Why do some countries approve a cancer drug and others don't?☆

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ABSTRACT

The term drug reimbursement describes the policy system that determines whether or not a drug is entitled to reimbursement within the healthcare system. Countries make different decisions regarding which cancer treatments to routinely provide. As a result, depending on the cancer drug-indication and the country assessing it, the decision can be Favourable, Favourable with restrictions or Non-Favourable. The main objective of this paper is to describe the differences in drug reimbursement decisions on cancer drugs across 10 European countries. This aim is achieved through testing a number of hypotheses that can explain the differences in these specific reimbursement decisions. First of all, we collect data on cancer drug decisions for 10 European countries, from 2002 to 2014. Secondly, the hypotheses are tested on this database. The results show that Social Health Insurance systems tend to take more Favourable decisions than the tax-based systems, that cost-effective drug-indications have a higher probability of reimbursement and that other countries are more likely to make a Favourable decision if NICE also make it. Moreover, our findings also corroborate that an economic evaluation requirement reduces the number of Favourable decisions, and that, during the global financial crisis, the number of Favourable decisions has been reduced, compared to Non-Favourable and restricted. To sum up, characteristics of the drug reimbursement system, drug particularities and the socioeconomic situation are the main factors determining the differences across countries.

Introduction

The term drug reimbursement describes the policy system that determines whether or not a drug is entitled to reimbursement within the healthcare system. The decisions taken by each healthcare system have an impact on the society, as they determine which drugs are made available for the patients. These are extremely important decisions, which mix the clinical and economic evidence with ethical judgements. Drug reimbursement encompasses the entire process from the submission of a reimbursement request to the final decision. In the last stage of the process, countries make different decisions regarding which treatments to routinely provide. As a result, depending on the drug-indication and the country assessing it, the decision can be Favourable, Favourable with restrictions or Non-Favourable.

Drug reimbursement has attracted attention from several authors, due to the different systems that exist. Various comparative analyses have been published recently [1–5], describing the different national models in the world. Due to these differences, depending on the drug-indication and the country assessing it, the final decision of reimbursement can differ across countries [3,6]. There are a number of descriptive and comparative studies analysing these differences [7–10] and some of them also include an empirical analyses [11–16]. These last studies are mainly based on the decisions taken in UK by either the National Institute for Health and Care Excellence (NICE) or the Scottish Medicine Consortium (SMC). Furthermore, none of these empirical studies have specifically analysed decisions on cancer drugs.

In particular, even if the European countries have common objectives for Health Technology Assessment (HTA) systems, the process is not homogenous. The operative processes and the organisations work differently across these countries. Our main objective is to describe the differences in drug reimbursement decisions on cancer drugs across 10 European countries. We explore a number

of hypotheses that can explain the differences in these specific reimbursement decisions. The overall hypothesis of this paper is that there are differences in cancer drugs decisions across Europe related to the characteristics of the drug reimbursement system, the drug particularities and/or the socioeconomic situation.

The paper is structured as follow. Hypotheses section defines the main hypotheses. The third section describes the data on cancer drugs reimbursement decisions. In Testing the Hypotheses section, the hypotheses are tested on the cancer database. Finally, these results are discussed in the last section.

Hypotheses

The overall hypothesis of this paper is that there are differences in cancer drugs decisions across Europe related to the characteristics of the drug reimbursement system, the drug particularities and/or the socioeconomic situation.

(1) The health system implemented in each country has an effect on the reimbursement decision. This first hypothesis is that the proportion of Favourable decisions (without restrictions) is higher in Social Health Insurance (SHI) systems than in tax-based systems. In the latter, the taxes collected are not only to be used for drug reimbursement, so there is an intrinsic competition for these funds.
(2) Countries with higher Public Health Expenditure (PHE) per capita tend to accept more drugs into the system than the countries with lower PHE per capita.
(3) A cost-effective drug-indication has a higher probability of reimbursement than a non-cost-effective one. Some authors have empirically tested this hypothesis during the last decade [11–16]. Their results were positively related with the previous statement.
(4) NICE is one of the most important HTA agencies around Europe. Their HTA analyses are considered among the most complete and strict. Thus, regardless of whether a country's decision precedes or follows a NICE decision, other countries will tend to say yes to drugs for which NICE make a Favourable decision (without restrictions). Whereas, they will be less likely to say no when NICE make a Non-Favourable decision.
(5) When the reimbursement decision-making requires an economic evaluation, the proportion of Favourable decisions is lower then when it is not required. This requirement differs across countries.
(6) Due to the global financial crisis, many austerity measures have been implemented in Europe. As a consequence, we anticipate proportionately fewer Favourable decisions, and more restricted and Non-Favourable decisions.

Database

The sample includes the pharmaceutical technology appraisals for cancer drugs that have been appraised in 10 European countries from January 2002 until November 2014. Our database collects the drug reimbursement decisions on 161 drug-indications for the 10 countries selected: Belgium, France, Germany, Netherlands, Poland, Portugal, Spain, Sweden and United Kingdom (England and Scotland analysed separately). These countries were selected because they each have a well-defined HTA process and publicly available information on their drug reimbursement procedures.

During the last decade, many new cancer drug-indication pairs have been appraised. The drugs selected to enter into our study were classified under "malignant disease and immunosuppression" on the SMC website. SMC was the starting point because

Table 1
Decision data by country (sources).

Country	Institution/database	Data source
England	NICE	HTA decisions from the NICE website.
Scotland	SMC	HTA decisions from the SMC website.
Sweden	TLV/NLT	HTA decisions from the TLV/NLT website. Validation from the TLV team.
Belgium	RIZIV INAMI	HTA decisions from the INAMI database (online). Validation of the data and information on MEA from the INAMI team.
Portugal	INFARMED	HTA decisions from INFARMED database (online). Information on the MEA from the INFARMED team.
Poland	AOTM	Database created by AOTM.
Spain	BOTPLUS	Database created by EASP and UCLM from BOTPLUS. Validation of data by GENESIS.
Germany	G-BA	HTA decisions from the G-BA website. Only decisions from 2011 onwards (AMNOG)
Netherlands	CVZ/MoH	Information on decisions provided by MoH.
France	HAS/MoH	Database created by the URC-ECO.

Source: own construction.

it appraises all the licensed drugs. However, the SMC list was validated, checking NICE decisions for any additional cancer drug-indication. After this process, the number of drug-indications was 161.

Table 1 reports the data source for each country. For some countries, all drug reimbursement decisions were publicly available through their websites, but for others, assistance was required from the National HTA Agencies or the National Government.

Decision outcome

The decision outcome describes the final decision regarding the adoption of the technology: Non-Favourable, Favourable with restrictions and Favourable. A decision is considered to be restricted only when it differs from the indication detailed in the marketing authorisation, for instance, when a positive recommendation is limited to a sub-group of those identified in the marketing authorisation, but it is not considered restricted when the recommendation is to purchase at the lowest acquisition cost.

Moreover, in order to capture all possible decisions, the decision variable has two other categories: non-submission and non-assessed. The first category collects the decisions where the reimbursement body asked the manufacturer to make a submission and it failed to do so. Under this category, there are only decisions from NICE and SMC, as the other countries do not document this information. The non-assessed category collects the drug-indications that have not been assessed by each country.

Table 2
Decision outcome total.

	Decisions (all countries)
Non-Favourable	**123 (7.75%)**
Restricted	**191 (12.04%)**
Favourable	**561 (35.35%)**
Non-submission	43 (2.71%)
Non-assessed	669 (41.16%)
Total	**1587 (100%)**

Source: own construction.

Table 3
Decision outcome per country.[a]

	Scotland		England		Belgium		Sweden		France	
Non-Favourable	**38**	**(23.60%)**	**34**	**(21.52%)**	**4**	**(2.52%)**	**5**	**(3.11%)**	**7**	**(4.43%)**
Restricted	**47**	**(29.19%)**	**22**	**(13.92%)**	**48**	**(30.19%)**	**6**	**(3.73%)**	**4**	**(2.53%)**
Favourable	**31**	**(19.25%)**	**39**	**(24.68%)**	**76**	**(47.80%)**	**40**	**(24.84%)**	**140**	**(88.61%)**
Non-submission	36	(22.36%)	7	(4.43%)	0	(0%)	0	(0%)	0	(0%)
Non-assessed	9	(5.59%)	56	(35.44%)	31	(19.50%)	110	(68.32%)	7	(4.43%)
Total	**161**	**100%**	**158**	**100%**	**159**	**100%**	**161**	**100%**	**158**	**100%**
	Poland		Portugal		Germany		Spain		Netherlands	
Non-Favourable	**27**	**(16.77%)**	**7**	**(4.35%)**	**1**	**(0.62%)**	**0**	**(0%)**	**0**	**(0%)**
Restricted	**47**	**(29.19%)**	**3**	**(1.86%)**	**0**	**(0%)**	**14**	**(9.59%)**	**0**	**(0%)**
Favourable	**20**	**(12.42%)**	**34**	**(21.12%)**	**20**	**(12.42%)**	**116**	**(79.45%)**	**45**	**(27.95%)**
Non-submission	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Non-assessed	67	(41.61%)	117	(72.67%)	140	(86.96%)	16	(10.96%)	116	(72.05%)
Total	**161**	**100%**	**161**	**100%**	**161**	**100%**	**146**	**100%**	**161**	**100%**

Source: own construction.

[a] Not all decisions per country sum up to 161, because some decisions predated the sample period (2002).

Table 2 summarises the decision outcomes. The database contains 1587 observations, 35% of them were Favourable decisions, while only 7.8% were rejected and 12% were restricted. Under the category of non-submission, there are only 43 decisions, accounting for 2.71% of the total. The non-assessed category is the highest with 41% of observations.

Table 3 presents this information by country. Germany, Portugal, Netherlands and Sweden have a higher number of non-assessed drugs. Under this category, some data limitations arise. For instance, for Germany, data on reimbursement decisions was only available from 2011 (AMNOG) and for Portugal from 2006. As a result, for these countries, drug-indications without decision were included under the non-assessed category. Comparing the other countries, France has assessed more cancer drug indications, followed by Belgium and Spain. Belgium, Poland and Scotland have the highest rates of restricted decisions.

Drug-indications per country

Graph 1 shows the outcome decision in terms of cancer type per country. When the coloured line reaches the outer circle, it means Favourable decision, when it stops in the middle, it means restricted and when it is blank, it means either rejected or non-assessed. The main result of this graph is that the probability of reimbursement differs across countries. For example, France and Spain tend to accept more cancer drugs, while Poland and Scotland restricts more decisions than the other countries.

Testing the hypotheses

Six hypotheses are proposed to explain differences in drug reimbursement decisions across these countries.

(1) SHI system vs. tax-based
   Half of the countries have a SHI system (Belgium, France, Germany, Netherlands and Poland) while the other half have a tax-based system (England, Portugal, Scotland, Spain and Sweden). The proportion of Favourable decisions (without restrictions) for SHI systems is hypothesised to be greater than the proportion for tax-based systems ($p_1 > p_2$).
   $p_1 = 69\%$—Of the 439 SHI system decisions 301 were Favourable.
   $p_2 = 60\%$—Of the 436 tax-based system decisions 260 were Favourable.
   A higher proportion of the decisions in SHI systems are Favourable (p-value = 0.0027).
(2) Higher PHE per capita vs. lower PHE per capita

Germany, Netherlands, France have the higher PHE per capita, while Poland, Spain and Portugal have the lower. Table 2 can be used to test this hypothesis, as it shows the decisions classified by country. However, there is not a clear pattern to ratify our hypothesis. The main problem is data availability. For Germany, Netherlands and Portugal, there are too few decisions. The only thing, that can be said, is that Poland restricts more than France. For both countries, there is enough data but a clear pattern cannot be determined across countries. As a consequence, this hypothesis is not supported.

(3) Cost-effective vs. non-cost-effective drug-indications
   This hypothesis is tested through the construction of a variable that determines the cost-effectiveness of each drug-indication. This variable is created out of the Incremental Cost-Effectiveness Ratio (ICER) from NICE or SMC decisions. Using NICE definition, it is assumed that a drug is considered cost-effective, when the drug-indication has an ICER below £30,000 per QALY. This variable has three categories: cost-effective, non-cost-effective and no ICER information. Applying it to our dataset, the hypothesis is tested running a two-sample proportion test. It compares the proportion of Favourable decisions (without restrictions) with cost-effective or non-cost-effective drug-indications ($p_1 > p_2$).
   $p_1 = 68\%$—Of the 296 cost-effective drug-indications 202 were Favourable.
 $p_2 = 59\%$—Of the 418 non cost-effective drug-indications 246 were Favourable.
   There is a higher probability of reimbursement for cost-effective drug-indications (p-value = 0.0071).
   In order to go more on detail, it is important to understand why non-cost-effective drug-indications had a 59% of Favourable decision. From these decisions, 40.65% were fulfilling the end of life criteria implemented by NICE in 2009. Moreover, 19% of this non-cost-effective/Favourable decisions, had a MEA and 24% were orphan drugs. As a result, all these particularities help explain why 59% of non-cost-effective drug-indications were still accepted.
(4) NICE vs. other countries' decisions
   Regardless of whether a country's decision precedes or follows a NICE decision, other countries will tend to say yes to drugs for which NICE make a Favourable decision (without restrictions). Whereas, they will be less likely to say no when NICE make a Non-Favourable decision. The proportions to be tested are the following:
   $p_1 = 75\%$—Of 230 decisions regarding drugs for which NICE made a Favourable decision 172 were Favourable in the other countries.
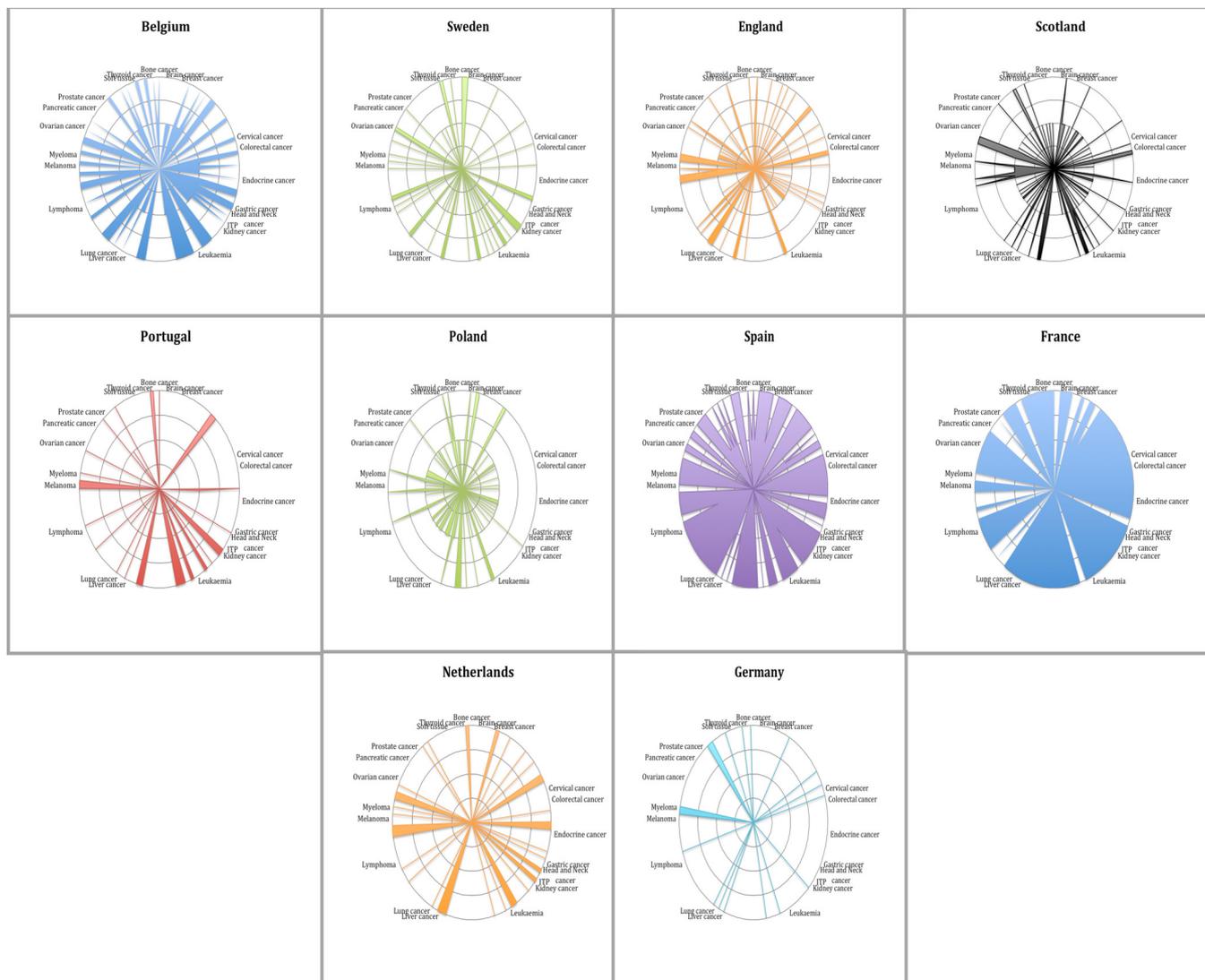
Graph 1. Drug-indications per country.

$p_2 = 33\%$—Of 223 decisions regarding drugs for which NICE made a Non-Favourable decision 72 were Non-Favourable in the other countries.

Thus, other countries are more likely to make a Favourable decision with respect to drugs for which NICE also make a Favourable decision, than to say no when NICE says no (p-value = 0.000).

(5) Economic evaluation required vs. non-required

The hypothesis that the proportion of Favourable decisions is lower when economic evaluation is required.

$p_1 = 33\%$—Of 421 decisions requiring an economic evaluation 184 were Favourable.

$p_2 = 93\%$—Of 121 decisions not requiring an economic evaluation 112 were Favourable.

The probability of a Favourable decision is lower when economic evaluation is required (p-value = 0.000).

(6) Global financial crisis

Decision outcomes are plotted for 2002–2014 in order to assess the effect of the global financial crisis on reimbursement decisions. Graph 2 shows that from 2008, when the economic crisis started, there was a drop in the percentage of Favourable decisions taken in these European countries. This drop was reflected in both, a sharp increase in Non-Favourable decisions
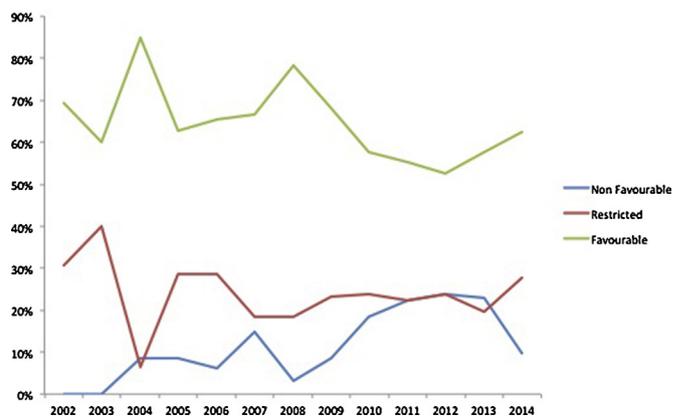
Graph 2. Decision outcomes 2002–2014.

and a moderate increase in Favourable but restricted decisions. Although there is not a systematic pattern for these three categories over time, it appears that the crisis, and consequent austerity measures, had an impact on the cancer reimbursement decisions.

Discussion

In this paper, our main objective has been to describe the differences in drug reimbursement decisions on cancer drugs across 10 European countries. We have explored a number of hypotheses that can explain the differences in these specific reimbursement decisions. As a general result, our overall hypothesis can be corroborated; there exist differences on cancer drug reimbursement decisions across the 10 European countries. The results of testing the six hypotheses showed that the characteristics of the drug reimbursement system, the drug particularities and the socioeconomic situation are the main factors determining these differences across countries.

Comparing our findings with previous studies [11–16], we also found that a cost-effective drug-indication (lower ICER) increases the probability of reimbursement. However, our analysis has gone further by including 10 countries and 875 decisions. The previous studies focused only on NICE [11–14] or SMC [16] and included fewer decisions (e.g. 77 decisions [15]). Another study, by Hernandez-Villafuerte et al. [17], showed that other countries tend to follow NICE decisions when NICE restricts or rejects the drug, but not when it gives a positive recommendation. Even if, in the hypothesis 4, all decisions are considered (before and after NICE), our results differ from this study. This difference may be related to the small number of decisions that they are analysing, as they note [17].

In terms of the other findings, to the best of our knowledge, there is no existing literature that has statistically tested these same hypotheses. Other descriptive and comparative studies analysed these differences through other perspectives, mainly looking at each reimbursement system criteria [e.g. 9,10]. The main contribution of this paper, compared to the existing literature, is that decisions are collected from 10 countries, that the number of decisions is much higher than the other studies and that it focus only on one therapeutic area.

Although, the results are satisfactory, during this research we encountered a number of limitations. The first one related to data collection, which was very time consuming and complicated. The principal reason is that not all the countries make their decisions publicly available or provide insufficient detail. For instance, German data is only available after 2011, Portugal after 2006 and Spain does not upload their decisions. These issues were overcome by contacting with national experts who helped us validating our database.

A further limitation concerns the large number of drug-indications, categorised as non-assessed (41%). The hypotheses only focused on assessed drug-indications. There are two possible explanations for non-assessment: (1) The manufacturer did not make a reimbursement submission in that country, for instance, the crisis situation might have had a deterrent effect. (2) The MoH decided not to look at that particular drug-indication. In addition, it is possible that a drug-indication was assessed but not reported.

The third important limitation is that each hypothesis was tested one at a time. It is possible that there is correlation among these factors. So, the explanation of these differences is more complex than trying to define it factor by factor. Another particular limitation relates to the construction of the variable defining the cost-effectiveness of each drug-indication. Even if each country has its own particularties, for simplicity, NICE or SMC definitions were used.

The descriptive and comparative analysis done in this paper has helped to answer our hypotheses, however, this method is not enough to define the differences in drug reimbursement decisions across countries. These limitations can be overcome by designing a taxonomy that collects all the characteristics of the drug reimbursement system, the drug particularities and the socioeconomic situation of each country. Applying this classification to the cancer database, we can then specify an econometric model that will be able to capture all the information and show the main variables determining the differences. Moreover, it will be important to take into account that these factors might be correlated among them and there might be time dependency. This will be done in future research.

Conflict of interest

There are no conflicts of interest for any of the authors. All authors freely disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work.

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