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International variability in the reimbursement of cancer drugs by publically funded drug programs

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ABSTRACT

Purpose

Evaluate inter-country variability in the reimbursement of publically funded cancer drugs, and identify factors such as cost containment measures that may contribute to variability.

Methods

As of February 28, 2010, licensed indications for 10 cancer drugs (bevacizumab, bortezomib, cetuximab, erlotinib, imatinib, pemetrexed, rituximab, sorafenib, sunitinib, and trastuzumab) were obtained from the drug registries of 6 licensing authorities corresponding to 13 countries or regions: Australia, Canada (Ontario), England, Finland, France, Italy, Germany, Japan, New Zealand, the Netherlands, Scotland, Sweden, and the United States (Medicare Parts B and D). Number of licensed indications reimbursed by public payers and the use of cost containment measures were obtained by survey of health authorities involved in reimbursement and through public documents.

Results

The 48 identified licensed indications varied between agencies (range: 36–44 indications). Finland, France, Germany, Sweden, and the United States reimbursed the highest percentage of indications (range: 90%–100%). Canada (54%), Australia (46%), Scotland (40%), England (38%), and New Zealand (25%) reimbursed the least. All 5 countries with the lowest rate of reimbursement incorporated a cost-effectiveness analysis into reimbursement decisions and rejected submissions for reimbursement mainly because of lack of cost effectiveness; in New Zealand, lack of cost effectiveness was the second leading cause of rejection after excessive cost. In 9 countries, risk-sharing agreements were used to contain costs. Indications initially not recommended for reimbursement (9 in Australia, 5 in Canada, and 3 in England, New Zealand, and Scotland) were subsequently approved with risk-sharing agreements or special pricing arrangements.

Conclusions

Reimbursement of publically funded cancer drugs varies globally. The cause is multifactorial.

KEY WORDS

Reimbursement, cancer, drugs, risk-sharing agreements

1. INTRODUCTION

Expenditures on cancer drugs are rising globally. Costs are expected to grow because cancer rates are rising [1], cancer drug costs are typically higher than average drug costs [2], and cancer drugs represent a high percentage of drugs in development [3].

Many countries fund cancer drugs through public reimbursement programs. Such funding facilitates equal access for citizens by eliminating direct costs to patients. The rising costs of cancer drugs have forced many countries to implement mechanisms to offset costs. Those mechanisms may compromise access to cancer drugs and lead to inter-country variation in use and reimbursement [4,5]. Increasingly, the value of a drug is being considered, and funding might be denied or limited if there are concerns that funding the drug may reduce available resources to fund aspects of health care other than cancer or to make other types of expenditures altogether. Cost-effectiveness analysis (CEA), an economic analysis that relates health gains attributed to a drug to the net cost associated with that drug's use, is being applied by several public payers to guide reimbursement decisions [6–8].

Cancer drugs are specialized medicines that have narrow licensed indications, often particular to any one or a combination of tumour site, chemotherapy regimen, and sequence of treatment. Public payers

typically limit reimbursement to those narrow indications. As costs rise, countries have opted to control utilization by restricting off-label use or limiting reimbursement to subpopulations with the greatest benefit as determined by CEA.

Public payers have also started to negotiate risk-sharing agreements (RSAS) or special pricing arrangements (SPAS) with pharmaceutical companies in an effort to control costs [9]. Price–volume agreements, rebates, volume caps, price caps, schemes involving free drug, and outcome-based payments are all forms of RSAS. The number of RSAS has grown recently, likely because of patient, physician, and pharmaceutical company pressure on governments to fund costly new treatments. However, the impact of such agreements on reimbursement has not been fully assessed.

The objective of the present study was to evaluate inter-country variability in access to cancer drugs by reviewing the number of indications reimbursed by public drug programs for 10 cancer drugs and by identifying factors that lead to variation, including the use of cost-containment mechanisms.

2. METHODS

2.1 Countries and Drugs

For this study, we selected 12 countries or regions that have both universal health care and a national or regional public drug reimbursement program that covers most drug costs. The United States was included for comparison, although Medicare is a social insurance program that is not universal and is responsible for only 20%–30% of overall drug costs [7,10]. Thus, the following 13 countries were included: Australia, Canada (Ontario), England, Finland, France, Italy, Germany, Japan, New Zealand, the Netherlands, Scotland, Sweden, and the United States (Medicare Parts B and D). In Canada, reimbursement of drugs is a responsibility of each province and territory; Ontario, Canada's most populated province, was therefore included in the present study. England and Scotland were assessed independently because they make their own funding recommendations [11].

To ensure coverage of a variety of tumour sites, mechanisms of action, and routes of administration, 10 cancer drugs licensed after 1995 were selected: bevacizumab, bortezomib, cetuximab, erlotinib, imatinib, pemetrexed, rituximab, sorafenib, sunitinib, and trastuzumab.

2.2 Licensed Indications

In the present work, the term "licensing" is used to describe granting of marketing authorization. The number of licensed indications for the 10 selected cancer drugs as of February 28, 2010, were obtained from drug product registries of the following licensing authorities of the 13 countries studied: the Therapeutic Goods Administration (Australia); Health Canada (Ontario); the European Medicines Agency (EMEA); the Ministry of Health, Labour and Welfare (Japan); the Medicines and Medical Devices Safety Authority (New Zealand); and the Food and Drug Administration (United States) [12–17]. If a licensed indication had since been broadened or restricted, the up-to-date indication was included. Indications approved for diseases other than cancer were excluded, as were uses of imatinib for rare conditions (hypereosinophilic syndrome, dermatofibrosarcoma protuberans, chronic eosinophilic leukemia, and aggressive systemic mastocytosis). Off-label use was defined as a drug prescribed for a use or in a manner not licensed by authorities.

2.3 Reimbursed Indications

A survey was sent directly to health authorities that make funding decisions for cancer drugs (Table I). The survey asked about the indications reimbursed as of February 28, 2010, for the 10 cancer drugs and about the role of CEA and negotiations with pharmaceutical companies in reimbursement decisions. In certain cases in which information obtained from the survey was insufficient, follow-up with the health authorities and a review of public documents, including published pharmaceutical lists, were conducted [16,18–25].

For Australia, England, France, Germany, Italy, Japan, New Zealand, the Netherlands, and Scotland, indications reimbursed were obtained from national bodies that make funding decisions for both oral and intravenous cancer drugs. In Canada, data for oral drugs were obtained from the Ontario Drug Benefit Plan and the Exceptional Access Program; for intravenous drugs, data were obtained through Cancer Care Ontario's New Drug Funding Program [21–23]. In Sweden, the Dental and Pharmaceutical Benefits Board (Tandvårds-och läkemedelsförmånsverket, TLV) makes listing decisions for oral cancer drugs on the National Reimbursement System and occasionally for intravenous cancer drugs [7,26]. Swedish data were obtained from the TLV and from hospitals if the indication had not been reviewed by the TLV. Data for oral drugs in Finland were obtained through the Social Insurance Institution of Finland and, for intravenous drugs, from hospitals [7,26]. When using hospital data for Sweden and Finland, an indication was listed as reimbursed if it was funded by 1 or more hospitals. Medicare Part B and Part D were included for the United States.

2.4 Reimbursement Decisions

Reasons for advisory committees not recommending reimbursement, and factors that led to subsequent approval were further studied in 5 countries with the least number of indications reimbursed. Data were

TABLE I Global health authorities involved in reimbursement decisions for cancer drugs

Country	*Regulatory bodies*
Australia	Medicare Australia, in consultation with Pharmaceutical Benefits Advisory Committee
Canada	Ministry of Health and Long-Term Care, in consultation with the Committee to Evaluate Drugs (CED) and the Cancer Care Ontario CED subcommittee
England	National Health Service–England (NHS England), in consultation with the National Institute for Health and Clinical Excellence (NICE)
Finland	Social Insurance Institution (Kansaneläkelaitos)
France	French National Authority for Health (Haute Autorité de Santé), in consultation with the Transparency Commission
Germany	Federal Ministry of Health (Bundesministerium fuer Gesundheit), in consultation with the Joint Federal Committee (Gemeinsamer Bundesausschuss) and Institute for Quality and Economic Efficiency in Health Care (Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen)
Italy	National Health Service of Italy (Servizio Sanitario Nazionale), in consultation with Italian Medcines Agency (Agenzia Italiana del Farmaco)
Japan	The Ministry of Health, Labour and Welfare, in consultation with the Central Social Insurance Medical Council (Chuikyo)
Netherlands	Health Care Insurance Board (College voor Zorgverzekeringen), in consultation with Dutch Healthcare Authority (Nederlandse Zorgautoriteit)
New Zealand	Pharmaceutical Management Agency of New Zealand, in consultation with the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Cancer Treatments Subcommittee of PTAC
Scotland	National Health Service–Scotland (NHS Scotland), in consultation with Scottish Medicines Consortium
Sweden	Dental and Pharmaceutical Benefits Agency (Tandvårds-och läkemedelsförmånsverket)
United States	Medicare Part B (intravenous cancer drugs) and Medicare Part D (oral cancer drugs)

obtained directly from meeting minutes and from published documents of current advisory committees (Table I) [27–31]. Submissions reviewed by past advisory committees were excluded.

Cost effectiveness, excessive cost, or uncertain clinical benefit were deemed to have been the cause for not recommending reimbursement if those reasons were stated in public documents. Definitions of cost effectiveness and excessive cost were country-specific and were not standardized [32]. If advisory committees stated that approval was granted only if the drug price were to be lowered, a rejection because of excessive cost was listed.

2.5 Negotiations with Pharmaceutical Companies

Health authorities were questioned about unique methods used for purchasing the 10 cancer drugs, including RSAs and SPAs. For the United States and Japan, this information was obtained from published documents [9,33]. Risk-sharing agreements were defined as agreements between public payers and pharmaceutical companies to diminish the impact on the payer's budget brought about by either or both of uncertainty about the value of the medicine or the need to work within finite budgets [9]. Collectively, these RSAs included price–volume agreements, volume or dose caps, price caps, schemes involving free drug, rebates, or outcome-based payments (Table II). To prevent disclosure of confidential agreements, countries often used the term SPAs, which collectively included RSAs and price reductions.

3. RESULTS

3.1 Licensed and Reimbursed Indications

For the 10 selected drugs, we identified 48 licensed indications in total (Table III). Europe's EMEA had approved 44 indications; New Zealand, 44; Australia, 44; the United States, 40; Canada, 40; and Japan, 36.

Finland, Sweden, and the United States reimbursed 100% both of the total indications and of indications approved by their respective licensing authorities (Figures 1 and 2). Germany reimbursed 92% of the total indications ($n = 44$), which consisted of all licensed EMEA indications. France reimbursed 90% ($n = 43$), and Italy, 88% ($n = 42$) of the total indications, and those countries respectively reimbursed 95% and 91% of the licensed EMEA indications. The Netherlands reimbursed 77% ($n = 37$) of the total indications and 84% of EMEA-licensed indications.

TABLE II Definitions of risk-sharing agreements

	Risk-sharing scheme	*Definition*
Financial-based agreements		
a.	Price–volume agreements (also called budget-impact schemes)	Third-party payer and pharmaceutical manufacturer agree on a price based on a forecast volume of sales. If the actual sales volume exceeds the forecast, the price of the pharmaceutical may be revised downwards, or the manufacturer may be asked to pay a rebate.
b.	Price-capping	Third-party payer and pharmaceutical manufacturer agree on maximum monies spent for a drug per patient. Pharmaceutical manufacturer pays for the drug beyond this agreed amount.
c.	Volume- or dose-capping	Third-party payer and pharmaceutical manufacturer agree on a maximum number of cycles of treatment or dose of drug reimbursed per patient. Pharmaceutical manufacturer pays for the drug beyond this agreed amount.
d.	Free drug or discounts	Pharmaceutical manufacturers agree to provide free drug or discounts on the drug for a period of time to third-party payers.
e.	Rebates	The pharmaceutical manufacturer offers a rebate to third-party payers for the cost of increased expenditure over set annual subsidization caps or thresholds.
Performance- or outcome-based agreements		
		Pharmaceutical manufacturer refunds agreed monies, provides free drug, or agrees to a price reduction if a desired health outcome is not reached.

Japan reimbursed 75% (n = 36) of the total indications, which was 100% of its licensed indications.

The 5 countries that reimbursed the fewest of the total indications were Canada at 54% (n = 26), Australia at 46% (n = 22), Scotland at 40% (n = 19), England at 38% (n = 18), and New Zealand at 25% (n = 12). Reimbursement in Australia included the uses of trastuzumab in advanced breast cancer, which were not listed on the Pharmaceutical Benefits Scheme but rather were funded through Medicare Australia's Herceptin Program [34].

In Germany and Japan, licensing appeared to be the limiting step to cancer drug access, because reimbursement is generally predicated by licensing, and off-label indications are not reimbursed [7,33,35]. Licensing approval facilitated access in Germany, because the EMEA approved 44 of the 48 total identified licensed indications. On the other hand, access in Japan was limited by licensing approval. Japan had the least number of licensed indications, which resulted in reimbursement for only 75% of the total indications.

Licensing approval of additional indications after marketing authorization of a drug did not appear to affect reimbursement in Finland, Sweden, and the United States because off-label use was permitted. Medicare plans in the United States reimburse indications that are off-label when the evidence is sufficient to support that use [24,25]. In Sweden, bortezomib and trastuzumab were approved for reimbursement on the National Reimbursement System for use at the discretion of treating medical oncologists, illustrating their ability to prescribe for off-label indications. Also, in both Finland and Sweden, off-label indications for intravenous cancer drugs were reimbursed by hospitals if included in the hospital's practice-based guidelines created by medical oncologists. Consequently, reimbursement varied by the individual cancer centre. For example, the off-label indication of bevacizumab for the treatment of glioblastoma had variable coverage in Finnish and Swedish hospitals.

3.2 Cost Effectiveness, Cost, Submissions

Of the 13 countries studied, 8 (Australia, Canada, England, Italy, the Netherlands, New Zealand, Scotland, and Sweden) factored a CEA into reimbursement decisions for cancer drugs.

The 5 countries with the fewest number of indications reimbursed (Australia, Canada, England, New Zealand, and Scotland) implemented a CEA into reimbursement decisions for cancer drugs. The leading reason for a non-recommendation of reimbursement by the current advisory committees in most of those countries was that the drug was deemed not cost-effective. New Zealand was an exception, with the main reason being that the drug had an excessive cost (Figure 3). In all 5 countries, 52%–74% of initial submissions for reimbursement were not recommended. However, many drugs were subsequently recommended for reimbursement, with a final approval rate of 46%–74% for all indications reviewed (Figure 4). In New Zealand, pharmaceutical companies submitted the fewest indications for consideration of reimbursement, with 26 submissions (Figure 4). Those 26 included the indications reviewed by PHARMAC (the entity that manages the pharmaceutical schedule on behalf of the Health Funding Authority) and a list of cancer drugs in use before 2002 that were termed "the cancer basket" [36].

TABLE III Indications approved by licensing authorities as of February 28, 2010, for 10 cancer drugs

Drug	*Indication*	*Agency and jurisdiction*					
		TGA (Australia)	*HC (Canada)*	*EMEA (Europe)*	*MHLW (Japan)*	*Medsafe (N.Z.)*	*FDA (U.S.A.)*
Bevacizumab							
a.	Metastatic colorectal cancer: 1st line with fluoropyrimidine-based chemotherapy	√	√	√	√	√	√
b.	Metastatic colorectal cancer: 2nd line with fluoropyrimidine-based chemotherapy	√		√	√	√	√
c.	Metastatic colorectal cancer: 3rd line with fluoropyrimidine-based chemotherapy	√		√	√	√	
d.	Metastatic breast cancer: 1st line in with paclitaxel or docetaxel	√	√	√		√	√
e.	Non-squamous metastatic non-small-cell lung cancer: 1st line with platinum chemotherapy	√	√	√	√	√	√
f.	Glioblastoma multiforme: 2nd line as monotherapy	√				√	√
g.	Metastatic renal cell carcinoma: 1st line with interferon alfa	√		√		√	√
Bortezomib							
a.	Multiple myeloma: 1st line with melphalan and prednisone in patients not eligible for stem-cell transplantation	√	√	√		√	√
b.	Multiple myeloma: 2nd line as monotherapy	√	√	√	√	√	√
c.	Multiple myeloma: 3rd line as monotherapy	√	√	√	√	√	√
d.	Mantle cell lymphoma: 2nd line as monotherapy		√				√
Cetuximab							
a.	Metastatic colorectal cancer, EGFR-expressing: 1st line with chemotherapy	√		√	√	√	
b.	Metastatic colorectal cancer, EGFR-expressing: 2nd line with chemotherapy	√	√	√	√	√	√
c.	Metastatic colorectal cancer, EGFR-expressing: 3rd line with chemotherapy	√	√	√		√	√
d.	Metastatic colorectal cancer, EGFR-expressing: after irinotecan, or intolerant to irinotecan and oxaliplatin as monotherapy	√	√	√	√	√	√
e.	Locally advanced head-and-neck cancer: 1st line with radiotherapy	√	√	√	√	√	√
f.	Metastatic head-and-neck cancer: with cisplatin	√		√	√	√	√
Erlotinib							
a.	Metastatic or locally advanced metastatic non-small-cell lung cancer: 2nd line as monotherapy	√	√	√	√	√	√
b.	Metastatic or locally advanced metastatic non-small-cell lung cancer: 3rd line as monotherapy	√	√	√		√	√
c.	Metastatic pancreatic cancer: with gemcitabine	√		√		√	√
Imatinib							
a.	Chronic myelogenous leukemia (chronic, accelerated, blast), Ph+: 1st line	√	√	√	√	√	√
b.	Acute lymphoblastic leukemia, Ph+: 1st line monotherapy or with chemotherapy	√	√	√	√	√	
c.	Acute lymphoblastic leukemia, Ph+: after relapse as monotherapy	√	√	√	√	√	√
d.	Myelodysplastic syndrome, with *PDGFR* gene rearrangements	√	√	√		√	√
e.	Unresectable or metastatic gastrointestinal stromal tumour, c-Kit (Cd117)–positive	√	√	√	√	√	√
f.	Resected gastrointestinal stromal tumour, c-Kit (CD117)–positive, high risk of relapse: adjuvant	√	√	√	√	√	√

TABLE III Continued.

Drug	*Indication*	*Agency and jurisdiction*					
		TGA (Australia)	*HC (Canada)*	*EMEA (Europe)*	*MHLW (Japan)*	*Medsafe (N.Z.)*	*FDA (U.S.A.)*
Pemetrexed							
a.	Non-squamous metastatic or locally advanced non-small-cell lung cancer: 1st line with cisplatin	√	√	√	√	√	√
b.	Non-squamous metastatic or locally advanced non-small-cell lung cancer: 2nd line as monotherapy	√	√	√	√	√	√
c.	Pleural mesothelioma: 1st line with cisplatin	√	√	√	√	√	√
Rituximab							
a.	Follicular lymphoma, CD20-positive: 1st line with chemotherapy	√	√	√	√	√	√
b.	Follicular lymphoma, CD20-positive: 2nd line as monotherapy	√	√	√	√	√	√
c.	Follicular lymphoma, CD20-positive: maintenance therapy after response to chemotherapy	√	√	√		√	√
d.	Diffuse large B-cell lymphoma, CD20-positive: with CHOP chemotherapy	√	√	√	√	√	√
e.	Chronic lymphocytic lymphoma: with chemotherapy	√	√	√		√	√
Sorafenib							
a.	Unresectable hepatocellular carcinoma	√	√	√	√	√	√
b.	Metastatic renal cell carcinoma: 1st line if unsuitable for or intolerant to cytokine therapy	√	√	√	√	√	√
c.	Metastatic renal cell carcinoma: 2nd line after failure of cytokine therapy	√	√	√	√	√	√
Sunitinib							
a.	Metastatic renal cell carcinoma: 1st line	√	√	√	√	√	√
b.	Metastatic renal cell carcinoma: 2nd line	√	√	√	√	√	√
c.	Unresectable or metastatic gastrointestinal stromal tumour: 2nd line after imatinib	√	√	√	√	√	√
Trastuzumab							
a.	Metastatic breast cancer, HER2-positive: 3rd line monotherapy	√	√	√	√	√	√
b.	Metastatic breast cancer, HER2-positive: 1st line with paclitaxel	√	√	√	√	√	√
c.	Metastatic breast cancer, HER2-positive: 1st line with docetaxel	√	√	√	√	√	
d.	Metastatic breast cancer, HER2-positive: with vinorelbine		√		√		
e.	Metastatic breast cancer, HER2-positive: with aromatase inhibitors	√	√	√	√	√	
f.	Metastatic breast cancer, HER2-positive: with capecitabine		√		√		
g.	Metastatic gastric or gastroesophageal junction, HER2-positive: 1st line with cisplatin and capecitabine or 5-fluorouracil			√			
h.	Early breast cancer, HER2-positive: adjuvant	√	√	√	√	√	√

TGA = Therapeutic Goods Administration; HC = Health Canada; EMEA = European Medicines Agency; MHLW = Ministry of Health, Labour and Welfare; Medsafe = Medicines and Medical Devices Safety Authority; FDA = Food and Drug Administration; EGFR = epidermal growth factor receptor; Ph+ = Philadelphia chromosome–positive; PDGFR = platelet-derived growth factor receptor; CHOP = cyclophosphamide–doxorubicin–vincristine–prednisone; HER2 = human epidermal growth factor receptor 2.

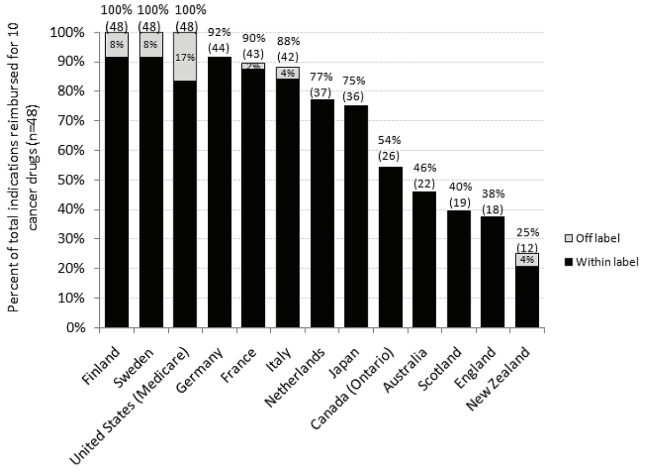

*FIGURE 1 Percentage of all licensed indications (*n *= 48) reimbursed for 10 cancer drugs as of February 28, 2010.*

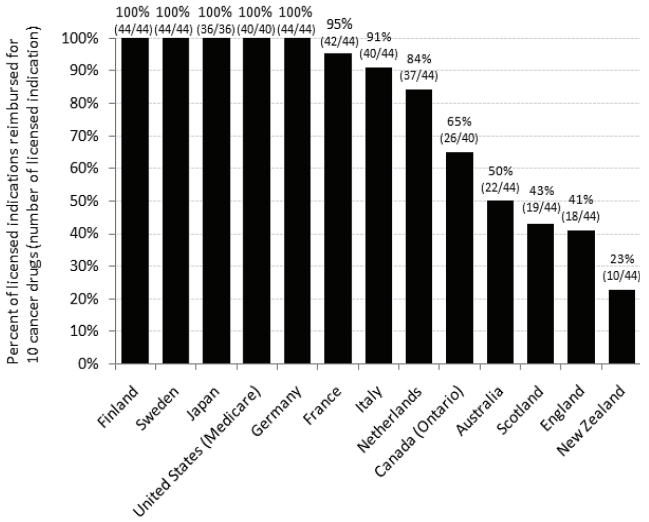

FIGURE 2 Percentage of indications licensed by local agencies [European Medicines Agency, n *= 44; U.S. Food and Drug Administration,* n *= 40; Health Canada,* n *= 40; Medsafe (N.Z. Medicines and Medical Devices Safety Authority),* n *= 44; Ministry of Health, Labour and Welfare (Japan),* n *= 36; and Therapeutic Goods Administration (Australia),* n *= 44] reimbursed for 10 cancer drugs as of February 28, 2010.*

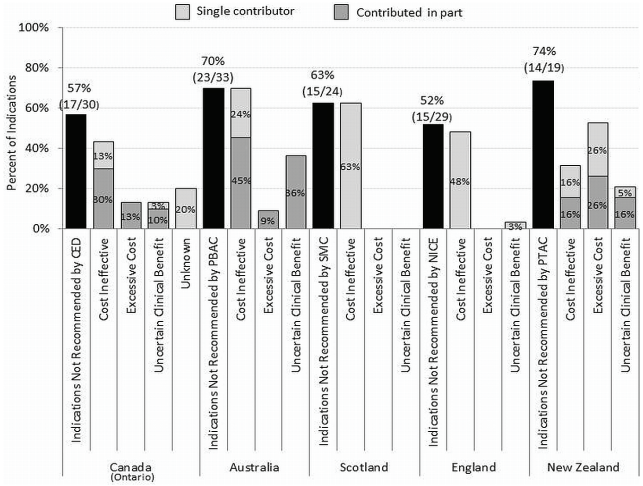

FIGURE 3 Number of indications reviewed and not recommended for reimbursement by current advisory committees for 10 cancer drugs as of February 28, 2010, and factors contributing to the indication not being recommended. CED = Committee to Evaluate Drugs (Ontario, Canada); PBAC = Pharmaceutical Benefits Advisory Committee (Australia); SMC = Scottish Medicines Consortium (Scotland); NICE = U.K. National Institute for Health and Clinical Excellence (England); PTAC = Pharmacology and Therapeutics Advisory Committee (New Zealand).

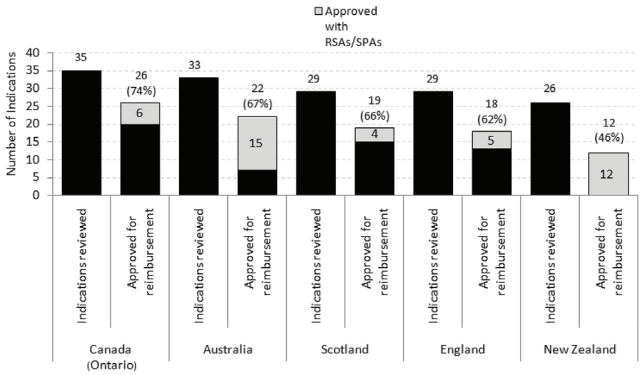

FIGURE 4 Number of indications for 10 cancer drugs submitted by pharmaceutical companies to public payers for consideration of reimbursement as of February 28, 2010, and the approval rates for those indications with and without risk-sharing agreements (RSAs) or special pricing arrangements (SPAs).

Of the 5 countries with the broadest number of indications reimbursed, 4 (Finland, France, Germany, and the United States) did not use CEA in their decisions to reimburse cancer drugs. Japan also did not use CEA, and although it did not rank in the top 5 countries, Japan did reimburse 100% of its own country's licensed indications. Alternative methods used to control drugs costs in Finland, France, and Germany were price cuts and pricing controls [7,37].

3.3 RSAs and SPAs

Of the 13 studied countries, 9 had implemented RSAs for at least 1 of the cancer drugs studied; Finland, Germany, Japan, and the Netherlands had not. Publically known RSAs or SPAs applied to varying numbers of funded indications (Figure 4): in New Zealand, 12 of 12 (100%); in Australia, 15 of 22 (68%); in England, 5 of 18 (28%); in Ontario (Canada), 6 of 26 (23%); and in Scotland, 4 of 19 (21%). In Canada, 5 indications and, in each of Australia, England, New Zealand, and Scotland, 3 indications that were not initially recommended for reimbursement—in part because of lack of cost-effectiveness or because of excessive cost—were then subsequently approved with RSAs or SPAs. In Australia, 6 additional indications were approved with RSAs or SPAs in conjunction with restrictions on the population eligible for the drug or after provision of additional clinical data.

4. DISCUSSION

To our knowledge, the present study is the first to document international variability in access to cancer drugs, measured by the number of licensed indications reimbursed by public payers. Our findings indicate that Finland, France, Germany, Sweden, and the U.S. Medicare program have the broadest access to publically funded cancer drugs. A recent report commissioned by the Department of Health in the United Kingdom documented variability in access to new cancer drugs across 14 countries based on usage data derived from sales by IMS Health Incorporated (Danbury, CT, U.S.A.) [5]. In that study, France, Germany, and the United States were also among the 5 countries with the most access, and Australia, the United Kingdom, Canada, and New Zealand were among those with the lowest access. As expected, those results are similar to our findings, given that drug use generally increases with reimbursement [11,38].

According to our results, the factors that affected the number of indications reimbursed in a country were

- number of indications licensed,
- off-label regulations,
- use of CEA and how stringently it is applied,
- the number of indications submitted for consideration of reimbursement by pharmaceutical companies, and
- whether countries negotiate RSAS or SPAS (or both) with pharmaceutical companies.

4.1 Cost Effectiveness and Cost

A number of concerns have been identified by the public and physicians about the implementation of CEA in reimbursement decisions, including lack of transparency, post-regulatory agencies taking a restrictive view with respect to endpoints used to show efficacy, and a lack of standardization of cost-effectiveness thresholds between and within health care systems [32]. The World Health Organization has attempted to standardize cost-effectiveness thresholds and to relate them to a country's gross domestic product [39].

We identified 8 countries that implement CEA into the review process for cancer drug reimbursement, but in Sweden, Italy, and the Netherlands, CEA had little impact on reimbursement decisions for the 10 cancer drugs studied. Sweden's TLV does not have a defined threshold to the CEA and is willing to accept higher thresholds for patient groups with initial low quality of life or life expectancy, such as those with cancer [8,40,41]. Thus, disease severity appeared to be an overriding variable. However, regions within Sweden can subsequently restrict use based on perceived cost-effectiveness and budget availability [42]. In Italy, all 10 drugs studied are listed as Class H (hospital) drugs [43]. As such, significant savings can be achieved because drugs bought directly by hospitals are granted a minimum 50% discount by pharmaceutical companies [43]. That discount, together with a fixed national drug expenditure, reduces the usefulness of a CEA for the 10 drugs [8,43]. The Netherlands incorporates CEA for medicines on a "high-cost drug list," which contains hospital drugs that are 80% reimbursed by its National Health Insurance [44]. Of the 10 drugs we studied, 6 were on that list. Their analysis is conducted after reimbursement approval and, at the time of preparation of this article, had not yet been conducted for the latter 6 drugs.

Australia, Canada, England, New Zealand, and Scotland review a CEA with each reimbursement submission [45–48]. In Australia, Canada, England, and Scotland, most rejections for reimbursement were based on a lack of cost-effectiveness; in New Zealand, lack of cost-effectiveness was the second leading cause. Those rejections for lack of cost-effectiveness have contributed to less publically funded access to cancer drugs than is seen in the remaining countries studied here. The foregoing 5 countries tend to have a threshold—albeit not predefined—for acceptable cost effectiveness, with limited exceptions made for cancer drugs [49]. However, the National Institute for Health and Clinical Excellence in England recently granted leniency to drugs offering a survival benefit to patients near the end of life [50]. In New Zealand, the decision to reject drugs for reimbursement, with excessive cost being the main reason, may be a result of a fixed budget for oral medications (unlike budgets in Australia, Canada, Scotland, and England).

4.2 Submissions

The number of reimbursement submissions from pharmaceutical companies received and reviewed by advisory committees varied between countries. New Zealand had the lowest number of submissions reviewed and has acknowledged that pharmaceutical companies bring applications to their country later than to others; officials attribute this situation to their robust approach to funding decisions and the attractiveness of larger markets [51]. Many indications submitted by pharmaceutical companies, although not initially recommended for reimbursement in the 5 countries with the least number of indications reimbursed, were eventually approved. That finding may suggest that, in an effort to reduce time to reimbursement, clinical advisory committees and pharmaceutical companies may need to make improvements in their discussions about acceptable submission requirements before the actual submission is made.

4.3 Negotiations Between Pharmaceutical Companies and Public Payers

Most of the countries studied were negotiating RSAS with pharmaceutical companies. As other authors

have documented, details of RSAs, with the exception of those in England and Scotland, are not transparent [9,52]. In countries that incorporate CEA into reimbursement decisions and also in countries that do not (such as France, where price–volume agreements are a central element in controlling expenditure), RSAs and SPAs have led to improved access to cancer drugs [7,53,54]. France incorporates a two-step rating system based on clinical need and efficacy over existing treatments, which is subsequently used by France's economic committee to negotiate prices and RSAs. In the United States, the incentives for pharmaceutical companies to negotiate with public payers to offset costs are limited because, by law, Medicare must reimburse cancer drugs [24], thereby limiting the program's negotiating leverage. However, because of rising out-of-pocket expenses for patients, pressure on companies to use cost containment measures, including RSAs, has been building [55,56].

Although RSAs appear to be an effective method to reduce costs, they are accompanied by the administrative burdens of patient monitoring and information submission [57]. Schemes such as volume- and price-capping have also been criticized for being unsupported by clinical evidence [58]. Thus, price negotiations may be a more simplistic way of reducing costs [59].

4.4 Limitations

Reimbursement decisions are complex and may be influenced by variables not reviewed in the present study. Private drug insurance is available in many of the countries studied, and in certain circumstances, it can fund drugs not publically reimbursed [60,61]. In the United States particularly, private drug insurance covers most drug costs, and thus our results relate to relatively smaller number of eligible Medicare patients [7]. Also, restriction to subpopulations was occasionally added to the reimbursed label compared with the licensed indication, thus restricting patients eligible for a drug despite reimbursement approval [62]. Finally, it is beyond the scope of the present study to correlate reimbursement with clinical outcomes.

5. CONCLUSIONS

Reimbursement of cancer drugs by publically-funded drug programs varies globally; the causes are multifactorial. Australia, Canada, England, New Zealand, and Scotland have the most restricted access to publically-funded cancer drugs, and reimbursement rejections occur mainly because of insufficient cost-effectiveness or excessive cost. Negotiations between public payers and pharmaceutical companies through RSAs and SPAs are being used internationally for cost containment with respect to cancer drugs and have resulted in increased reimbursement.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors have no conflicts of interest to disclose. Each author had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PKC, SG, and MET were involved in conception and design. PKC collected data, with contributions from MM, BG, and LY. PKC analyzed the data and, with the help of MM, drafted the manuscript, with critical revisions by the remaining authors.

8. REFERENCES

1. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010;19:1893–907.
2. Savage P. Development and economic trends in cancer therapeutic drugs in the U.K. from 1955 to 2009. *J Oncol Pharm Pract* 2012;18:52–6.
3. Nagle PC, Nicita CA, Gerdes LA, Schmeichel CJ. Characteristics of and trends in the late-stage biopharmaceutical pipeline. *Am J Manag Care* 2008;14:226–9.
4. Jonsson B, Wilking N. Market uptake of new oncology drugs. *Ann Oncol* 2007;18(suppl 3):iii31–48.
5. Richards M. *Extent and Causes of International Variations in Drug Usage. A Report for the Secretary of State for Health.* London, U.K.: Central Office of Information; 2010. [Available online at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_117977.pdf; cited May 10, 2011]
6. Clement FM, Harris A, Li JJ, Yong K, Lee KM, Manns BJ. Using effectiveness and cost effectiveness to make drug coverage decisions—a comparison of Britain, Australia and Canada. *JAMA* 2009;302:1437–43.
7. United Kingdom, Office of Fair Trading (OFT). *Pharmaceutical Price Regulation Scheme. Annexe K: International Survey of Pharmaceutical Pricing and Reimbursement Schemes.* London, U.K.: OFT; 2007. [Available online at: http://www.oft.gov.uk/shared_oft/reports/comp_policy/oft885k.pdf; cited May 10, 2011]
8. Ettelt S, Nolte E, Thomson S, Mays N. *The Systematic Use of Cost-Effectiveness Criteria to Inform Reviews of Publicly Funded Benefits Packages. Final Report.* London, U.K.: London School of Hygiene and Tropical Medicine; 2007. [Available online at: http://www.international-comparisons.org.uk/IHC%20Report%20CEA%20of%20existing%20interventions%202007.pdf; cited May 10, 2011]

9. Adamski J, Godman B, Ofierska–Sujkowska G, *et al.* Risk sharing agreements for pharmaceuticals: potential consideration and recommendations for European payers. *BMC Health Serv Res* 2010;10:153.
10. United States, Department of Health and Human Services, Centers for Medicare and Medicaid Services (CMS). *National Health Expenditure Projections 2009–2019.* Baltimore, MD: CMS; 2010. [Available online at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads//proj2009.pdf; cited April 26, 2012]
11. United Kingdom, Office of Fair Trading (OFT). *Pharmaceutical Price Regulation Scheme. Annexe B: Review of* NICE, SMC, AWMSG. London, U.K.: OFT; 2007. [Available online at: http://www.oft.gov.uk/shared_oft/reports/comp_policy/oft885b.pdf; cited December 28, 2010]
12. Australia, Department of Health and Ageing, Therapeutic Goods Administration (TGA). eBS Australian Register of Therapeutic Goods: Medicines [Web resource]. Canberra, Australia: TGA; n.d. [Available at: https://www.ebs.tga.gov.au/ebs/ANZTPAR/PublicWeb.nsf/cuMedicines; cited May 10, 2011]
13. European Medicines Agency (EMEA). Home > Find Medicine > Human Medicines > European Public Assessment Reports [Web resource]. London, U.K.: EMEA; n.d. [Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125; cited May 10, 2011]
14. Health Canada (HC). Home > Drugs and Health Products > Drug Products > Drug Product Database Online Query [Web resource]. Ottawa, ON: HC; n.d. [Available at: http://webprod.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng; cited May 10, 2011]
15. New Zealand, Medicines and Medical Devices Safety Authority (Medsafe). Medicines Data Sheets [Web resource]. Wellington, N.Z.: Medsafe, n.d. [Available at: http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp; cited May 10, 2011]
16. Japan, Pharmaceuticals and Medical Device Agency (PMDA). PMDA Approved Products [Web resource]. Tokyo, Japan: PMDA; n.d. [Available at: http://www.pmda.go.jp/english/service/approved.html; cited May 10, 2011]
17. United States, Department of Health and Human Services, Food and Drug Administration (FDA). FDA Approved Drug Products [Web resource]. Bethesda, MD: FDA; n.d. [Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; cited May 10, 2011]
18. Japan, Ministry of Health, Labour and Welfare (MHLW). Health Insurance Bureau [Web page]. Tokyo, Japan: MHLW; n.d. [Available at: http://www.mhlw.go.jp/english/org/policy/p34-35.html; cited May 10, 2011]
19. Australia, Department of Health and Ageing (DHA). Pharmaceutical Benefits Scheme [Web resource]. Canberra, Australia: DHA; n.d. [Available at: http://www.pbs.gov.au/html/home; cited May 10, 2011]
20. New Zealand, PHARMAC (Pharmaceutical Management Agency). Online Pharmaceutical Schedule [Web resource]. Wellington, N.Z.: PHARMAC; n.d. [Available at: http://www.pharmac.govt.nz/Schedule; cited May 10, 2011]
21. Cancer Care Ontario (CCO). New Drug Funding Program [Web page]. Toronto, ON: CCO; n.d. [Available at: http://www.cancercare.on.ca/toolbox/drugs/ndfp; cited May 10, 2011]
22. Ontario, Ministry of Health and Long-Term Care (MHLTC). Drugs funded by Ontario Drug Benefit (ODB) Program [Web resource]. Toronto, ON: MHLTC; n.d. [Available at: http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html; cited May 10, 2011]
23. Ontario, Ministry of Health and Long-Term Care (MHLTC). Ontario Public Drug Programs: Exceptional Access Program [Web page]. Toronto, ON: MHLTC; n.d. [Available at: http://www.health.gov.on.ca/english/providers/program/drugs/eap_mn.html; cited May 10, 2011]
24. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med* 2009;360:626–33.
25. American Society of Clinical Oncology. Reimbursement for cancer treatment: coverage of off-label drug indications. *J Clin Oncol* 2006;24:3206–8.
26. Martikainen J, Rajaniemi S. *Drug Reimbursement Systems in EU Member States, Iceland and Norway.* Helsinki, Finland: The Social Insurance Institution; 2002. [Available online at: http://www.kela.fi/in/internet/liite.nsf/ABID/030303101726PN/$File/Drug_reimbursement.pdf; cited May 10, 2011]
27. Australia, Department of Health and Ageing (DHA). Outcomes of Pharmaceutical Benefits Advisory Committee Meetings [Web resource]. Canberra, Australia: DHA; 2007. [Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-outcomes_full.htm; cited May 10, 2011]
28. Ontario, Ministry of Health and Long-Term Care (MHLTC). EO Decisions and CED Recommendations [Web page]. Toronto, ON: MHLTC; n.d. [Available at: http://www.health.gov.on.ca/english/providers/program/drugs/ced_rec_table.html; cited May 10, 2011]
29. United Kingdom, National Health Service, National Institute for Health and Clinical Excellence (NICE). NICE Guidance [Web resource]. London, U.K.: NICE; n.d. [Available at: http://guidance.nice.org.uk; cited May 10, 2011]
30. Scottish Medicines Consortium (SMC). SMC Advice Directory [Web resource]. Glasgow, Scotland: SMC; n.d. [Available at: http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory; cited May 10, 2011]
31. New Zealand, PHARMAC (Pharmaceutical Management Agency), Pharmaceutical and Therapeutics Advisory Committee (PTAC). Meeting Minutes of the Pharmacology and Therapeutics Advisory Committee [Web resource]. Wellington, N.Z.: PTAC; n.d. [Available at: http://www.pharmac.govt.nz/PTAC/PTACminutes; cited May 10, 2011]
32. Mullins CD, Ogilvie S. Emerging standardization in pharmacoeconomics. *Clin Ther* 1998;20:1194–202.
33. Japan Pharmaceutical Manufacturers Association (JPMA). *Pharmaceutical Administration and Regulations in Japan.* Tokyo, Japan: JPMA; 2010: 179–94. [Available online at: http://apps.who.int/medicinedocs/documents/s18577en/s18577en.pdf; cited May 10, 2011]
34. Australia, Department of Human Services, Medicare. Home > For Health Professionals > Other programs—Information for Health Professionals > Late Stage Metastatic Breast Cancer [Web page]. Canberra, Australia: Medicare; n.d. [Available

at: http://www.medicareaustralia.gov.au/provider/patients/late-breast-cancer.jsp; cited May 10, 2011]
35. Gress S, Niebuhr D, May U, Wasem J. Reform of prescription drug reimbursement and pricing in the German social health insurance market: a comparison of three scenarios. *Pharmacoeconomics* 2007;25:443–54.
36. New Zealand, PHARMAC (Pharmaceutical Management Agency). Important Events in PHARMAC's History [Web page]. Wellington, N.Z.: PTAC; n.d. [Available at: http://www.pharmac.govt.nz/AboutPHARMAC/history; cited May 10, 2011]
37. Kresge N, Donahue P. Drugmakers May Lose as Merkel Bids to Break Price "Monopoly" [Web article]. New York, NY: Bloomberg; 2010. [Available online at: http://www.bloomberg.com/news/2010-11-11/astrazeneca-drugmakers-may-face-added-german-price-pressures.html; cited November 26, 2011]
38. Morgan SG, McMahon M, Mitton C, *et al.* Centralized drug review processes in Australia, Canada, New Zealand, and the United Kingdom. *Health Aff (Millwood)* 2006;25:337–47.
39. Rawlins M. Paying for modern cancer care—a global perspective. *Lancet Oncol* 2007;8:749–51.
40. Wettermark B, Godman B, Andersson K, Gustafsson LL, Haycox A, Bertele V. Recent national and regional drug reforms in Sweden—implications for pharmaceutical companies in Europe. *Pharmacoeconomics* 2008;26:537–50.
41. Carlson P on behalf of the National Centre for Priority Setting in Health Care. *Resolving Health Care's Difficult Choices. Survey of Priority Setting in Sweden and Analysis of Principles and Guidelines on Priorities in Health Care.* Linköping, Sweden: PrioriteringsCentrum; 2008.
42. Wettermark B, Persson ME, Wilking N, *et al.* Forecasting drug utilization and expenditure in a metropolitan health region. *BMC Health Serv Res* 2010;10:128.
43. Lo Scalzo A, Donatini A, Orzella L, Cicchetti A, Profili S, Maresso A. Italy: health system review. *Health Syst Transit* 2009;11:1–216. [Available online at: http://www.euro.who.int/__data/assets/pdf_file/0006/87225/E93666.pdf; cited July 22, 2011]
44. Netherlands Organization for Health Research and Development (ZonMw). Efficiency Studies: High Cost Medicines [Web page]. The Hague, Netherlands: ZonMw; n.d. [Available at: http://www.zonmw.nl/en/programmes/efficiency-studies-high-cost-medicines/programme/; cited May 10, 2011]
45. United Kingdom, National Health Service, National Institute for Health and Clinical Excellence (NICE). *Guide to the Methods of Technology Appraisal*. London, U.K.: NICE; 2007. [Available online at: http:www.nice.org.uk/media/8AE/5C/TAMethodsGuideUpdateFINALFORCONSULTATION281107.pdf; cited May 10, 2011]
46. Australia, Department of Health and Ageing (DHA). Pharmaceutical Benefits Advisory Committee: 1995 Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee: Including Major Submissions Involving Economic Analyses [Web resource]. Canberra, Australia: DHA; 2000. [Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-pubs-pharmpac-gusubpac.htm; cited May 10, 2011]
47. Ontario, Ministry of Health and Long-Term Care (MHLTC). *Ontario Guidelines for Economic Analysis of Pharmaceutical Products.* Toronto, ON: MHLTC; 1994. [Available online at: http://www.health.gov.on.ca/english/providers/pub/drugs/dsguide/docs/economic.pdf; cited May 10, 2011]
48. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004;13:437–52.
49. New Zealand, Pharmaceutical Management Agency (PHARMAC). *How Should High Cost Medicines Be Funded? Paper for Public Consultation.* Wellington, N.Z.: PHARMAC; 2006. [Available online at: http://www.pharmac.govt.nz/pdf/HCM.pdf; cited May 10, 2011]
50. United Kingdom, National Health Service, National Institute for Health and Clinical Excellence (NICE). *Appraising Life-Extending, End of Life Treatments.* London, U.K.: NICE; 2009. [Available online at: http://www.nice.org.uk/media/88A/F2/SupplementaryAdviceTACEoL.pdf; cited May 10, 2011]
51. Cancer Control New Zealand (CCNZ). *Coming—Ready or Not: Planning for Cancer Innovations in the New Zealand Health System.* Wellington, N.Z.: CCNZ; 2009. [Available online at: http://cancercontrolnz.govt.nz/sites/default/files/Innovations%20Report.pdf; cited May 10, 2011]
52. Robertson J, Walkom EJ, Henry DA. Transparency in pricing arrangements for medicines listed on the Australian Pharmaceutical Benefits Scheme. *Aust Health Rev* 2009;33:192–9.
53. Sermet C, Andrieu V, Godman B, Van Ganse E, Haycox A, Reynier JP. Ongoing pharmaceutical reforms in France: implications for key stakeholder groups. *Appl Health Econ Health Policy* 2010;8:7–24.
54. Grandfils N. *Drug Price Setting and Regulation in France.* Paris, France: Institut de recherche et documentation en économie de la santé; 2008. [Available online at: http://www.irdes.fr/EspaceAnglais/Publications/WorkingPapers/DT16DrugPriceSettingRegulationFrance.pdf; cited May 10, 2011]
55. Pollack A. *Genentech Caps Cost of Cancer Drug for Some Patients.* Santa Monica, CA: Consumer Watchdog; 2006. [Available online at: http://www.consumerwatchdog.org/patients/articles/?storyId=14384&bIndex=0; cited May 10, 2011]
56. Morgan S, Kennedy J. Prescription drug accessibility and affordability in the United States and abroad. *Issues Int Health Policy* 2010;1408:1–12. [Available online at: http://www.commonwealthfund.org/~/media/Files/Publications/Issue%20Brief/2010/Jun/1408_Morgan_Prescription_drug_accessibility_US_intl_ib.pdf; cited May 10, 2011]
57. Williamson S, Thomson D. A report into the uptake of patient access schemes in the NHS. *Clinical Pharmacist* 2010;2:268–70.
58. Marin A. *A Vast Injustice: Investigation into the Ministry of Health and Long-Term Care's Decision-Making Concerning the Funding of Avastin for Colorectal Cancer Patients.* Toronto, ON: Ombudman Ontario; 2009. [Available online at: http://www.ombudsman.on.ca/Files/Sitemedia/Documents/Investigations/SORT%20Investigations/avastinweb-en.pdf; cited November 26, 2011]
59. Williamson S. Patient access schemes for high-cost cancer medicines. *Lancet Oncol* 2010;11:111–12.

60. Cancer Care Ontario (CCO). Report of the Provincial Working Group on the Delivery of Oncology Medications for Private Payment in Ontario Hospitals. Toronto, ON: CCO; 2006. [Available online at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13638; cited May 10, 2011]
61. Chafe R, Dhalla IA, Dobrow M, Sullivan T. Accessing unfunded cancer drugs in publicly funded hospitals. *Lancet Oncol* 2009;10:306–7.
62. United Kingdom, National Health Service, National Institute for Health and Clinical Excellence (NICE). TA176: Colorectal cancer (first line)—cetuximab (TA176) [Web page]. London, U.K.: NICE; 2009. [Available at: http://guidance.nice.org.uk/TA176; cited May 10, 2011]

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