drugs. For four drugs, Part D prices were the same or slightly higher than the AWP. On average, the AWP was higher than the ASP and Part D by 11% and 3%, respectively.

On average, Australian prices were lower than US prices: 36%, 41%, and 24% lower than AWP, ASP, and Part D, respectively. Only one drug—gefitinib—was priced higher in Australia, in fact, 54% higher than the average US price. The greatest price differential was observed with oxaliplatin, where the price was 79% lower in Australia compared with the AWP. Here, the large difference is likely accounted for by the availability in Australia of several generic alternatives listed in the PBS alongside the branded version.

Coverage

A comparison of coverage differences between countries, broken down by percentage of drugs covered, level of cost sharing, and coverage restrictions, is given in Table 3. Due to the split in coverage between Medicare Parts B and D, we distinguish coverage between the 10 physician-administered and 9 self-administered drugs.

In Australia, the PBS listed 12 (63%) of the 19 TGA-approved NMEs and biologics targeting cancer in the Schedule of Benefits for the indications examined; five were physician and seven were self administered. All 12 listed products were designated as authority required. Of these, six had initiation requirements placed on them that were more restrictive than the TGA labeling, whereas nine were assigned continuation rules based on proof of treatment response. Furthermore, seven required step therapy, and bevacizumab was the only drug not subject to quantity limits. Patient

Table 2 – Price comparisons for oncology NMEs in the United States and Australia.

Drug generic name (brand name)	Dose size	Package size	United States ($USD)			Australia PBS		AU ($US PPP)/US price ratio		
			AWP	ASP+6%	Part D	$US	$US PPP	PBS/AWP	PBS/ASP	PBS/Part D
Arsenic trioxide (Trisenox)	1 mg/ml	10 × 10-ml ampules	43.58	39.69	—	37.52	29.01	0.666	0.731	—
Imatinib mesylate (Gleevec)	400-mg tablets	30 tablets	144.68	—	144.26	121.56	93.97	0.650	—	0.651
Oxaliplatin (Eloxatin)	5 mg/ml	40-ml vial	115.69	72.40	—	31.28	24.18	0.209	0.334	—
Fulvestrant (Faslodex)	50-mg/ml	5-ml syringe	192.66	174.31	—	—	—	—	—	—
Geftinib (Iressa)	250-mg tablets	30 tablets	68.08	—	58.91	119.47	92.36	1.357	—	1.568
Bortezomib (Velcade)	3.5-mg/vial	1 vial	1468.20	1418.70	—	1629.18	1259.42	0.858	0.888	—
Pemetrexed (Alimta)	500-mg/vial	1 vial	2890.26	2683.39	—	1583.40	1224.04	0.424	0.456	—
Erlotinib (Tarceva)	150-mg tablet	30 tablets	145.82	—	139.04	102.67	79.37	0.544	—	0.571
Sorafenib (Nexavar)	200-mg tablets	120 tablets	56.33	—	57.60	—	—	—	—	—
Dasatinib (Sprycel)	70-mg tablets	60 tablets	120.45	—	120.31	100.27	77.52	0.644	—	0.644
Sunitinib (Sutent)	50-mg capsules	28 capsules	305.47	—	282.64	229.25	177.22	0.580	—	0.627
Nilotinib (Tasigna)	200-mg capsules	112 capsules	67.54	—	68.62	45.62	35.27	0.522	—	0.514
Temsirolimus (Torisel)	30 mg/kit	1 kit	1410.89	1320.50	—	—	—	—	—	—
Lapatinib (Tykerb)	250-mg tablets	150 tablets	25.04	—	24.56	22.52	17.41	0.695	—	0.709
Alemtuzumab (Campath)	30 mg/ml	3 × 1-mL vials	1982.70	1838.07	—	—	—	—	—	—
Bevacizumab (Avastin)	25 mg/ml	16-ml vial	171.88	152.43	—	108.56	83.92	0.488	0.551	—
Cetuximab (Erbitux)	2 mg/ml	100-ml vial	11.52	10.54	—	—	—	—	—	—
Panitumumab (Vectibix)	20 mg/ml	20-ml vial	203.70	184.93	—	—	—	—	—	—
Everolimus (Afinitor)	10-mg tablets	28 tablets	—	—	214.11	—	—	—	—	—

ASP, average sales price; AWP, average wholesale price; NMEs, new molecular entities; PBS, Pharmaceutical Benefits Scheme; PPP, purchasing power parity.

Table 3 – Coverage, cost sharing, and coverage restrictions of cancer drugs in the United States and Australia.

	% Covered	Cost sharing*	Coverage restrictions, %		
			PA	QL	ST
Physician administered (n = 10)					
US	100	20%	0	0	0
Australia	50	US$31.00	100	90	0
Self-administered (n = 9)					
US	93	25%-50%	70	41	4
Australia	78	US$31.00	100	100	78

PA, prior authorization; QL, quantity limits; ST, step therapy; US, United States.
* Per prescription.

cost sharing ranged from zero for concessional beneficiaries to a maximum of AU$33.30 per prescription.

For the US Medicare population, no Part B drugs were denied coverage. There was, however, a total of 22 LCDs and policy articles issued for nine of the 10 drugs. Of these, two referred to policies on uses related to nononcologic indications. The remaining 20 LCDs clarified the types of on- and off-label indications covered by the carrier or MAC. The CMS issued one national coverage determination that applies to all Medicare Part B carriers and contactors granting coverage of oxaliplatin, cetuximab, and bevacizumab and related treatment costs for certain off-label indications among patients enrolled in CMS-identified clinical trials.

Within Medicare Part D, the PDPs covered 93% of the drugs. Eight of the nine drugs were listed on the highest cost-sharing tier for all 10 plans. The remaining drug, gefitinib, was denied coverage by six plans. Among the four plans that included it in the formulary, three placed it in the highest cost-sharing tier. Only two PDPs required step therapy, applying it to two drugs. All 10 plans required prior authorization for at least one drug, with eight plans requiring prior authorization for at least six drugs. Six plans tagged at least one product with quantity limits.

Co-insurance was the sole method of cost sharing for both Part B and Part D drugs. A 20% co-insurance was applied to all physician-administered (Part B) drugs [35]. Percentages ranged between 25% and 50% regardless of tier placement for self-administered drugs (Part D). In both instances, the combination of high prices and rates of co-insurance translates into significant out-of-pocket costs. To illustrate, a 50% co-insurance rate on the lowest published Part D PDP 30-day prescription price for imatinib mesylate (~US$4328) implies an out-of-pocket cost to the patient of US$2164. In addition, there were differences in Parts B and D in terms of maximum out-of-pocket costs. Although these are not capped for Part B beneficiaries, out-of-pocket costs for Part D enrollees are set according to the thresholds outlined by the defined standard benefit. In 2009, the standard benefit included a US$295 deductible, followed by co-insurance of 25% up to the initial coverage limit of $896.25 in annual out-of-pocket costs ($2700 in total expenses). After the initial coverage limit was reached, 100% of costs were paid by the beneficiary (the so-called donut hole) until the catastrophic threshold was reached at $4350 ($6153.75 in total expenses), at which point, a co-insurance rate of 5% was applied [36]. Subsidies are also available on a sliding income scale to low-income individuals, including those who qualify for Medicaid (i.e., dual eligibles). In some instances, benefits provided to low-income beneficiaries in Part B may eliminate all cost sharing, whereas Part D enrollees may have their cost sharing waived or be subject to substantially reduced copayments of between $1.10 and $6.00 per prescription per month.

In Table 4, we show that the institutional requirements to gain PBS listing in Australia can result in substantial delays. For some drugs, the time between TGA approval and PBAC recommendation was the most significant cause of delays in access. Although the average was 15.8 months, there was a wide range across the sample. Imatinib mesylate was recommended just 1 month after approval, whereas decisions on pemetrexed and bevacizumab took as long as 43 months. There were several reasons for such long delays. Some, such as that for bevacizumab, were the result of companies postponing application to the PBAC. In this case, the drug was approved by the TGA in February 2005, but did not receive its first decision from the PBAC (refusal to recommend) until March 2008. On the other hand, some drugs had difficulty in securing recommendation despite promptly submitted applications. For example, pemetrexed received a deferral from the PBAC just 5 months after approval. However, until its recommendation in November 2007, it was issued two refusals.

After PBAC recommendation, the delay in PBS listing was shorter, averaging 5.3 months. The total time between TGA approval and PBS listing varied greatly, with fewer than 12 months elapsing for four drugs, two drugs having a 1- to 2-year lag, and three drugs with a more than 3-year delay. Overall, the average total delay between regulatory approval and PBS listing was 23.8 months. There was a total of seven drugs that had yet to be recommended by the PBAC despite TGA approval. Five of these had been submitted for review but were denied listing and the other two had yet to be submitted. Finally, two drugs obtained listing in the Schedule of Benefits for indications other than those included in our analysis.

In the US, there was an average interval of 16.3 months between US FDA approval and coding for Medicare Part B drugs. This is not to say that there was an actual delay in market access after US FDA approval. Rather, before the assignment of a permanent J code, the CMS assigns a less specific temporary code. Although this allows billing and reimbursement of the drug over the interim, there can be a lack of clarity on what is being reimbursed (i.e., specific doses), which may result in uneven uptake during this period.

Discussion

We assessed patient access to newly approved oncology drugs in the US and Australia in terms of marketing availability, coverage, and patient out-of-pocket costs. These drugs represent a special case, mainly because of their high cost, but also the general perception that many only offer modest benefits. This poses a challenge to payers worldwide, public and private, who need to balance patient access and cost containment.

A stated goal of the Australian PBS is to "provide timely access to the medicines that Australians need, at a cost individuals and the community can afford" [37]. Our analysis suggests mixed results. Prices and beneficiary out-of-pocket costs are lower. The maximum copayment of AU$33.30 under the PBS averages to just 1% of the PBS listed price. The safety net for general and concessional beneficiaries alike further limits total out-of-pocket costs for beneficiaries. This contrasts sharply with the US where co-insurance rates per treatment cycle or prescription for enrollees not qualifying for a low-income subsidy are as high as 50%, and maximum out-of-pocket costs can potentially exceed US$4350 annually. On the other hand, the "fourth hurdle" in Australia is restricting product availability and coverage, in addition to prolonging the time between regulatory approval and reimbursement. Taking into account the fact that the TGA approved less than 60% of the NMEs and biologics between 2000 and 2009 compared to the US and the PBS covered just more than 60% of TGA-approved prod-

Table 4 – Time delay between regulatory approval and reimbursement.

Drug generic name (brand name)	US medicare part B		Australia PBS			Delay (mo)			
	USFDA approval	HCPCS J code added	TGA approval	Recommended by PBAC	PBS listing	Total US	Aus TGA approval to PBAC rec.	Aus PBAC recommendation for PBS listing	Total Aus
Arsenic trioxide (Trisenox)	9/25/2000	11/1/2002	2/6/2009	3/1/2009	8/1/2009	16	1	5	6
Imatinib mesylate (Gleevec)	5/10/2001	—	8/13/2001	9/1/2001	—*	—	1	—	—
Oxaliplatin (Eloxatin)	8/9/2002	1/1/2004	2/27/2001	6/1/2001	—*	17	4	—	—
Fulvestrant (Faslodex)	4/25/2002	1/1/2004	3/6/2006	—†	—	21	—	—	—
Gefitinib (Iressa)	5/5/2003	—	4/28/2003	7/1/2004	12/1/2004	—	15	5	20
Bortezomib (Velcade)	5/13/2003	1/1/2005	2/14/2006	7/1/2007	11/1/2007	20	17	4	21
Pemetrexed (Alimta)	2/4/2004	1/1/2005	6/30/2004	11/1/2007	1/1/2008	11	41	2	43
Erlotinib (Tarceva)	11/18/2004	—	1/30/2006	3/1/2008	8/1/2008	—	26	5	31
Sorafenib (Nexavar)	12/20/2005	—	9/27/2006	—‡	—†	—	—	—	—
Dasatinib (Sprycel)	6/28/2006	—	1/15/2007	3/1/2007	8/1/2007	—	2	5	7
Sunitinib (Sutent)	1/26/2006	—	9/14/2006	7/1/2009	12/1/2009	—	34	5	39
Nilotinib (Tasigna)	10/29/2007	—	1/17/2008	3/1/2008	8/1/2008	—	2	5	7
Temsirolimus (Torisel)	5/30/2007	1/1/2009	6/4/2008	—‡	—	20	—	—	—
Lapatinib (Tykerb)	3/13/2007	—	6/28/2007	12/1/2007	5/1/2008	—	6	5	11
Alemtuzumab (Campath)	5/7/2001	1/1/2009	5/10/2006	—†	—	20	—	—	—
Bevacizumab (Avastin)	2/26/2004	1/1/2005	2/24/2005	7/1/2008	7/1/2009	11	41	12	53
Cetuximab (Erbitux)	2/12/2004	1/1/2005	9/25/2007	—‡	—§	11	—	—	—
Panitumumab (Vectibix)	9/27/2006	1/1/2008	5/14/2008	—‡	—	16	—	—	—
Everolimus (Afinitor)	3/30/2009	—	6/08/2009	—‡	—	—	—	—	—

Aus, Australia; HCPCS, Health Care Procedure Coding System; TGA, Therapeutic Good Administration; PBAC, PBS, Pharmaceutical Benefits Scheme; US, United States; USFDA, U.S. Food and Drug Administration.

* Unable to verify listing date due to unavailability of PBS editions before August 2003.

† Drug has not been reviewed by the PBAC.

‡ PBAC recommendation has been refused for the initial FDA-approved indication.

§ Listed in Schedule of Benefits for indications not included in the analysis.

ucts, a little more than one-third (35%) of USFDA-approved drugs attained PBS coverage, after an average delay of more than 23 months.

It has been suggested that the PBS operates as a means of purchasing outcomes [15]. Although this statement would require corroborative evidence to be validated, it underscores that final determinations about price, copayment level, and restrictions on coverage reflect the intent on the part of the Australian reimbursement authority to institute a systematic, transparent, outcomes-based approach to optimizing clinical and cost-effectiveness given a fixed set of health-care resources.

By contrast, drug reimbursement decisions in the US appear less evidence and outcomes based and not necessarily guided by clinical (and cost) effectiveness considerations [38]. Perhaps this has contributed to relatively few limits on oncology drug coverage in the US. Indeed, at least for the Medicare population, there is a high percentage of covered oncology drugs. Although less stringent evidence-based reimbursement criteria account for a relatively high percentage of covered drugs, numerous legal requirements also play a role. For physician-administered drugs, Medicare Part B carriers/MACs are required by law to include cancer drugs that have received what is described as a "medically accepted indication." This is often interpreted liberally to include uses approved by the US FDA as well as off-label uses reported in peer-reviewed journals and officially recognized compendia [39]. For self-administered Part D oncology drugs, the CMS protected drug class regulations apply; that is, Part D plans must include on their formularies "all or substantially all" USFDA-approved drugs in the antineoplastics class.

Because information on product submissions and denials for market authorization was unavailable, one aspect of market availability that remains unknown is why less than 60% of the drugs in our data set were approved by the TGA. Similar to the USFDA, the TGA is mandated to assess safety, efficacy, and quality at standards equal to those of comparable countries [40]. Therefore, stringency of regulatory approval can more or less be ruled out as a factor. However, it could be that sponsor companies are unwilling to market certain products in Australia, knowing the hurdles that they face post-approval to obtain coverage by the PBS. In this respect, the PBAC may act as a deterrent to submissions for marketing authorization, although hard evidence is inconclusive [9].

The key barriers to access in Australia appear to be marketing availability and coverage, whereas the key barrier to access in the US is patient out-of-pocket costs, i.e., ability to pay. Our results raise the question of whether speedier access to virtually all new cancer treatments in the US at the expense of higher prices and patient out-of-pocket costs is justified in terms of outcomes.

Early work suggests the Australia system has been able to operate with lower prices [41] and limits on access without compromising health outcomes [42,43]. The most recent data available from the 1990s and early 2000s indicates comparable survival for breast, colon, and prostate cancer for patients in the US and Australia [43]. Of course, there is much uncertainty about the precise role access to cancer drugs plays in determining survival. Clearly, survival outcomes are a function of other factors as well, such as early detection. Although beyond the scope of this study, future research could begin to examine the influence that each of these factors has on patient-level outcomes.

Of note are differences in coverage of off-label uses, mentioned previously. Off-label prescribing is common in the US. According to a report published by the National Comprehensive Cancer Network, 50% to 75% of all uses of anticancer drugs in the US are off-label [44]. Furthermore, the number of medically accepted off-label uses for some oncology therapeutics outnumbers those that are approved [45]. Coverage under Medicare Part B is statutorily defined in Section 1861 (t)(1) and (2) of the Social Security Act, so long as the use is deemed "medically accepted," i.e., listed in officially recognized compendia or supported in the peer-reviewed literature. Additionally, 39 states require payment for off-label uses of USFDA approved drugs by Employment Retirement Security Act plans.

Detailed evidence is unavailable regarding the prescribing of off-label oncology drugs in Australia. The PBAC has not established formal policies, although the automatic use of prior authorization for all covered products as well as PBAC's authority to track physician prescribing and request justification for prescriptions made outside PBS restrictions suggests the unapproved use of oncology drugs is strongly discouraged [46].

Such restrictions may impede access to certain beneficial off-label uses of cancer drugs. In the US, although payers commonly impose coverage restrictions, few actually exclude off-label reimbursement, and many practitioners view off-label prescribing as an important avenue for advancing clinical practice [47]. Given that many cancer drugs have evidence to support their off-label use, strict limitations to only approved indications may deny access to important treatment alternatives.

In the US, some politicians and policymakers have expressed concern that explicit use of comparative (cost) effectiveness may impede patient access by reducing therapeutic options [48,49]. There is also ambivalence among patients and providers about explicit priority setting. The fear exists that by circumscribing prescribing decisions, CER would trump patient preferences and physician autonomy. The current method of seemingly "muddling through elegantly" [50], however, appears incapable of striking a fiscally sustainable balance between cost and access, particularly with respect to cancer drugs. Like Australia, spending on cancer treatments in the US continues to grow at double-digit rates, which has led to a squeezing of payer and patient budgets [51]. This is having an immediate impact on who gets treated and who does not. To illustrate, a recent survey of medical oncologists indicates that aggregate drug spending and patient out-of-pocket expenses are influencing prescribing decisions, which leads to haphazard resource allocation decisions and concomitant inequities across the population of cancer patients [52]. In the absence of establishing a systematic evidence base for the coverage decision-making process, the patchwork of current decision tools may prove inadequate for controlling costs, improving outcomes, and reducing inequities.

Should the US decide to embark on a path toward more systematic use of CER, there are formidable challenges inherent to the US system that will need to be addressed, among which are

- Payer fragmentation: The diffuse system of public and private payers and differences in the size and scope of benefits provided (e.g., medical vs. pharmacy benefits) will likely make the uptake of comparative (cost) effectiveness evidence segmented and uneven.
- Existing evidence base: The existing evidence base used by policymakers is primarily generated by randomized, controlled trials (RCTs), often fraught with methodological issues and limitations [53,54].

To address payer fragmentation, there is room for building a more systematic and better coordinated infrastructure for sharing evidence in the US. The immediate goal should not necessarily be to eliminate disparities in payer coverage policies or erect new barriers to access, but instead encourage a more informed process of decision making by closing the gap between what we know and what we do in pharmaceutical care. Accordingly, CER could assist in this effort, for instance, by establishing a clearinghouse for systematic reviews conducted by multiple evidence-based practice centers, each uniquely suited to different constituencies [55].

Integral to this endeavor will be augmenting the existing evidence base by incorporating multiple methods of research, including observational studies. RCTs are designed to evaluate which

intervention works best within a carefully controlled sample and setting against a placebo. Observational studies, on the other hand, examine more complex care settings and include broad or vulnerable patient populations over a longer follow-up period. This underscores the intent of CER: to identify which interventions work best in typical patient-care settings for a wide range of patients.

Recent federal efforts to stimulate CER, including $1.1 billion allocated by the American Recovery and Reinvestment Act and the Patient-Centered Outcomes Research Institute established under the Health Care and Education Reconciliation Act, may usher in a more systematic means of collecting and disseminating research findings on drugs' clinical (and cost) effectiveness. As a result, this may lead to a more evidence-based system of resource allocation. Given the importance that Americans generally attach to pluralism and choice, however, such an evidence-based system would have to be tailored to meet local circumstances and preferences. This, in turn, implies that variation in prescribing patterns as well as differences in terms of payer reimbursement would persist.

Conclusion

In neither Australia nor the US do all patients who might benefit from cancer drugs necessarily have access to them. This is because no health-care system can provide every medical intervention that offers benefits to everyone. Hence, every system must confront the question of how and on what basis to deny potentially beneficial care to some people, at least some of the time.

The Australian system makes reimbursement decisions using an explicitly evidence-based approach, whereas evidence in the US is used on an ad hoc basis. The key barriers to access in Australia are marketing availability and coverage, whereas the key barrier to access in the US is patient out-of-pocket costs, i.e., ability to pay. Our analysis points to a possible trade-off in market access to oncology drugs. Although more oncology drugs are available in the US and a higher percentage of those drugs are covered, the evidence-based approach adopted by Australia is associated with lower prices, thereby improving affordability for payers and patients for those medications deemed cost-effective by the reimbursement authority.

Given that the number of expensive cancer drugs with modest benefits is increasing, reimbursement will continue to be a key challenge for decision makers in all health-care systems. On this point, while keeping in mind significant philosophical differences between health-care systems, policymakers may be well served by cautiously drawing lessons from the experiences, both positive and negative, of systems that have already integrated economic evaluations into decision making [42]. In the case of Australia, for example, the use of CER has not been universally accepted because it has resulted in restrictions in access that have generated considerable controversy [56]. Nonetheless, the PBS is able to make hard choices regarding cancer drug reimbursement, balancing multiple, sometimes competing, objectives such as efficient priority setting and equitable distribution of resources, without compromising overall survival outcomes.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi:10.1016/j.val.2011.05.004, or if hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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